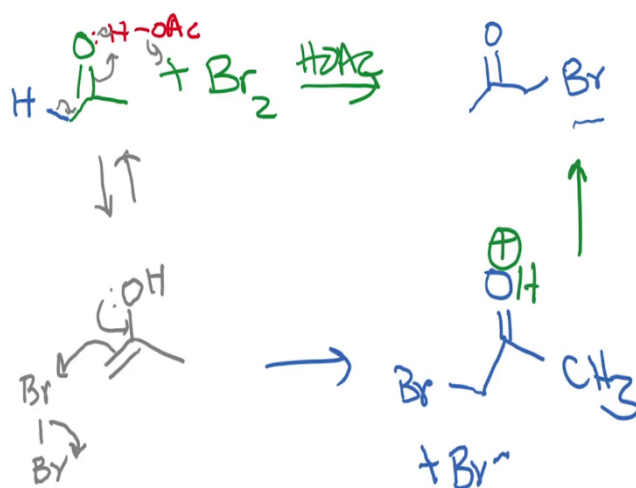


Introductory Organic Chemistry - II
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Reactions of Enols and Enolates

Welcome back. So, in today's lecture, we are going to look at certain reactions of enols and enolates. In the past couple of lectures, we have, really looked at in detail about how you can generate these enols, and how you can generate these enolates. And also, the stability of enols and enolates and so on and so forth.

So, I hope all of you have a very strong foundation in this chemistry, because if you understand the chemistry related to these enols and enolates, then the rest of the semester becomes fairly straightforward. Because at least 70 percent of what is remaining, focuses on various reactions of enols and enolates and combination thereof.

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So, what we will do today, or in this lecture, is we will look at some basics of reactions of enols and enolates. I think we are all familiar with the alkylation reaction of enols and enolates. So, I am not going to spend a lot of time on that. But we will spend some time on the reaction known as the Aldol reaction. I think many of you are already familiar with the reaction.

But we will reintroduce or revise this reaction once in this lecture, and then we will move on to various combinations of or various aspects of aldol reaction chemistry. And so, before we

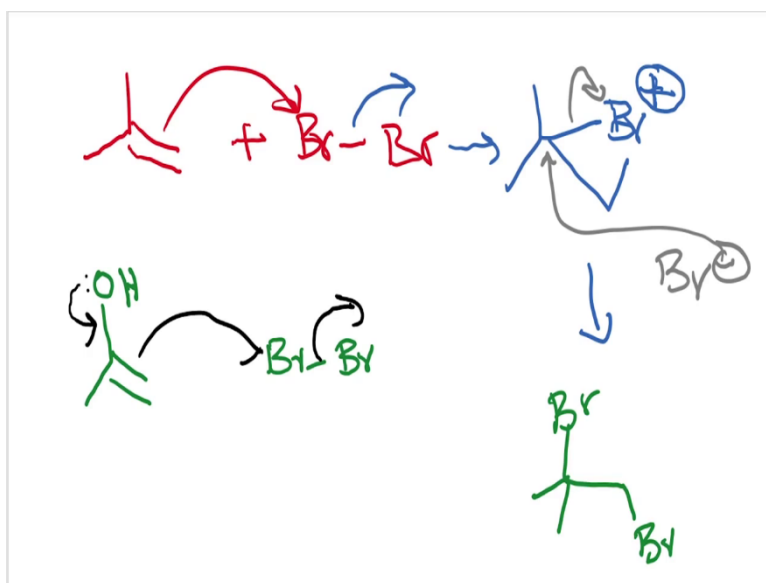
go into Aldol, let us just start with a simple reaction of both enols and enolates, which is halogenation reaction. So, let us say we take a ketone.

And react it with bromine in the presence of acetic acid. So, here acetic acid is used as a solvent and many of you know that acetic acid is an excellent acid but that is essentially in aqueous media. As a solvent, acetic acid is best weak acid. And so, it can produce a proton, but it is not as efficient as it would be in water.

