Introductory Organic Chemistry II
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Module 03
Lecture 25
Tutorial - 3

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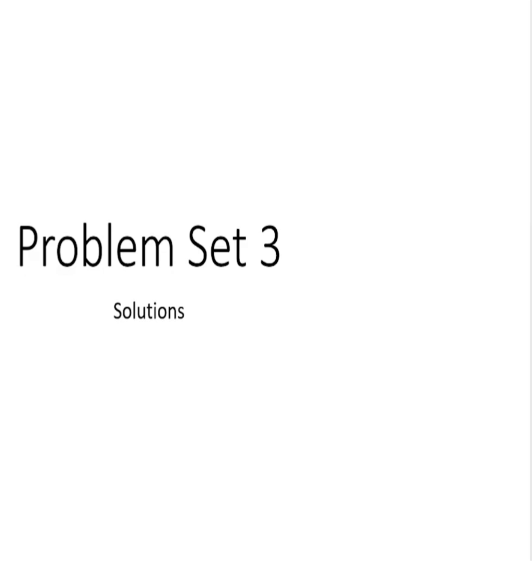
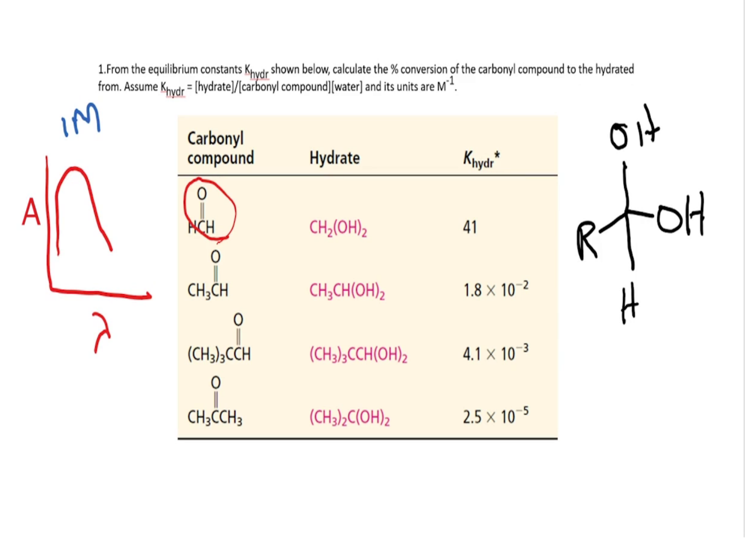


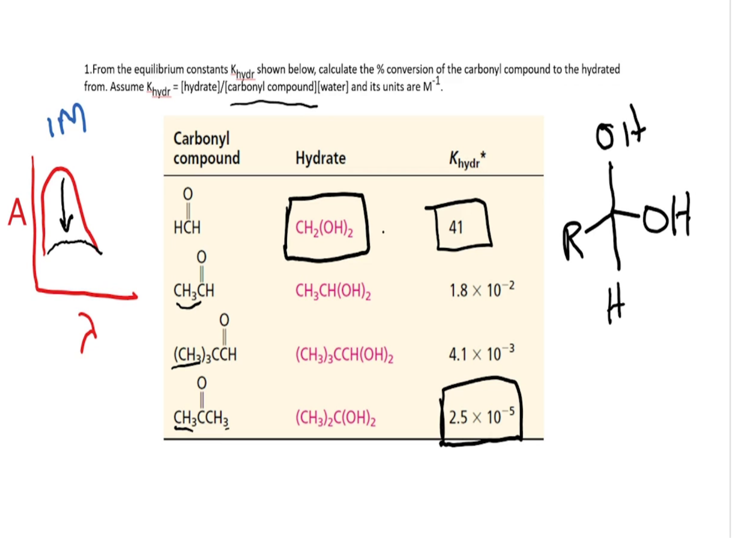
Problem Set 3

Solutions



1.From the equilibrium constants K_{hydr} shown below, calculate the % conversion of the carbonyl compound to the hydrated from. Assume K_{hydr} = [hydrate]/[carbonyl compound][water] and its units are M^{-1}.

Carbonyl compound	Hydrate	K_{hydr}*
$\mathrm{H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H}$	$CH_2(OH)_2$	41
$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H}$	$CH_3CH(OH)_2$	1.8×10^{-2}
$\mathrm{(CH_3)_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH}$	$(CH_3)_3CCH(OH)_2$	4.1×10^{-3}
$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_3}$	$(CH_3)_2C(OH)_2$	2.5×10^{-5}



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$CH_3\overset{\overset{O}{\|}}{C}H$	$CH_3CH(OH)_2$	1.8×10^{-2}
$(CH_3)_3\overset{\overset{O}{\|}}{C}CH$	$(CH_3)_3CCH(OH)_2$	4.1×10^{-3}
$CH_3\overset{\overset{O}{\|}}{C}CH_3$	$(CH_3)_2C(OH)_2$	$\boxed{2.5 \times 10^{-5}}$

So now, let us discuss the problem set 3. So, the first question in problem set 3 is about the formation of hydrate. So, as we know, aldehydes and ketones can form diols and the diols are geminal diols. And so, the structure of these geminal diols are something like this. And so, you could have R and then H, if it is an aldehyde for example. And so, you can measure the equilibrium constant and the way you would do this is aldehydes and ketones have a very nice absorption pretty much in the UV visible region.

