Introduction to Organic Chemistry II

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Lecture 32

Special Topic - E1CB reaction

So, welcome to this session on a special reaction, which is called as the E1 Conjugate Base reaction, E1CB reaction. So, it is basically an elimination reaction, and we are going to look at it now.

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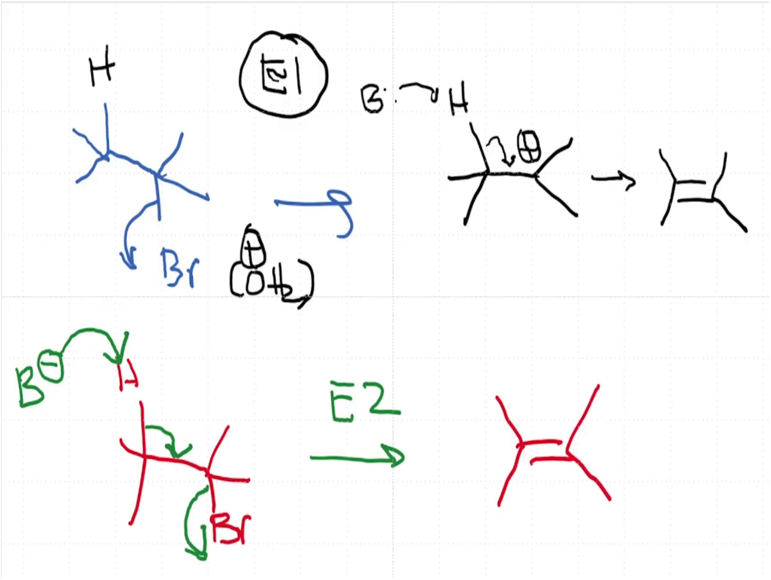

So, you already have a good idea about the two major mechanisms for elimination reaction. The first one is E1 where you have let us say a system like this, and you have the loss of bromide or you could also have OH_2^+, which can be lost, et cetera, et cetera.

So, this is going to be lost and you are going to produce a carbocation. And once this carbocation is formed multiple things can happen, including substitution, et cetera, but one possibility is that this can sort of lose a proton and this proton loss can be facilitated by a weak base, and this gives you the eliminated product. So, this mechanism is referred to as E1.

Now, we also know the other important mechanism that we are familiar with, which is the E2. So, in E2, you normally use a strong base. So, you would use B^-, and this base can be something like tertiary butoxide and what it is going to do, is it is going to abstract this hydrogen, and this results in a formation of the double bond and loss of bromide.

So, there are similarities in the two mechanisms, in that there is going to be a loss of the bromide and abstraction of H^+, but this is a concerted step. So, that means that complete mechanism happens in one step. And this gives you the eliminated product as shown here.

So, these are the two major classes of elimination mechanisms. There are some important differences. The first difference is in kinetics. So, E1 is a first order reaction, and whereas E2 is a second order reaction that is dependent on the, both the reactants, that is, the base as well as the bromide or halide. And the second important mechanistic aspect is that E2 is a concerted step, that means it is a single step reaction, and whereas E1 is a multiple step reaction. And there are probably other important differences such as the selectivity.

So, for example in E1 you invariably end up with a mixture of eliminated and substituted products. In E2 if you use a strong base, and if you have a fairly good leaving group and if it is directly hindered you are going to end up with the eliminated product.