So, I think again, this is a reaction that probably you are already familiar with, but let me just recap this. So, the product of bromination, in the presence of acetic acid is this α -bromoketone. And, the way we would propose a mechanism is through the formation of an enol. So, what happens is you have an acetic acid, this carbonyl can pick up a proton from here, and kick out acetate, and in the process, it can form an enol.

So, this is something that we are quite familiar with. So, you will have O, and H, and this is a double bond over here, and over here the methyl remains intact. So, now being an enol, you can propose that this enol can react with Br. And this is going to give you C double bond O, CH_3 remains intact, and then you have a new bond between this carbon and this bromine, and so that is shown here, $\text{CH}_3\text{C}=\text{OH}^+\text{CH}_2\text{Br}$. And, Br^- would be the byproduct. And keep in mind that this is still protonated. So, if it loses a proton, it is going to give you this product.

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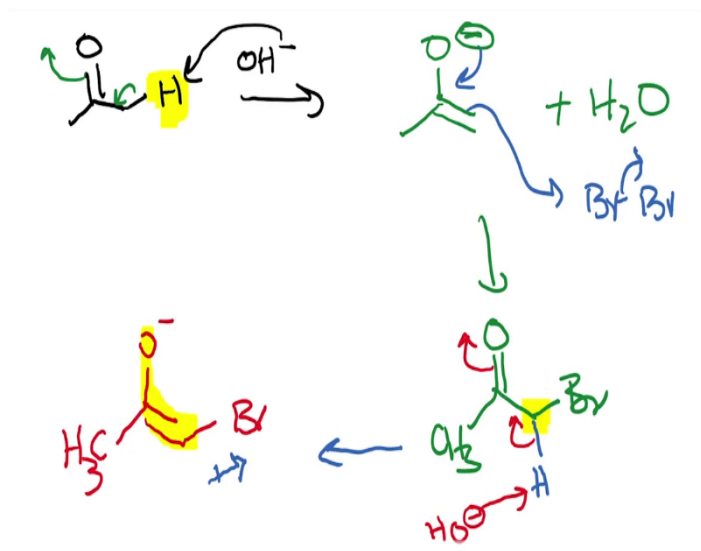


Now, this reaction can be compared with the reaction of an olefin, which we have already looked at in some detail. And so, if you have this olefin plus bromine, this attacks over here,

and then you have loss of Br^- , and you already know that it has good evidence that it produces a cyclic bromonium ion. And so, this is fine. So, then, opening up of this by the bromide that ensues, goes over here. And you kick this out, and the product that you form would be the dibromide.

So, this is something that you guys are already quite well versed with. Now, if you compare the enol bromination versus the olefin bromination, so let us say we take this enol versus this, I think if you see the arrow pushing process, it is pretty comparable. So, you have bromine over here. And let me just show you that this arrow is identical. There is no difference here. The only difference between the enol bromination and the olefin. One major difference is that it is pushed by the electron pair, that comes from oxygen. So, that is an important difference in this reaction. And so, enols are particularly more reactive than olefins.

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Now, this bromination can also be done through bases, I think we already know that, an enol and enolate can be produced using a catalytic amount of base. So, you just add in a small amount of, let us say, sodium hydroxide. So, sodium hydroxide can come and pick up this proton, and you will generate an enolate. So, the negative charge, and water is the byproduct over here.

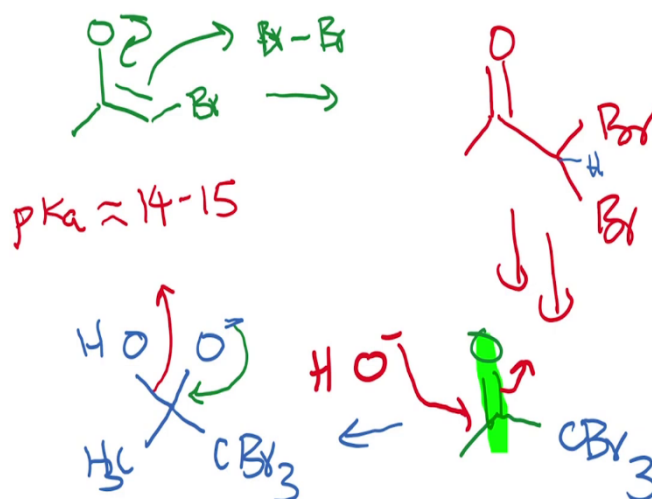
So now, this enolate, you can imagine that it attacks Br_2 , and it kicks out this bromide ion, and you get $\text{CH}_3\text{C}=\text{OCHBr}$. And the byproduct here is bromide anion. So, this is perfectly fine, I think it is quite reasonable to propose this. The only challenge in this whole process is that