And so, monitoring the absorption of the aldehyde you can determine the rate constant. So, the way the experiment is done is that you would take the aldehyde and this is the absorption and this is lambda and so you would measure the absorption of the aldehyde in an organic solvent maybe you can put it in acetonitrile or THF or something and measure the absorption.

And now, let us say we start with 1 molar of the aldehyde and measure the absorption you will get some value, then you make the same 1 molar solution in water. So, when you do this in water, what will happen, as what may happen is that the aldehyde or ketone will convert to the hydrate. So, the hydrate does not have an absorption at this wavelength.

So, therefore, you will find that this absorption goes down when in water. And so, by measuring this difference in absorption, you can estimate how much of aldehyde has formed the diol. And so, you can experimentally determine the concentration of the carbonyl compound which is the what you started with and you can get the carbonyl compound after you added water.

And if you assume that the water concentration is 55 molar or whatever, you can estimate the concentration of water and the concentration of hydrate will be a difference in these two values. So, this is an experimentally determined value. And so, you get an equilibrium constant of 41 with formaldehyde and as the substitution on this aldehyde goes up and if you form a ketone, the value of the equilibrium constant goes down. So, the question here is what is the percentage conversion of the carbonyl compound to the hydrated form.

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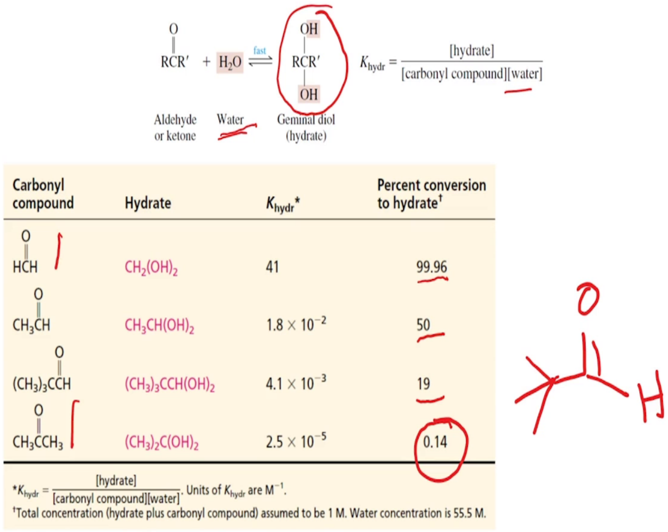

$$R\overset{\overset{O}{\|}}{C}R' + H_2O \overset{\text{fast}}{\rightleftharpoons} R\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}R' \qquad K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$$

Carbonyl compound	Hydrate	K_{hydr}*	Percent conversion to hydrate†
$H\overset{\overset{O}{\|}}{C}H$	$CH_2(OH)_2$	41	99.96
$CH_3\overset{\overset{O}{\|}}{C}H$	$CH_3CH(OH)_2$	1.8×10^{-2}	50
$(CH_3)_3C\overset{\overset{O}{\|}}{C}H$	$(CH_3)_3CCH(OH)_2$	4.1×10^{-3}	19
$CH_3\overset{\overset{O}{\|}}{C}CH_3$	$(CH_3)_2C(OH)_2$	2.5×10^{-5}	0.14

*$K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$. Units of K_{hydr} are M^{-1}.

†Total concentration (hydrate plus carbonyl compound) assumed to be 1 M. Water concentration is 55.5 M.

So, I have worked out the answer the way you would do this is you would take the aldehyde concentration and water concentration, and then you, like I told you this is an experimentally measurable value and then you divide this and you get the $K_{hydration}$. So, from this K_{hydr} if you assume that the concentration of water is 55.5 molar, then you can find out the percentage of conversion to hydrate.

So, the value for formaldehyde if you work this out is 99.96. The value for acetaldehyde is 50, this is percent and for tertiary butyl aldehyde which is shown here the value is 19. And lastly, for acetone it is 0.14. So when moving from formaldehyde to acetone, you have completely reverse the percentage conversion to the hydrate.

