Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Synthesis

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Module No # 03
Lecture No # 13
Future Aspects of Oxidations using Fetizon's Reagent: Mechanism and Stereochemistry

Hello everyone welcome to today's lecture in which we will have a little recap of last lecture in brief and then we will proceed with the remaining path of the oxidation what we did last time was introduce Prevost reaction and it is modification.

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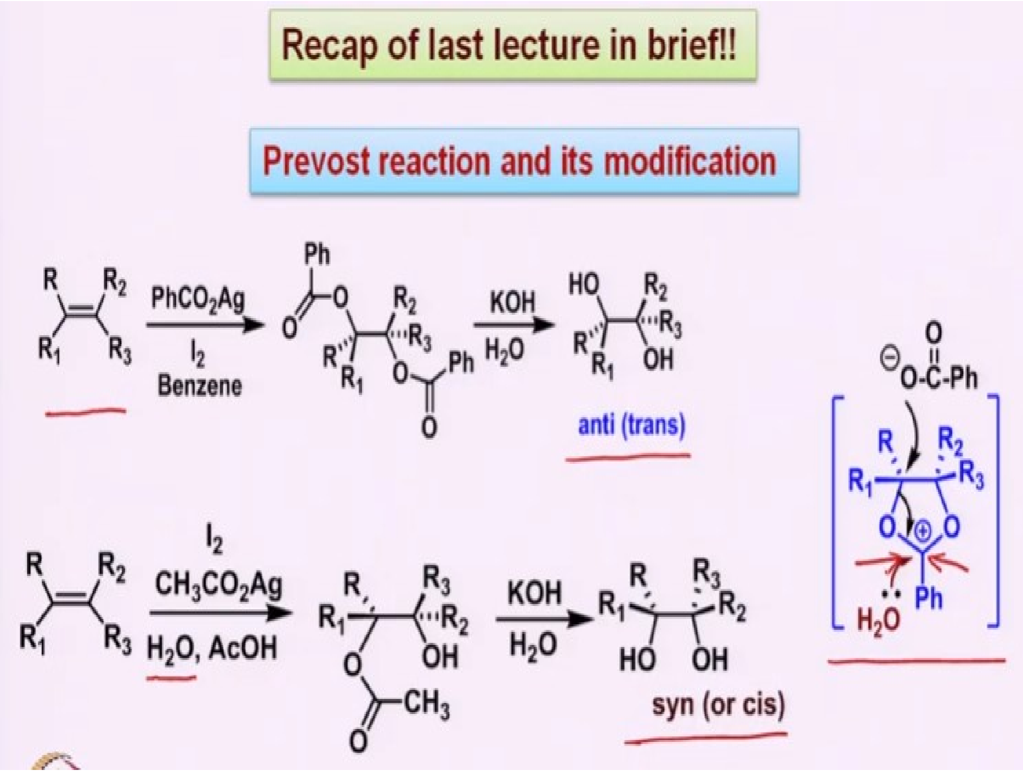

Recap of last lecture in brief!!

Prevost reaction and its modification

I have shown on this slide that we start with a olefin like this and in the presence of silver acetate and iodine we get eventually a trans or an anti-diol. So if one wants to get cis or syn diol like this the Woodward modification in which water is added leads to Syn or cis diol. And the main important intermediate was this intermediate here which is a cyclic intermediate having a positive charge on the middle carbon here.

And if the trans diol is to be obtained where there is no water used the nucleophile that is benzoate anion attacks from the top and in the case of syn diol to be formed water attacks on to this particular carbon atom here. And this is the main difference that we had seen last time and we saw that the attack of the iodine takes place from the side where there is less steric hindrance.