when we move from this enolizable carbonyl, the product that we are generating is very interesting, because this CH, this carbon, over here, if you pick up another proton from here, for example, what you would generate is a more stabilized enolate.

So, if you see here, let me just remove this bromide, because we have already covered that part, but imagine that hydroxide ion attacks here, and you generate the enolate. So, the enolate, that is produced is $\text{CH}_2^-\text{OC}=\text{CHBr}$. So, at this moment, I am not worried about the stereochemistry. But let us assume that this kind of an intermediate is produced.

Now, perhaps due to the electronegativity of the bromine, this is going to be some pulling of electrons in the direction. And it is going to stabilize this enolate much better. So, what happens is that your hydroxide that is present, can now pick up this next enolate, I mean, they can generate the enolate from the first product, and it produces another enolate.

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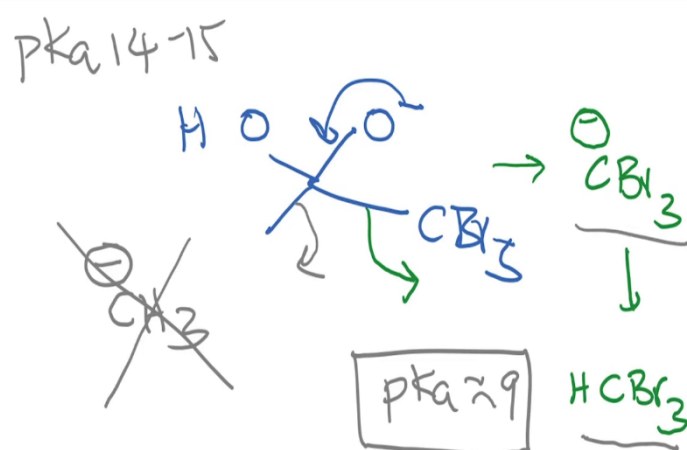
So, this next enolate actually, if it reacts, it is going to give you, if it reacts with bromine chemistry is the same and it is going to give you the product, which is the dibromide. And subsequently, I am not going to show the arrows over here, but you can very easily understand that you can form this CBr_3^- over here. Now, the challenge over here is that this, what you are doing in this process is that you are doing two things, one is that if you have an enolizable hydrogen, then the acid-base reactions are, generally speaking, much faster than other reactions.

Other than maybe radical reactions for example, but generally speaking acid-base reactions are quite facile. Now, since you do have an enolizable hydrogen on the side, but what you also have is a very reactive carbonyl. So, this carbonyl is quite reactive. And so, you will have the reaction of this carbonyl might be quite facile. And so, hydroxide ion can attack over here and produce this intermediate that we are all quite familiar with, which is the tetrahedral intermediate.

So, you have a CH_3 , and then you have a CBr_3 . So, the interesting aspect of this kind of intermediate is that, this is like a typical tetrahedral intermediate that we get during nucleophilic addition or substitution to carbonyl compounds. So, the first step of the nucleophilic substitution reaction is an addition reaction, followed by which forms a tetrahedral intermediate, and then the collapse of the tetrahedral intermediate gives you the product.

So, now, if you think about this chemistry over here, what can happen is that this moves in over here, and it has two choices, this intermediate, choice number one is that it kicks out hydroxide ion, and then that gives you back the starting material. Now, in order to understand this, the pK_a of water is around 14 or 15. So, that is not a very easy process, but it can happen. But the interesting thing is that, if you let me just redraw this intermediate on the next page. So, that we can discuss this in little bit of a detail.