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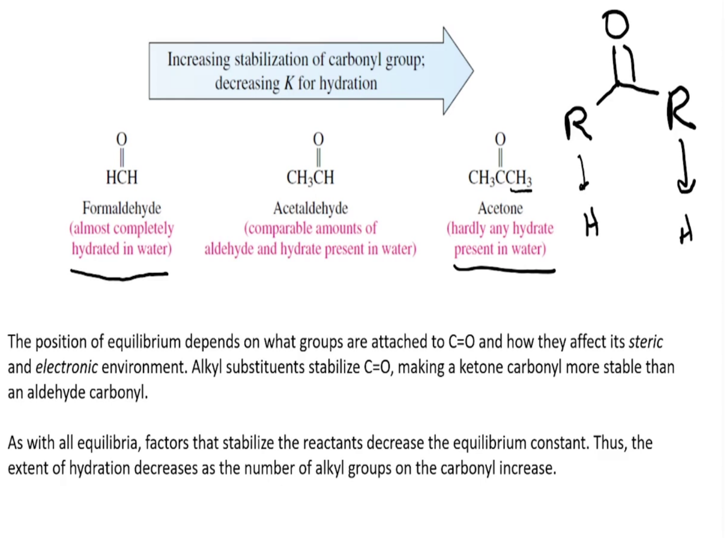

Increasing stabilization of carbonyl group; decreasing K for hydration

$H\overset{O}{\overset{\|}{C}}H$

Formaldehyde

(almost completely hydrated in water)

$CH_3\overset{O}{\overset{\|}{C}}H$

Acetaldehyde

(comparable amounts of aldehyde and hydrate present in water)

$CH_3\overset{O}{\overset{\|}{C}}CH_3$

Acetone

(hardly any hydrate present in water)

The position of equilibrium depends on what groups are attached to C=O and how they affect its *steric* and *electronic* environment. Alkyl substituents stabilize C=O, making a ketone carbonyl more stable than an aldehyde carbonyl.

As with all equilibria, factors that stabilize the reactants decrease the equilibrium constant. Thus, the extent of hydration decreases as the number of alkyl groups on the carbonyl increase.

So, one of the ways in which we want to understand this is that as you know, it is an equilibrium between the carbonyl and the hydrate. And so, the position of the equilibrium depends on what groups are attached to C=O. So, which is obvious in the case of formaldehyde, acetaldehyde, and acetone. So, formaldehyde as we found out, it does not have any aldehyde in solution in water, whereas, acetone hardly has any hydrate present in water.

So, therefore, like with many other effects, they depend on both sterics and electronics. So, the alkyl substituent, as we have, as you might have studied earlier, stabilizes this carbonyl compound, and therefore, the position of the equilibrium can be altered by adding more alkyl groups on this position. So, if you have R versus H, once you replace the H with an R, then the ketone becomes more stable.

So, therefore, though the reactant of this molecule of this equilibrium, which is the carbonyl compound gets more stable, and therefore, the population of the ketone increases, and therefore, the equilibrium constant is going to change. So, there is an important example of how you can use experimental data to make interpretations about the stability of various participants in an equilibrium.

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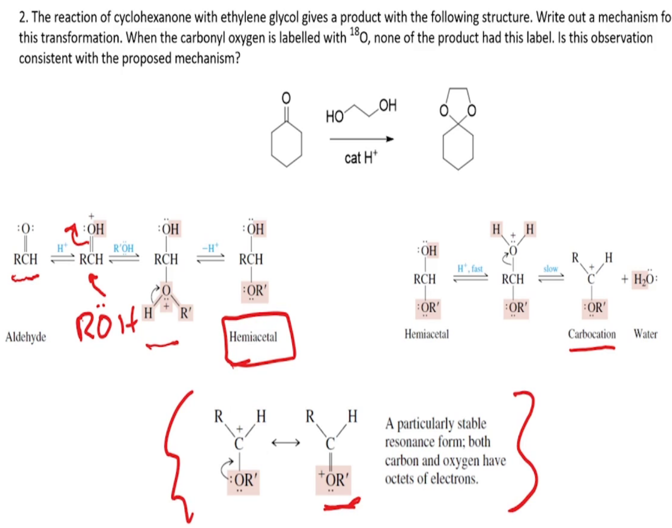

2. The reaction of cyclohexanone with ethylene glycol gives a product with the following structure. Write out a mechanism for this transformation. When the carbonyl oxygen is labelled with ^{18}O, none of the product had this label. Is this observation consistent with the proposed mechanism?

A particularly stable resonance form; both carbon and oxygen have octets of electrons.

Now, let us move on to the next question, which is to propose a mechanism of the reaction of cyclohexanone with ethylene glycol, and it gives you this cyclic acetal as the product. And there is another piece of information that is given, which is that the carbonyl oxygen, if it is labelled, then none of the product had this label in the what has been shown. So, now, how does this mechanism go forward?

So, in general a mechanism of acetal formation goes in the following way, the aldehyde gets protonated and after the aldehyde gets protonated the alcohol which is R-OH, can attack in this, and then you push this electrons back here and you form this kind of an intermediate. If this loses a proton, then you form a Hemiacetal. So, the formation of Hemiacetal is pretty straightforward. And now, the Hemiacetal can further undergo protonation.

So, one of the ways in which it can undergo protonation is to give you back this kind of intermediate, but it can also undergo protonation at the OH and that gives you this protonated water and protonated water can leave and you can generate a carbocation. So, now this carbocation is particularly interesting because it can form a resonance form, such as shown here, which is extremely stable because both the carbon and oxygen have octet of electrons. So, therefore, this might be one of the reasons why this kind of an intermediate can be produced.