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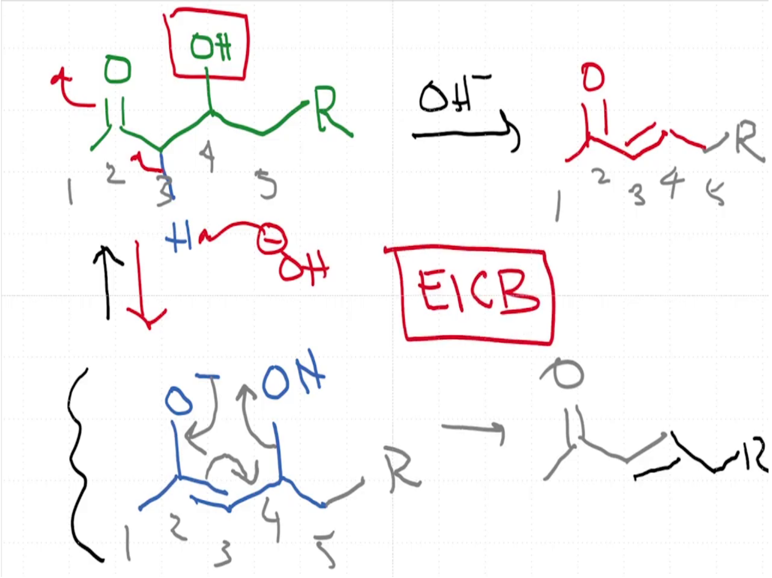

Now, what we look at now, is another important mechanism. And here is the reaction that we want to first understand. So, here is a compound. I am just going to call this as R. And when this is exposed to hydroxide ion, the product that is formed is this. So, let me just number it so that we can clearly understand this. 1, 2, 3, 4, 5, and this whole thing is 6. So, 1, 2, 3, 4, 5, and this is 6. So, you get this as the product.

Now, the important thing here is that the hydroxide is basically the leaving group here, and this is a pretty terrible leaving group. We know that hydroxide ion is among the poorer leaving groups. So, it is unlikely that you are going to have the hydrogen abstraction and loss of hydroxide ion in a single step. And carbocation formation is also very unlikely because you are in strong base and there is no real reason for OH^- to leave. So, considering both these situations, we may propose a mechanism which is quite different.

So, the first step in this mechanism is our familiar reaction, which is basically the formation of the Enolate. So, let us push these arrows and, and write out the enolates. So, you get O^-. And now, let me just number it so that we are consistent. 1, 2, 3, 4, 5 and this is the R group. Now, in the second step one can imagine that this kind of a rearrangement can occur where hydroxide ion is lost and you get the olefin. Here, right here there is a product. So, now this is one of the possibilities.

There are two important things here. The first one is that this reaction is probably a reversible reaction because we know that the enolate formation is a reversible reaction. And the second step, which is the rearrangement of the enolate or to produce this α, β-unsaturated ketone is likely the rate-determining step. So, therefore if you figure out the kinetics here, this is a first order reaction and not a second order reaction. And the second part of this is that if you see this compound here, this is actually the conjugate base of the starting material. So, therefore this mechanism is called as E1 Conjugate Base or E1CB.

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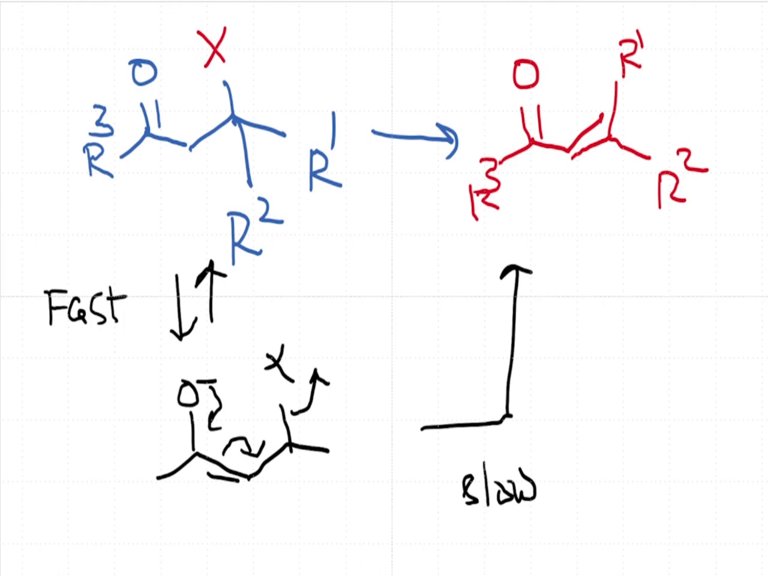