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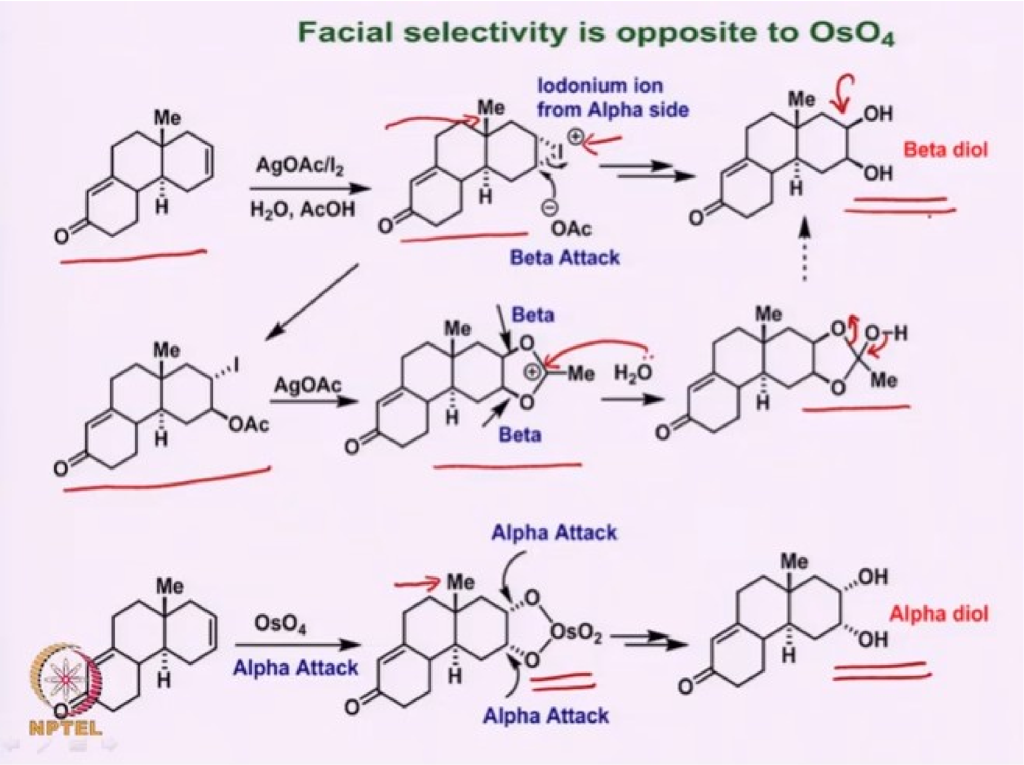
Facial selectivity is opposite to OsO_4

For example when we took a case something like this here the iodonium ion that is formed like this was from the alpha side. And this iodonium ion then gets attacked by the acetate ion from the beta side and forming intermediate of this type. This is something that I had not elaborated last time so I want to show you how a cis diol is obtained which is from the beta side. So if the iodonium ion is formed from the alpha side as shown here and that is because this group methyl group is beta oriented.

Then you get the attack of the acetate from the beta side and alpha iodo and beta acetoxy this intermediate is obtained which in the presence of silver acetate. Now forms and intermediate of this kind in which both the carbon oxygen bonds are beta oriented which then water attacks on to this particular centre forming this intermediate which then breaks off and eventually gives upon hydrolysis beta diol.

So the beta diol is has come because of 2 reasons one is that iodine attacks from the alpha side and the water presence is responsible for the beta diol formation which is cis diol. On the other hand when osmium tetroxide is used as I discussed last time since methyl group is beta oriented the osmium tetroxide attacks from the alpha side and that gives alpha diol and that is also cis this is also cis but then then the stereochemistry is different Now this was something that we discussed it last time.