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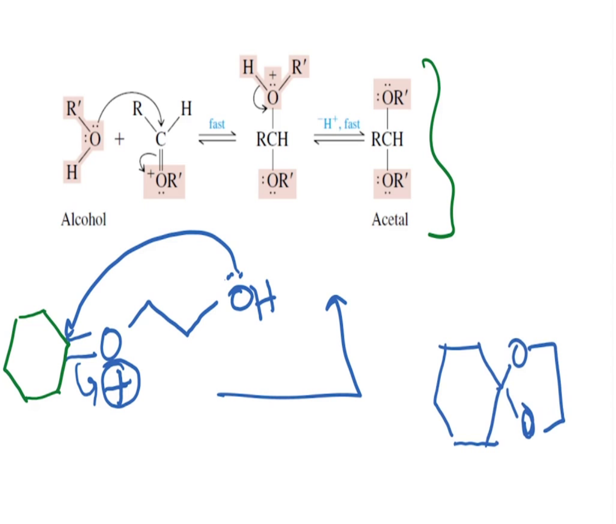

Now, if you attack on this intermediate, if another alcohol molecule attacks, then you are going to produce this kind of an intermediate which can lose a proton to give you the acetal. So, with cyclohexanone, if we draw the last step, so you get C_6H_{10} O^+ CH_2 CH_2 OH.

So, this is going to be your intermediate that is formed with cyclohexanone and ethylene glycol, the remaining steps are the same. So this attacks, it is an intramolecular attack and it gives you the product which is this. Now, how do we account for the labelled result.

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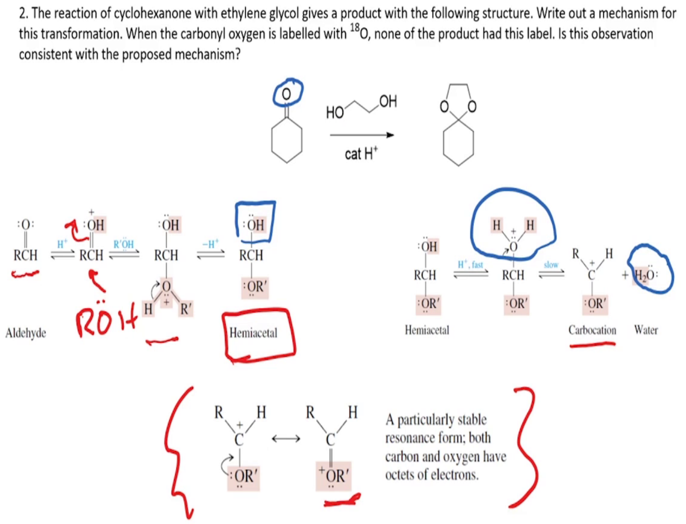

2. The reaction of cyclohexanone with ethylene glycol gives a product with the following structure. Write out a mechanism for this transformation. When the carbonyl oxygen is labelled with ^{18}O, none of the product had this label. Is this observation consistent with the proposed mechanism?

A particularly stable resonance form; both carbon and oxygen have octets of electrons.

So, if you notice, when we start with this with C=O being labelled, if you start with this oxygen which is being labelled, then you will find that particular oxygen is in this step here, and it is lost as water. And once the carbocation is formed, there is no exchange that happens, which will give you the intermediate that you look for, which is even if water exchanges, it is going to go back and it is still going to continue to be labelled.

And the water that is being kicked out is going to be labelled. What it tells you is that there is no exchange of oxygen between this ethylene glycol oxygen and this carbonyl oxygen. And I would say that yes, it is consistent with the proposed mechanism because in nowhere in the mechanism we propose that the ethylene glycol oxygen undergoes a exchange with the water.

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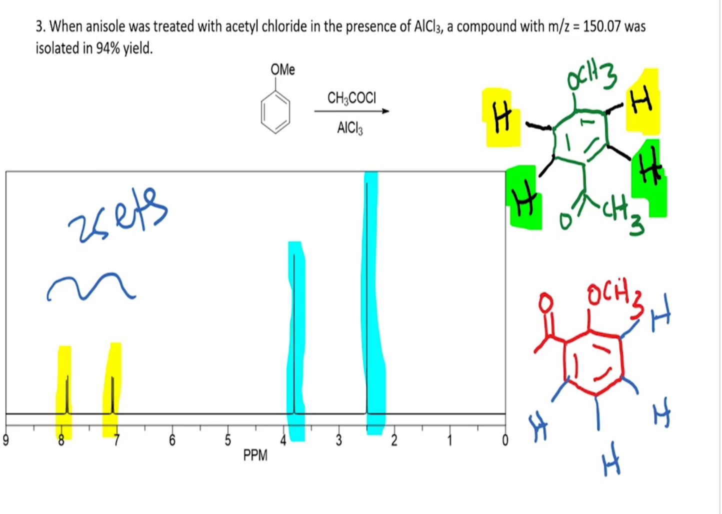

3. When anisole was treated with acetyl chloride in the presence of $AlCl_3$, a compound with m/z = 150.07 was isolated in 94% yield.