Now, as a general mechanism for this process, the way we would want to look at it is, we draw out R double bond O, let us say we have X over here, which is the leaving group, R^1, R^2, let us call, this is R^3. Now, the product that is formed is…, and the way we understand this mechanism is that there is going to be a fast-reversible reaction to produce the enolate, and then there is a slow elimination to kick out the product.

So, normally, as we know, hydroxide ion is clearly not a good leaving group in any situation but here we understand that hydroxide ion can leave because the enolate that is produced, the pKa of the ketone is around 20. And therefore, the enolate formation, the basicity of the ketone is substantially higher or the water is a much better acid when compared to the ketone and therefore the elimination or the loss of hydroxyl ion can occur in this kind of a situation.

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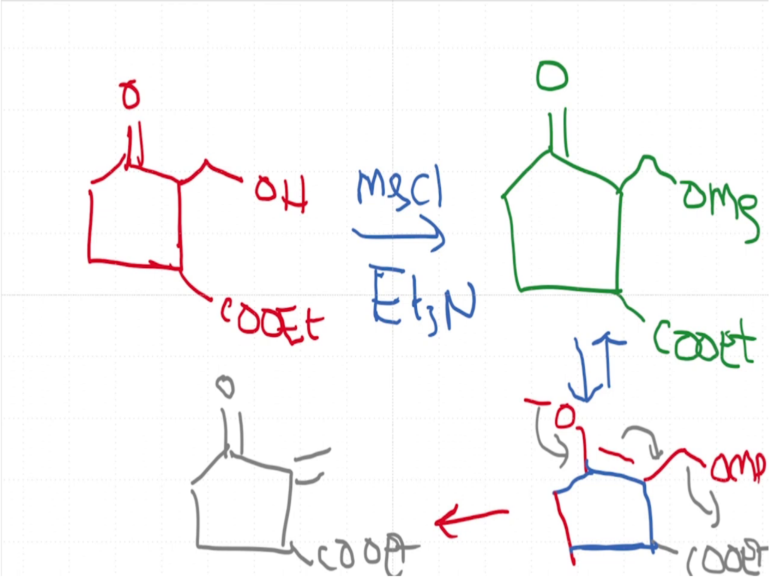

Now, let us look at a couple of examples. So, what we can also do, in one of these experiments that we want to conduct, is that since hydroxide ion, although it can leave in principle, but what we can also do is to promote this reaction by converting this into a better leaving group.

So, we can use Mesyl chloride or Tosyl chloride and, in the presence of a mild base such as triethylamine, and the product that we are expecting over here is OMs and COOEt. In presence of a mild base this can equilibrate to its corresponding enolate to produce the O minus, OMs. And based on the mechanism that we have already looked at, this is going to rearrange, kick out, and give you the final product which is an α, β-unsaturated ketone. And in this case the, the reaction yield is 100 percent.

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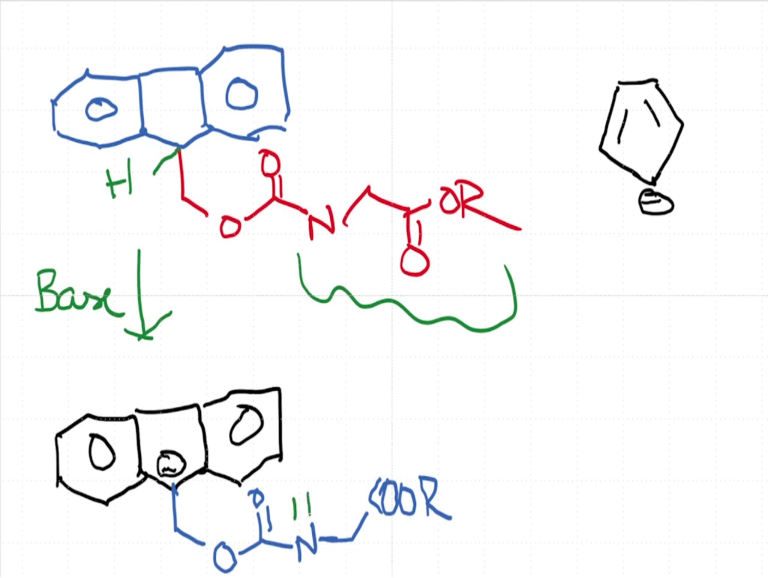