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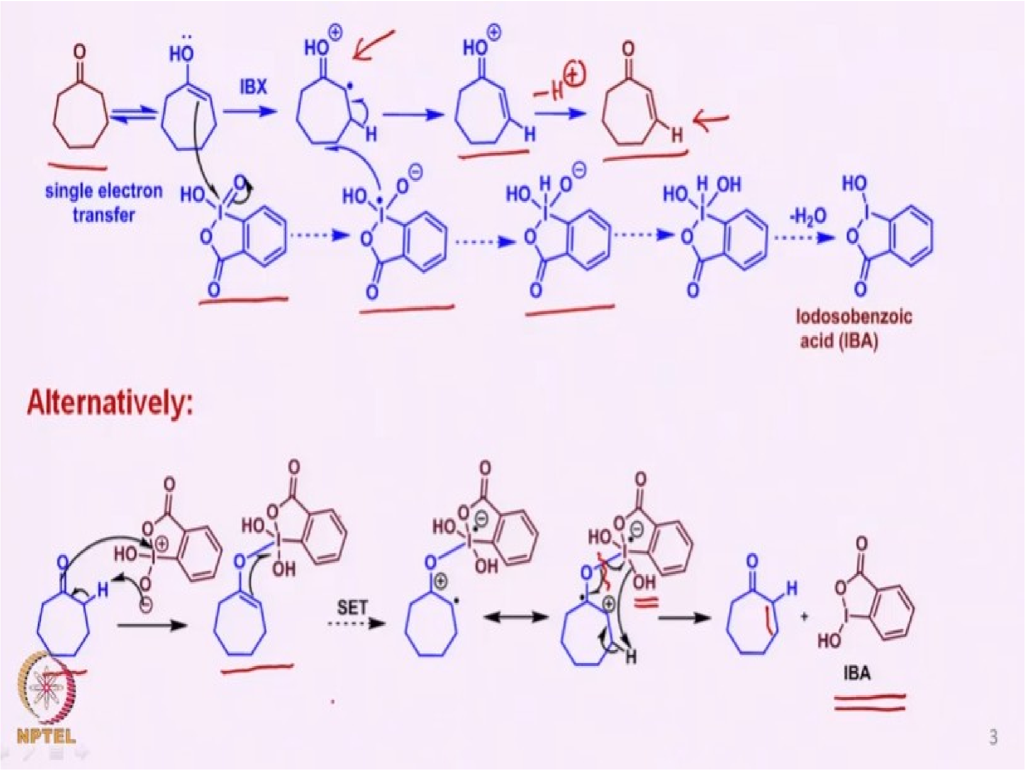

Now before I start on the silver carbonate celite oxidation I also want to briefly mention about something that we discussed last time that is conversion of a ketone into an enone using IBX. So this is the IBX that we used and what I showed that if the ketone is in the equilibrium with the enol there is a single electron transfer to the IBX which leads to the formation of a radical anion here and a radical cation here.

Now this radical cation then reacts by transferring a hydrogen radical to this radical anion which forms this intermediate and we get an oxonium ion here which looses the protons here to form the enone. Now like this and of course the reagent eventually forms the iodoso benzoic acid. Now this proximity of the transfer of an electron to the IBX can also all be alternatively explained that you have the ketone like this, where the IBX the negative charge on the oxygen takes up the proton from here.

And then this oxygen attacks on to the iodine forming this intermediate now this brings the double bond in close proximity with the reagent which is now having a bond between oxygen and iodine. Now you have a single electron transfer from here double bond to this iodine forming a radical cation and radical anion essentially joined to each other and then you have the loss of proton from here by the OH- and breaking of this particular oxygen iodine bond in a homolytic fashion to form there should be double bond here.

So and then of course the loss of iodoso benzoic acid so, this was an alternative way of explaining the same formation or conversion of ketone to enone.

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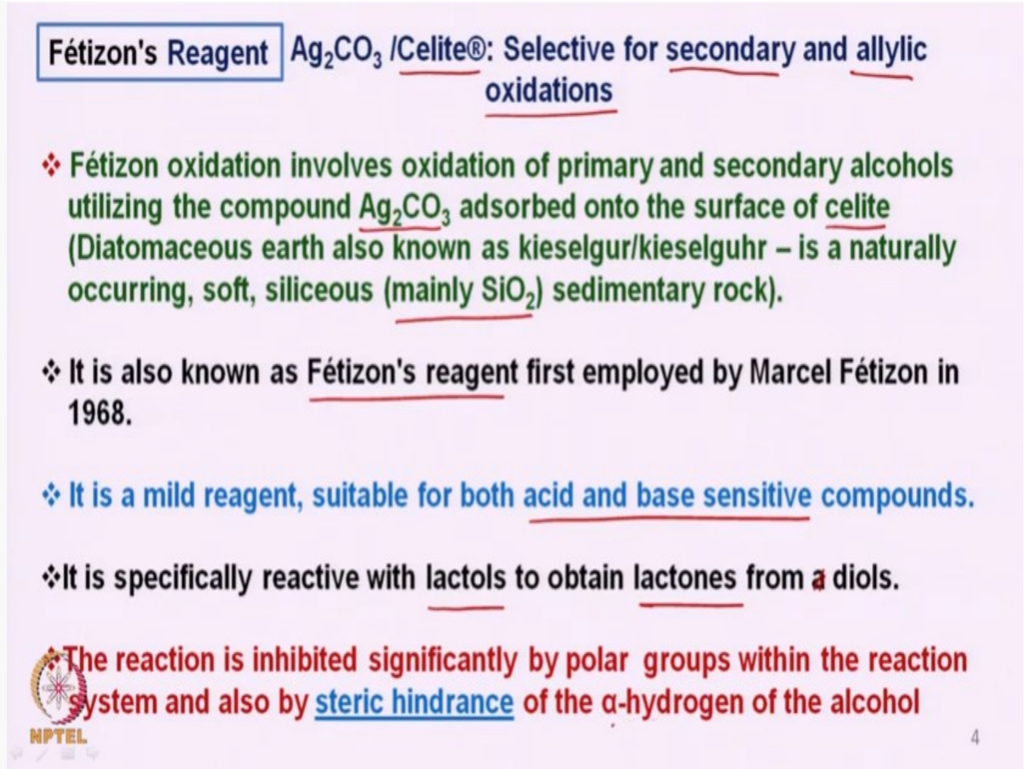