Let us move on to the next question. So, here, this is something that we have already discussed in class, I am going to go through this quickly. So, here, I know I am giving you a little bit of flavour of NMR. I am going to have a separate lecture on NMR. So, some of you can refer to that, but we do not need too many concepts of NMR here, we just need to understand that the number of peaks and so on, which is fairly reasonable to propose, given the information that we have.

So, if I look at this NMR spectrum, we have two peaks in the aromatic region and all the other peaks are in the aliphatic region. So, we are mainly interested in the peaks at the aromatic region. And keep in mind that the yield of the compound is 94 percent. So, if I look at the product that can be formed, the product has this hydrogen here, and this hydrogen here, which is two sets of hydrogens. Because these two hydrogens are identical. That is, I am going to colour it in yellow.

So, these two are the same and these two are the same if you look at symmetry-wise. So, therefore, you would see two sets of signals, which is what you see here in this NMR spectrum. So, therefore, the major product that is formed is the para compound. Now, in order to cross check this, let me draw out the peaks, I mean the hydrogens of the ortho-derivative, and you will find that there are going to be four sets of signals that would be produced if this was the major product.

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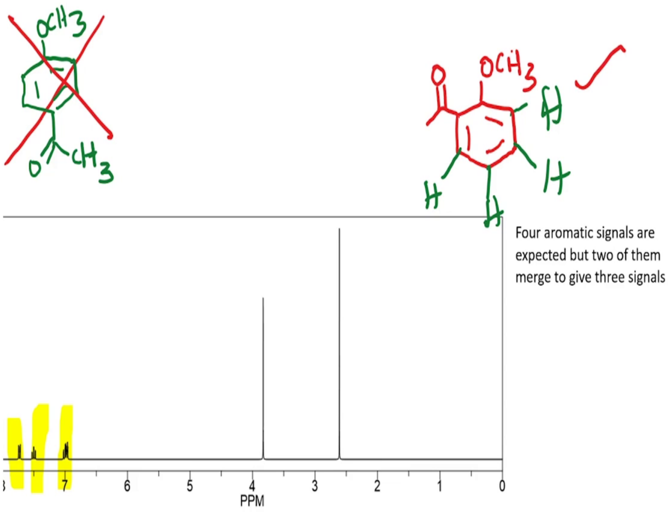

Four aromatic signals are expected but two of them merge to give three signals

And now, if you move on to the next slide, you find that you would expect that you will have four sets of signals that are going to be formed. But in fact, when you look at the NMR spectrum, if you stare at it hard enough, you will see only three sets of signals. And so, the reason for this is that two of the signals are merging to produce one signal.

And therefore, you see, only three distinct signals in the aromatic region, but nevertheless, what we can infer is even if you did not know this, what you can infer that this NMR spectrum does not correspond to this product, it would either correspond to this product or another derivative. But since the mass of this product is the same, it is quite likely that you can suggest that it would be the ortho compound.

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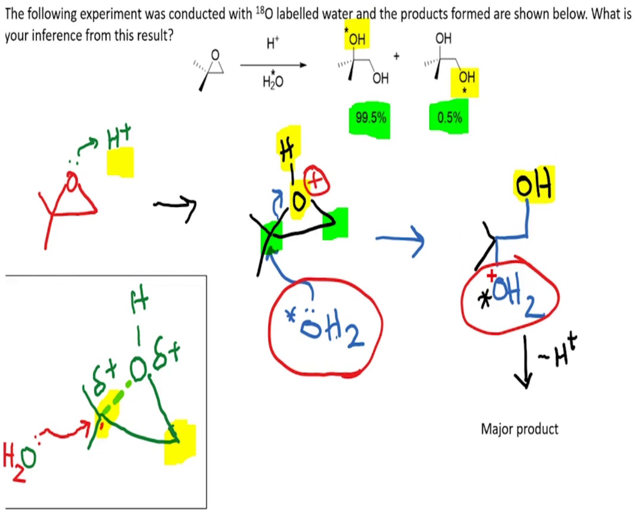

The following experiment was conducted with ^{18}O labelled water and the products formed are shown below. What is your inference from this result?

Now, let us move on to the next question. So, here, we have used ^{18}O labelled water. And we have attacked the epoxide with this molecule in the presence of H^+. So, in the presence of H^+, we could expect that you know this epoxide ring can be protonated. And you form this protonated epoxide. And now, this becomes a very, very good leaving group, because it is a neutral hydroxyl group that is leaving, and, the center, that is over here can get activated, or can be site for attack, or it can also attack at the other position.