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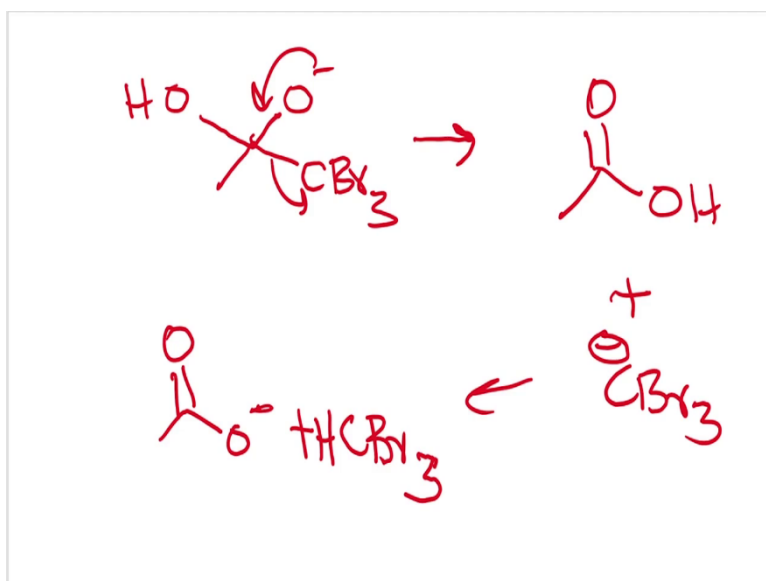


So, here is the, again, I am just redrawing the intermediate $\text{CH}_3\text{O}^-\text{C}(\text{OH})\text{CBr}_3$. So, now, what happens is that, you know when this comes back like I mentioned, you have two choices, one is the hydroxide ion can leave, but the other choice is that the CBr_3^- can be formed. And if this is formed, then you will eventually get CHBr_3 which is bromoform, like chloroform, there is bromoform, and there is iodoform.

But now, let us consider the feasibility of this process. So, the pKa of Bromoform is estimated to be around 9. And as I mentioned, the pKa of water is around 14 to 15. So, hydroxide ion as a leaving group is not a great leaving group in this case. And the last choice just to complete the discussion would be CH_3^- , and as you know the pKa of methane is like in 40's, definitely greater than 35.

So, this is really not going to happen. So, the loss of CH_3^- is unlikely. So, between the two choices, that is the formation of CBr_3^- and the formation of hydroxide ion, this the formation of CBr_3^- is dominant.

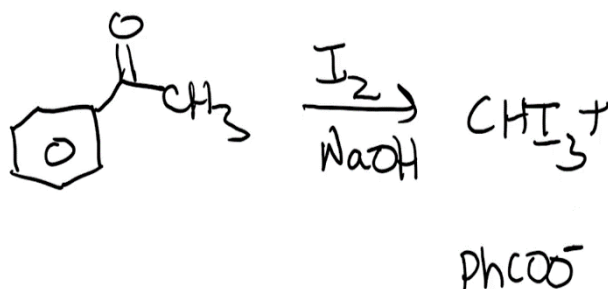
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And so, the product that you end up getting after the collapse of this tetrahedral intermediate, interestingly is actually a carboxylic acid. So, you get CBr_3^- , and once it collapses, you get $\text{CH}_3\text{C}=\text{OOH}$ and CBr_3^- . So now, of course, the pKa difference between these two are substantial, this is about 4 to 5 and this is about 9 for the conjugate acid. So, this is really going to pick up proton very quickly and you will form $\text{CH}_3\text{C}=\text{OO}^- + \text{CHBr}_3$. So, this is the what is known as the bromoform reaction.