Fétizon's Reagent Ag_2CO_3 /Celite®: Selective for secondary and allylic oxidations

- Fétizon oxidation involves oxidation of primary and secondary alcohols utilizing the compound Ag_2CO_3 adsorbed onto the surface of celite (Diatomaceous earth also known as kieselgur/kieselguhr – is a naturally occurring, soft, siliceous (mainly SiO_2) sedimentary rock).
- It is also known as Fétizon's reagent first employed by Marcel Fétizon in 1968.
- It is a mild reagent, suitable for both acid and base sensitive compounds.
- It is specifically reactive with lactols to obtain lactones from a diols.
- The reaction is inhibited significantly by polar groups within the reaction system and also by steric hindrance of the α-hydrogen of the alcohol

Now we go to the present Fetizon’s reagent which is silver carbonate celite reagent system which we discussed we introduced last time. It is essentially a useful for the selective oxidation of secondary and allylic alcohols. Now silver carbonate is adsorbed on the Celite this R means this. Fetizon’s oxidation involves oxidation of primary and secondary alcohols utilizing the compound silver carbonate. Which; is adsorbed on to the surface of celite which I discussed last time which is nothing but a mainly a silica gel sedimentary rock.

And it was introduced by Fetizon’s and that is reason why it is called as Fetizon’s reagent it is a mild reagent suitable for both acids and based sensitive compounds. Especially it is useful for the conversion of lactols to lactones which I will discuss in a while from now from diols The reaction is inhibited significantly by polar groups within the reaction system and also the by steric hindrance of the alpha hydrogen of the alcohol.

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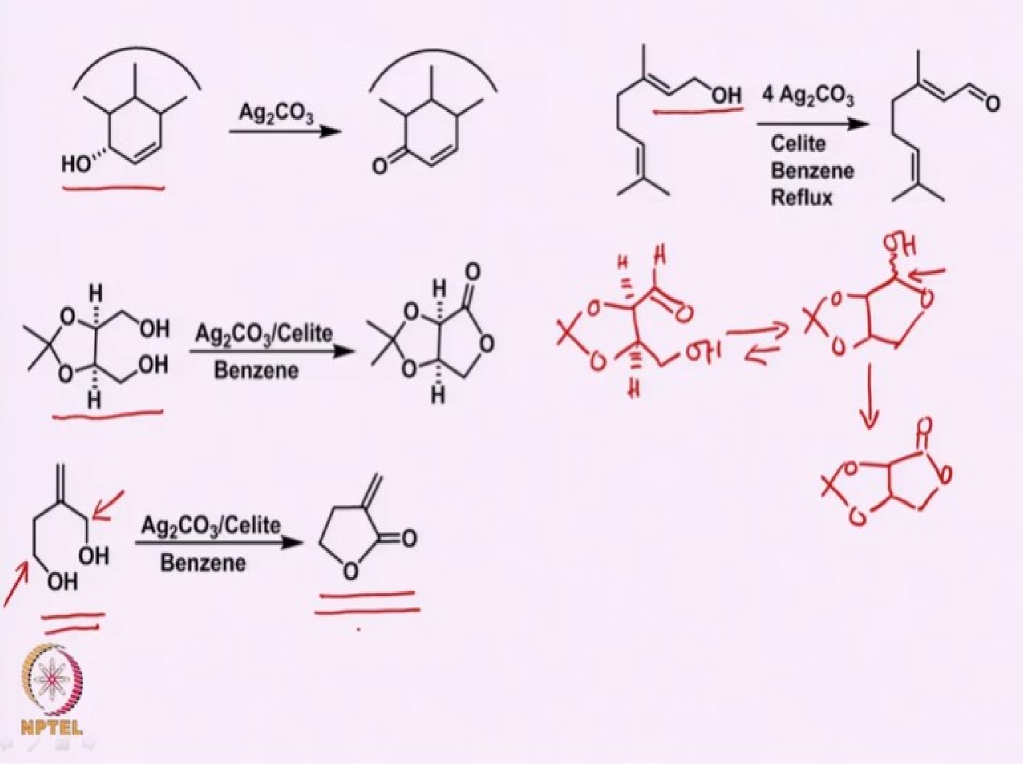