Now, given the result that we have, that is there is 99.5 percent of this and 0.5 percent of this, it is highly likely that the attack happens the way we have shown it, which is given here. So, it gives you this product with the oxygen label on it, which gives you the major product. Now, based on this proposal, what we can suggest is that, when water attacks, this di-substituted carbon, it almost seems like the bond that is between carbon and oxygen has already started breaking even before the attack of water, because that would produce a stronger positive charge over here and that makes the center more reactive.

So, this is something that we can infer that the carbon-oxygen bond after protonation has already started breaking. And therefore, between these two centers, that is between this center and this center, clearly the more substituted carbon is better suited, better able to accommodate the positive charge. And so, therefore, this bond breaks in preference to the other one. Now, looking at the labelling data, we can see that the label ends up on this carbon, that is water label ends up on this carbon, or it ends up on this carbon.

So, therefore, we do not find a situation where the label has gone to both carbons. So, what it also means is that there is no exchange going on between the water oxygen, and the epoxide oxygen.

So, this also could mean that this attack here may be an irreversible step. That is once you form this kind of an intermediate, this does not close back and kick out water, because if that happens, then what can happen is that this oxygen can also attack here and kick out water, and you will see the label ending up on both the carbons that is the both of the carbons will have labelled oxygens. So, that does not seem to happen.

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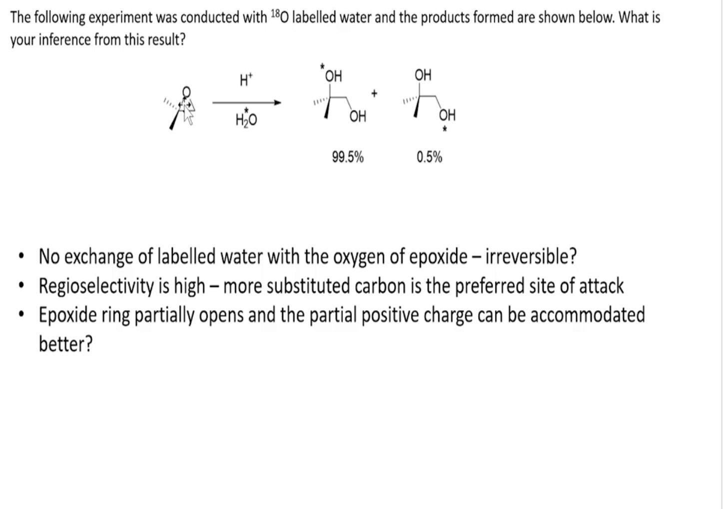

The following experiment was conducted with ^{18}O labelled water and the products formed are shown below. What is your inference from this result?

- No exchange of labelled water with the oxygen of epoxide – irreversible?
- Regioselectivity is high – more substituted carbon is the preferred site of attack
- Epoxide ring partially opens and the partial positive charge can be accommodated better?

So, based on this inference, what we can say is that it seems like there is no exchange of labelled water with oxygen of the epoxide. So, maybe once the epoxide ring is opened, it is an irreversible process. The second inference is that the regioselectivity of this process is quite high. And the more substituted carbon is the preferred site of attack.

What the way we might reason this out is that the epoxide ring maybe partially opens up and there is a partial positive charge on this epoxide ring after protonation. And that positive charge is better accommodated in the more substituted carbon and therefore that becomes the site of attack of water.

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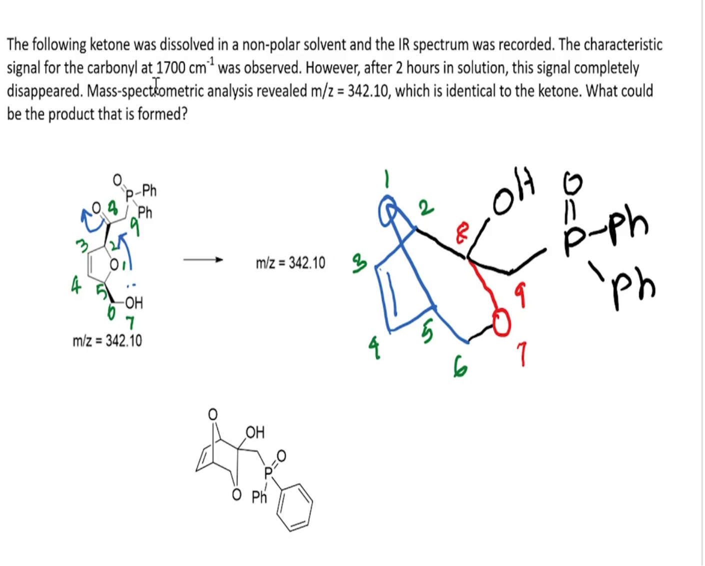

The following ketone was dissolved in a non-polar solvent and the IR spectrum was recorded. The characteristic signal for the carbonyl at 1700 cm^{-1} was observed. However, after 2 hours in solution, this signal completely disappeared. Mass-spectrometric analysis revealed m/z = 342.10, which is identical to the ketone. What could be the product that is formed?