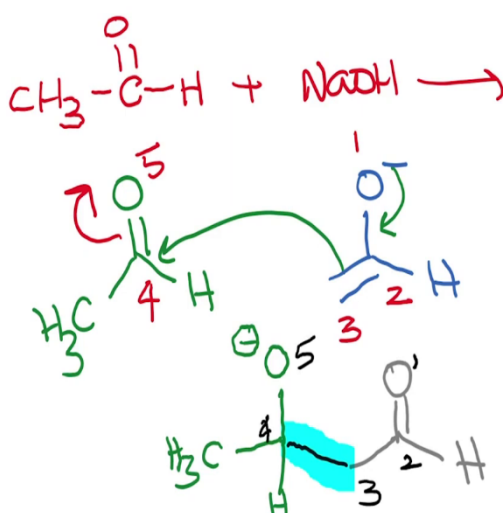
So therefore, the bromination of ketone while it is a very useful reaction, is normally done under acidic conditions, because under basic conditions, you do not have the ability to control the scope of the reaction, we are going to get the formation of products such as bromoform.

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So, as many of you may know that one of the tests for methyl ketones is the Iodoform test, so where you add iodine and NaOH. We will see the formation of a yellow compound which is iodoform, CHI_3 . And the other product is $PhCOO^-$. So, I will let you guys go back and draw the mechanism of this reaction. But this is one of the tests for the presence of a methyl ketone.

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Now, let us move on to the next topic, which is the aldol reaction. So, the aldol reaction very simply is, let us take a standard example of acetaldehyde, CH_3CHO . And when you react this with a base, when you add a base, what you would expect is the formation of the enolate. I

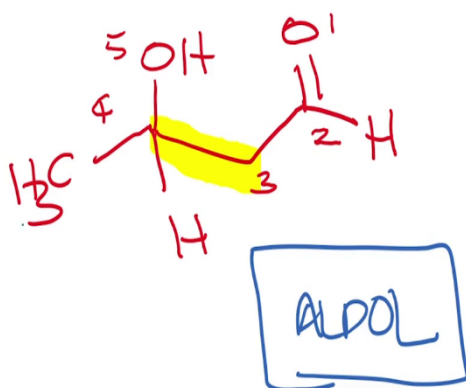
think all of you are quite familiar with this now. So, when you see a ketone and a base, one of the first reactions that you can think about is the formation of the enolate.

And now, this enolate is very interesting because it really does not have anything to react with, other than the compound that was used to generate the enolate, which is acetaldehyde. So, once this is formed, it attacks here, and it kicks this out. So now what I am going to do is, I am going to sort of number these carbons so that it is easy for us to follow this.

So let me start with this oxygen in here. So, let me call this as 1, this is 2, this is 3, this is 4, and this is 5. So, this is the numbering that I am going to follow, so that we understand what is going on. So, now, in this reaction, what has happened is that there is a bond between carbon 3 and carbon 4. So, let us keep the rest of the structure the same. So, you have a C double bond O, and there is a hydrogen. Now, let us keep this the same.

And now there is a new bond that is being formed between carbon 3 and carbon 4. Now, carbon 4 has, now C=O has become C-O⁻, and the hydrogen is here, and the methyl is here. So, this is the new bond that is being formed between carbon 3 and carbon 4. Let me just number this is 1, 2, 3, 4, and 5. So, this reaction, I will just draw it out on the next page, the product of this reaction is called the Aldol.