Lastly, we will look at one more example. And this example is very important and interesting because it is used in peptide chemistry as a protective group. So, the example that we are going to look at is the following. So, you have a benzene ring and then you have a five-membered ring and then you have another benzene ring attached to it. And this is the compound that we are going to consider.

Now, you can think about this that this is coming from the amino acid part and you can synthesize this compound using very simple chemistry. So, when this compound is exposed to a base, right, what one can sort of understand is that this hydrogen is actually quite acidic. And you can think about the reason why this is acidic because if you take cyclopentadiene, and if you make the cyclopentadienyl anion, the cyclopentadienyl anion is quite stable and it is attributed to aromaticity of this system.

So, similarly when you deprotonate here, it forms a very stable structure likely due to the aromaticity concept. So, let me just draw this carbanion like this, and then we have the remaining, rest of the molecule. Now, what can happen is a very interesting set of steps. So, I am just going to draw this once again in the next slide so, so that I can make some space.

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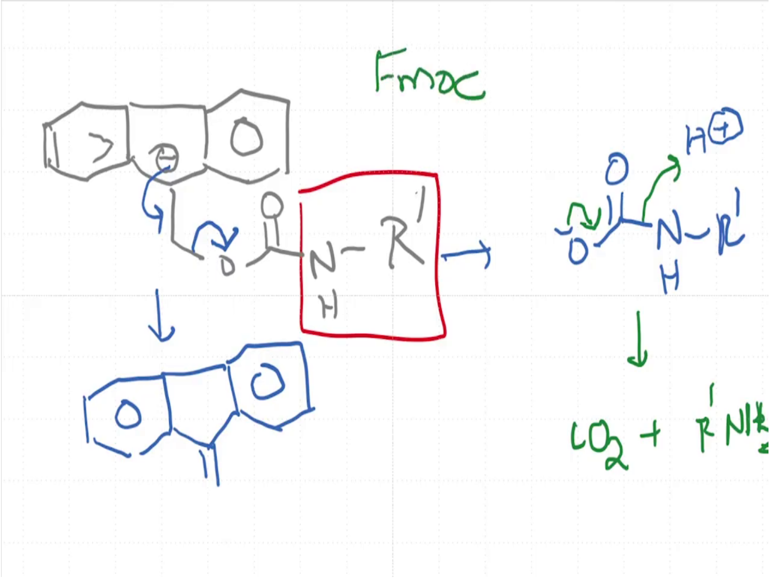

So, here is the carbanion, and O C double bond O NH R, I am just going to call this as R prime. So, what can happen is that this pair of electrons can move in here and this can actually be lost. So, when it moves, the product that is produced on one side is this olefin, and on the other side you get O^- C=O NH R'. So, what can happen is that if there is some H^+ that is floating around in solution, you can imagine that this can pick up this proton in the process and produce CO_2 and R' NH_2, so which is basically the amino acid product.

So, this is a very useful and important protective group because if your amino acid can be protected as this entity here then you are going to be able to carry out a number of other reactions on amino acid while you keep the amine part of it stable. And then whenever you want to deprotect, all you need to do is to add some amount of base and deprotect it. So, this is called as the Fmoc protecting group.