Now let us move on to the next question. So, here, I have labelled these carbons as 1 2 3 4 5 6 7 8. And so, this is an intramolecular reaction, where you get this product, which is 342.10, which is the same mass as the starting material. Now, what the clue that we have been given is that the peak at 1700 cm^{-1} has disappeared over two hours.

And so, therefore, you do not have any ketone in the product. So, the product that is formed is likely the attack of this alcohol on this carbonyl to give you a Hemiacetal as shown here. And my handwriting is quite terrible, so I have drawn this out using ChemDraw. So, this might be a good example of how compounds can give you different derivatives, like Hemiacetal, and so on, based on the reaction conditions. So, notice that under these conditions, the Hemiacetal does not give you back the starting material, because then you would see that the peak at 1700 would be restored.

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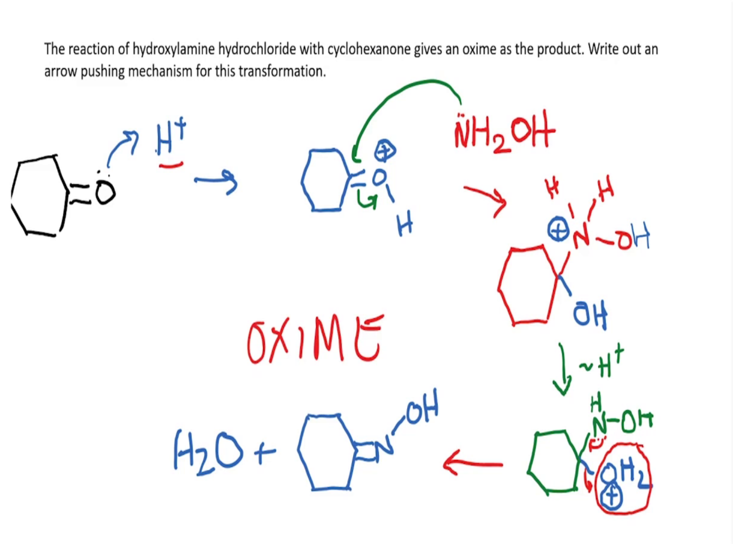
The reaction of hydroxylamine hydrochloride with cyclohexanone gives an oxime as the product. Write out an arrow pushing mechanism for this transformation.

Now, let us move on to the next question. So, this is a reaction of cyclohexanone with hydroxylamine hydrochloride. So, hydroxylamine hydrochloride has a full HCl molecule on it. So, that is what I am representing here as H^+. So, the carbonyl compound can get protonated to give you this intermediate. And now, this carbonyl is quite suitable for attack, and hydroxylamine can attack, giving you this kind of an intermediate.

And now a proton transfer can occur to give you the protonated water over here, which can then be kicked out by the formation of an Oxime. So, you can keep this mechanism in mind because this is something that we will come back to during rearrangements.

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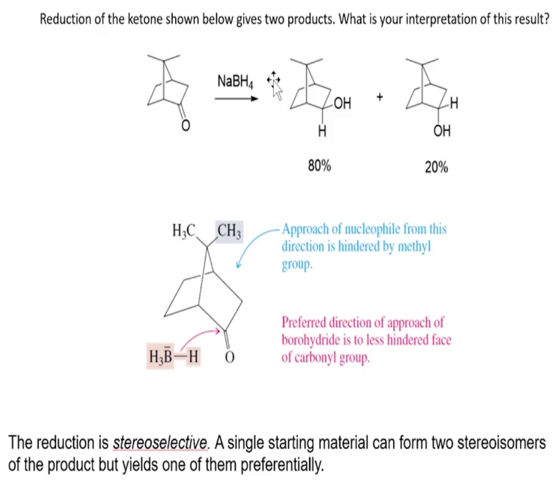
Reduction of the ketone shown below gives two products. What is your interpretation of this result?

Approach of nucleophile from this direction is hindered by methyl group.

Preferred direction of approach of borohydride is to less hindered face of carbonyl group.

The reduction is *stereoselective*. A single starting material can form two stereoisomers of the product but yields one of them preferentially.

Now, the next question is about reduction with sodium borohydride. And so, you get a mixture of 80 to 20. So, this is consistent with what we have observed before. That is, when you have two methyl groups on the norbornane, you end up with the top face being hindered by the presence of the methyl group. And so, the preferred direction of attack is from the bottom phase.

So, keep in mind that if you do not have the methyl group, then the attack from the top phase is preferred. So, nevertheless, you get a mixture of 80 to 20 in this case, and this kind of reaction is a stereoselective reaction because a single starting material can form two stereoisomers of the product, but it forms one of them preferentially.