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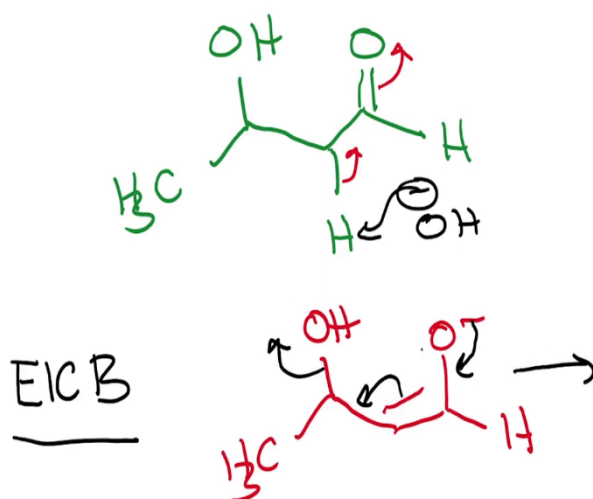
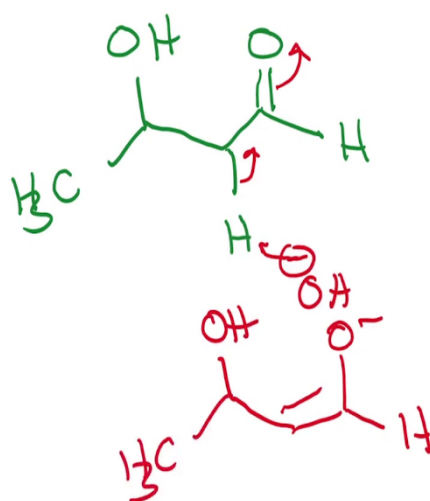


So, there is OH, H, CH₃. And there is an aldehyde over here. So, just to keep the same numbering 1, 2, 3, 4, 5. And this is the new bond that is formed between carbon 3 and carbon

4. So, the product is called aldol. And the reaction that we are going to look at is called the Aldol reaction.

So, this aldol product that is formed, can be isolated. And, we can store it even. But what happens is that normally, when you add a base, you do not add a large amount of base, I mean it is difficult to regulate the amount of base. And so, as you know the second hydrogen here, can also get deprotonated. So let me just draw this out again in the next page.

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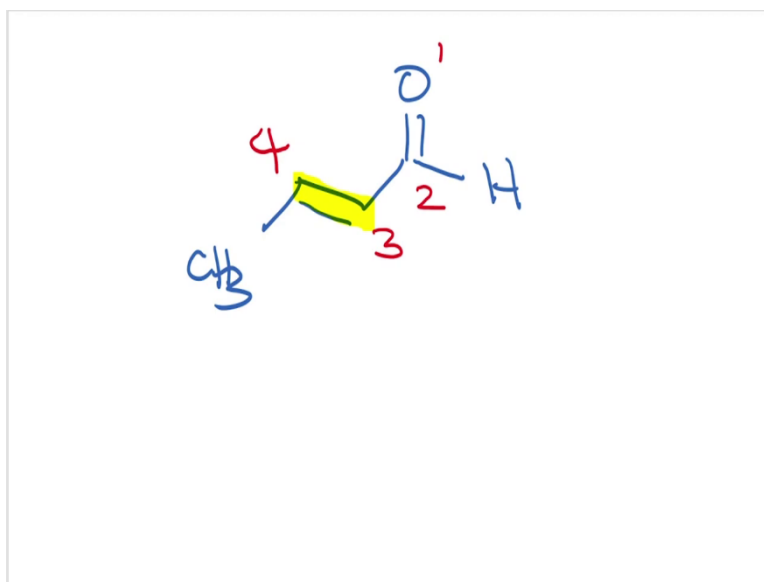


So, that, we can look at the reaction clearly. So, what can happen is that, you have this as the product, but as you know this hydrogen is also enolizable. And if you do not regulate the amount of base that is formed, so you can have hydroxide ion attacking this and you can

generate the enolate. So, there is no ambiguity here. I think this is pretty straightforward for us to propose. So, you get this enolate over here, and it forms OH, and it forms CH₃.

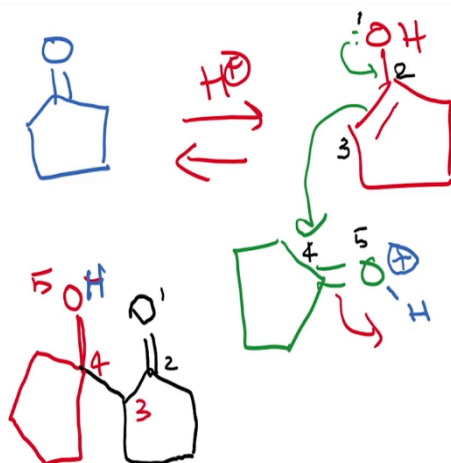
Now, the interesting thing about this kind of molecule is that you can have a, what is known as the E1cB reaction, which is Unimolecular Elimination (E1) conjugate base reaction. I think you have studied this in the previous semester. But in case you have not, do let me know, and I can have a session of this. But the reaction is fairly straightforward, you move this here, and you kick out hydroxide. And the product that you will get is the α , β -unsaturated aldehyde.