I gave this example last time that if we have this allylic alcohol of this type which is a secondary allylic alcohol or primary allylic alcohol or even normal primary alcohols. It is just that the reagent reacts faster with allylic or benzylic alcohols than with normal saturated alcohols and but then still the reaction does takes place. For example here in this case when symmetrical diol is taken and oxidation is carried out the first oxidation gives the aldehyde, which is like this and then there is equilibrium between the hydroxyl aldehyde and the lactol of this type.

Now this is a secondary alcohol and this gets oxidized to form the lactone now here we have another diol. But then the difference in this diol and the above diol is that we have one allylic alcohol and one non-allylic alcohol. So as I mentioned earlier the allylic alcohols are oxidized in preference to non-allylic alcohols. Therefore in this case there are 2 possibilities either this alcohols such the non-allyic primary alcohol gets oxidized or this allelic alcohol which is also primary can get oxidized.

But then there is the preference for the oxidation of the allylic alcohol and eventually what we get is this particular lactone which is gamma butyro lactone.

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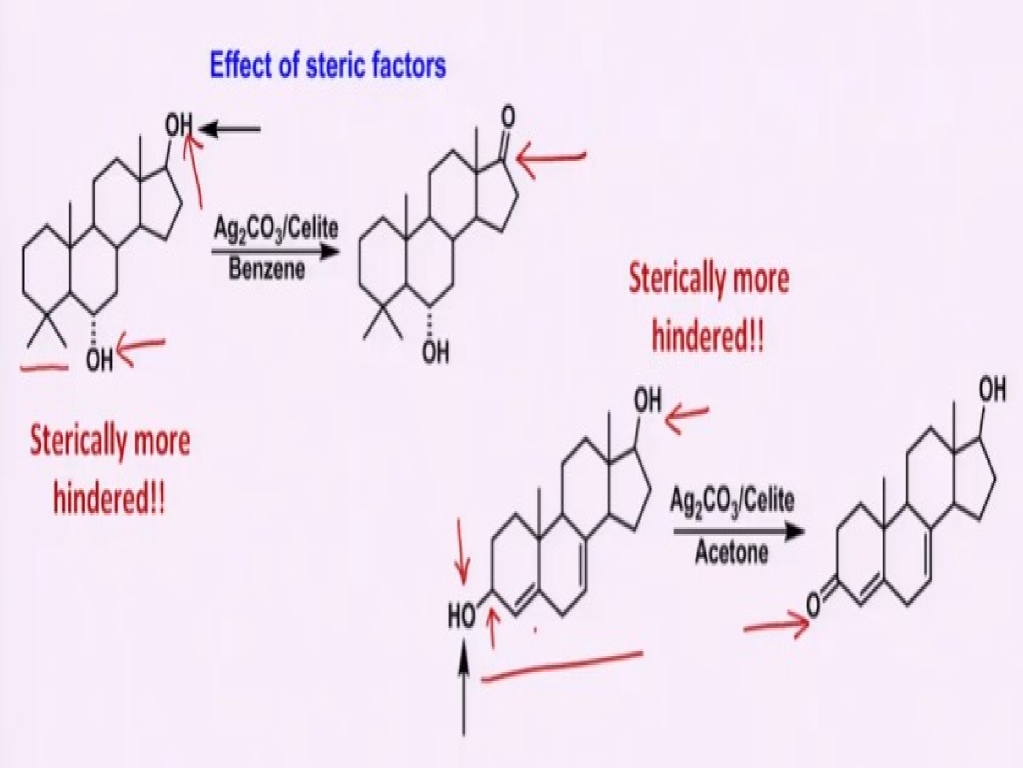

Effect of steric factors

Sterically more hindered!!