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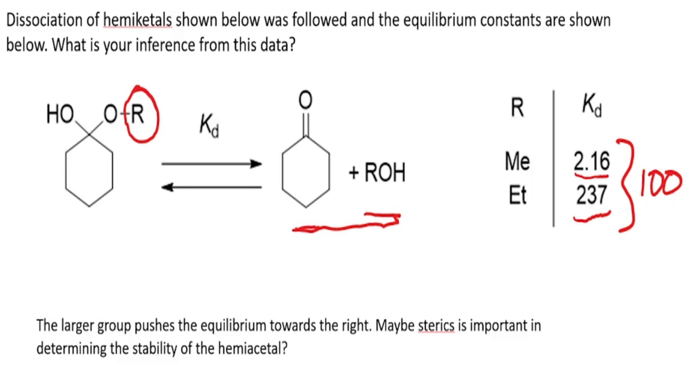
Dissociation of hemiketals shown below was followed and the equilibrium constants are shown below. What is your inference from this data?

R	K_d
Me	2.16
Et	237

The larger group pushes the equilibrium towards the right. Maybe sterics is important in determining the stability of the hemiacetal?

Now, let us move on to the next question. So, here is an example of a Hemiketal. So, this is a ketal derived from cyclohexanone. And so, this Hemiketal is in equilibrium with the ketone as well as the alcohol. So, if I measure the equilibrium constant, then the value that I get for the methyl compound is 2.16. Whereas for the ethanol derivative, I am getting 237. So, this difference is about 100-fold approximately.

So, what the inference that we can take from this experiment, although there are only two data points is that the larger the alkyl the more the equilibrium is pushed towards the right. So, keep in mind that this is K_d. So, that means that this is the equilibrium constant for dissociation. Now, this is something that we can infer from this data.

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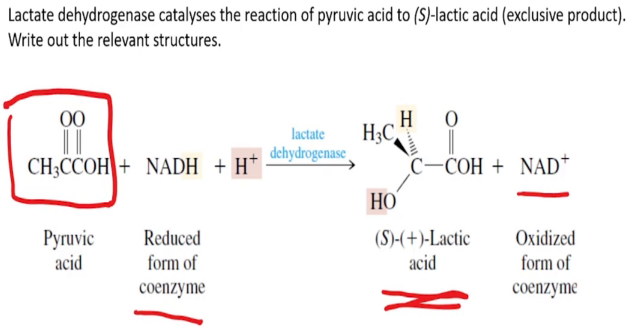

Lactate dehydrogenase catalyses the reaction of pyruvic acid to (*S*)-lactic acid (exclusive product). Write out the relevant structures.

Now, in the next question is about pyruvic acid forming lactic acid. So, the question here is that write out the relevant structures. So, just to give you some perspective here, lactate dehydrogenase takes pyruvic acid and converts it to lactic acid. And it uses this coenzyme, which is NADH, which is nicotinamide adenine dinucleotide, which is a source of hydride. And at the end of the reaction, you form NAD$^+$, which is the oxidized form of the coenzyme. And here is the structure of this lactic acid for your reference.

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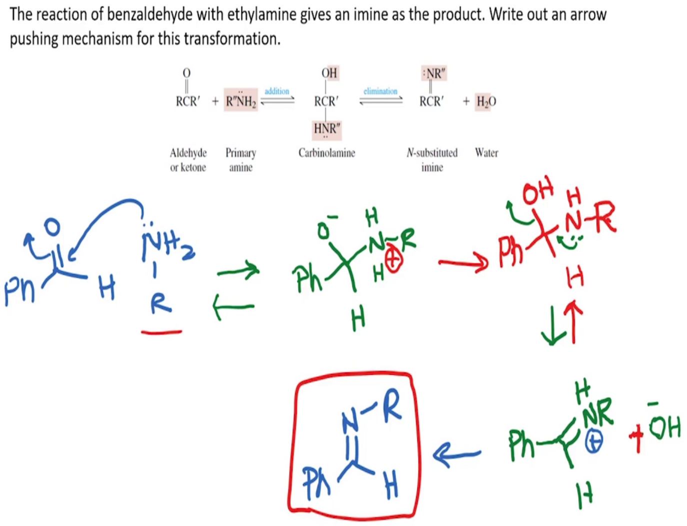

The reaction of benzaldehyde with ethylamine gives an imine as the product. Write out an arrow pushing mechanism for this transformation.

Now, let us move on to the last question, which deals with the reaction of benzaldehyde and ethylamine. So, the general mechanism is shown here. So if you take an aldehyde and react it with a primary amine, then what happens is that if it is done under neutral conditions, then the amine attacks and it gives you this alkoxide. So you can argue that this alkoxide is extremely unstable and it will not be formed. So, which is fairly reasonable. So, which is why I put an equilibrium arrow here. And so, but if it is formed, it can pick up a proton from this RNH_2^+ and then give you this alcohol.

And nitrogen lone pair can come in and kick out hydroxide. Again, hydroxide is a pretty bad leaving group. And so, you could argue that hydroxide will not be formed, which is also again, reasonable. And so, this is again, going to be your reversible reaction. So, hydroxide ion is going to come and attack and give you back this intermediate.

But eventually, because you have a larger concentration of the amine, it is going to form the imine. This is again something that we will take up again in the latter part of the course. And we will visit amine and enamine chemistry later.