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So, let us just recap, this is 1, 2, 3, 4, and the oxygen is gone, so you do not have number 5. But the new bond that is being formed here is this bond between carbon 3 and carbon 4. So, this is very useful for us to know because in terms of understanding synthesis, if you ever want to make this carbon-carbon bond, then you could do it through aldol reaction.

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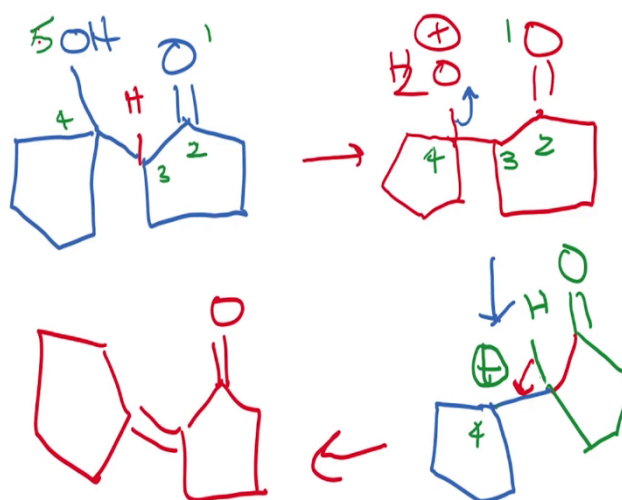


Now, to continue with this Aldol reaction, we will just look quickly at the acid-catalyzed reaction. So, you can have an acid-catalyzed Aldol reaction as well. So, the example that I am going to take is this cyclopentanone, and a cyclopentanone, let us say, in the presence of H^+ can produce the enol. So, I am not drawing out the arrow pushing mechanism to form the enol. But then once you form the enol. You can imagine that this enol can react with the ketone.

So, the ketone that is going to be produced here is this. So, again, let us number this so that it is easy for us to follow it. So, this is 1, this is 2, this carbon is 3, this carbon is 4, and this oxygen is 5. So, I am just going to draw the cyclopentanone the way it is drawn over here. So, with the top cyclopentanone is this, so you have 1, 2, and then there is a bond between carbon 3 and carbon 4. And this is 3, this is 4, and the carbon-oxygen bond is now going to be a single bond, and the cyclopentane ring is going to be the same.

So, this is something that you guys need to get used to now in this lecture. So, you will form this kind of a product, the only thing that I sort of neglected to mention is that it is quite likely that under acidic conditions, this is going to be protonated. So, you will end up with this OH over here and not the O minus. So, this is the Aldol product. And this Aldol product, which I am going to draw again in the next page.

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But the aldol product, can again do the same chemistry that we have looked at in the previous discussion. So, you have OH, then you have another 5-membered ring. So, what can happen is that this is definitely an enolizable hydrogen and this oxygen can also be protonated. So, now, let us first do the protonation of the oxygen and see what might result out of this.

So, you have OH_2^+ and C double bond O when you get this kind of intermediate. Now, you can imagine that there is a loss of water and if there is a loss of water, then you would get a carbocation that is being formed. And so, let me keep the numbering here, so that we do not get confuse, this is 1, 2, 3, 4, and this is 5

So, this is the carbon 4 is where the carbocation is going to be formed. So, let me just write that out. And now you have this is carbon 4, this is carbon 3, and there is your cyclopentanone that remains intact. And as you can suggest, this is quite an acidic hydrogen. And so, if this hydrogen is lost, then you can produce the product which would be your double bond. So, with that, we will close this lecture and we will continue shortly.