Sterically more hindered!!

Now effects of there are steric factors on this reaction for example if one takes a steroid molecule of this kind this particular hydroxy group versus this hydroxy group both are simple secondary hydroxy groups. And both can get oxidized however this particular hydroxy group is close to this germinal dimethyl group and also it is in the midst of the ring. Therefore it is sterically more hindered and there is a preferential oxidation of the hydroxy group which is on the top leading to the formation of the ketone on this particular position.

On the other hand if one takes the steroid molecule like this which has 2 different hydroxy groups one is this hydroxy groups here the other is this hydroxy group. Now relatively this hydroxy group here is less sterically hindered compared to this hydroxy group because this is away from the body of the system ring system whereas this is very close to the methyl group here.

Therefore there is a preferential oxidation of the hydroxy group which is here at this position and also it is allylic hydroxy group. So there is very clear steric effect on the oxidation of these alcohols with the Fetizon's reagent.

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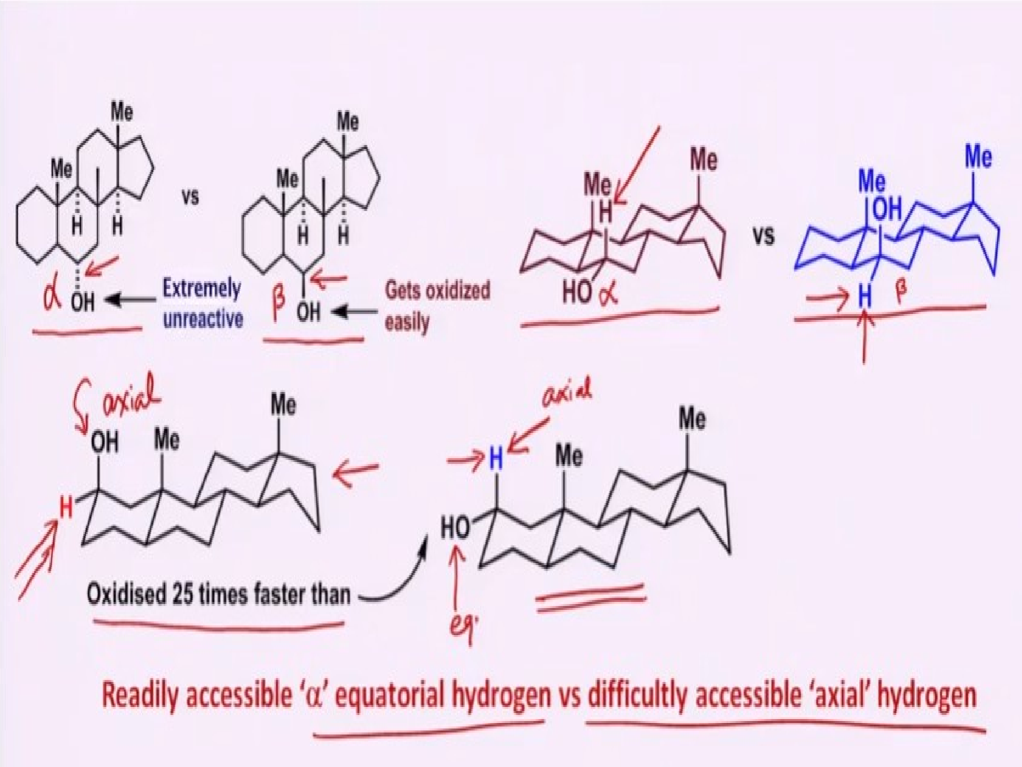

Readily accessible 'α' equatorial hydrogen vs difficultly accessible 'axial' hydrogen

Now there are few more examples which I want to show you here is that this particular molecule which has only one hydroxy group. But with the hydroxy group which is alpha oriented and in this case the only difference is that this is beta oriented. So has it has been found that this particular hydroxy group which is beta oriented gets oxidized faster than the hydroxy group which is alpha oriented.

Now the reason for that is that if we look's at the conformation of the molecule this is how the alpha hydroxy one looks like. And this is the one where the beta hydroxy group is here now when we see alpha hydroxy we have the hydrogen which needs to be oxidized is axial. Whereas here it is equatorial and this hydrogen which is axial is highly sterically hindered. And whereas this hydrogen which is equatorial oriented is less sterically hindered.

So that is the reason why the oxidation of the beta oriented hydroxy group takes place much faster because the hydrogen is equatorially oriented. In a similar fashion if one take this particular molecule which is here now has hydroxy group as axial, axially oriented but the hydrogen is equatorially oriented. On the other hand the hydroxy group on in this molecule is equatorially oriented but the hydrogen here is axially oriented.

So the access of the alpha equatorial hydrogen versus difficulty accessible axial hydrogen so this axial hydrogen is very difficult to get access of whereas, equatorial hydrogen here is easily accessible during the oxidation process. And that is the reason why the left hand side molecule having hydroxy group in an axial position gets 25 times faster oxidized than this particular molecule.

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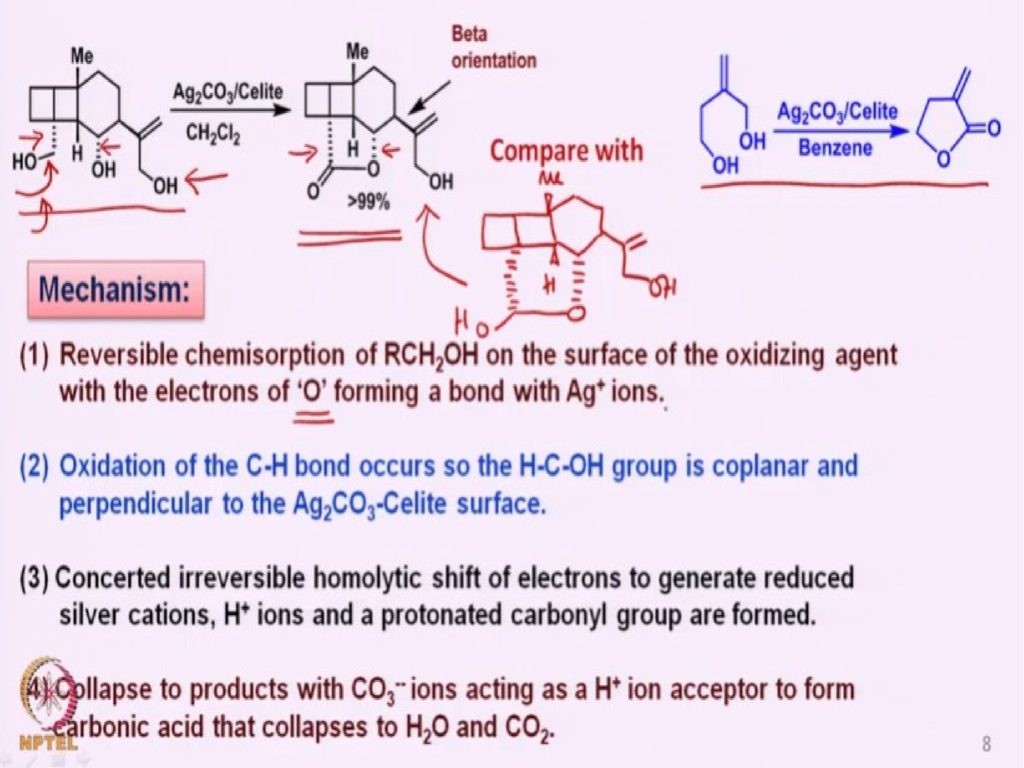

Mechanism:

(1) Reversible chemisorption of RCH_2OH on the surface of the oxidizing agent with the electrons of 'O' forming a bond with Ag^+ ions.

(2) Oxidation of the C-H bond occurs so the H-C-OH group is coplanar and perpendicular to the Ag_2CO_3-Celite surface.

(3) Concerted irreversible homolytic shift of electrons to generate reduced silver cations, H^+ ions and a protonated carbonyl group are formed.

(4) Collapse to products with CO_3^{--} ions acting as a H^+ ion acceptor to form carbonic acid that collapses to H_2O and CO_2.

Here now we have another example where we have a triol as I mentioned earlier that the allylic alcohols are oxidized faster than non-allylic alcohol. But it also depends on many other factors. For example here we have the stereochemistry orientation although this is an allylic alcohol which should get oxidized. But then what happens here is this particular primary alcohol gets oxidized first and then there is a lactone formation which is then leading to the formation of this lactone via the corresponding lactol.

So here what we are trying to emphasize is that we have this particular position of the alpha oriented. So what we will get is something like this and then lactol here that means this primary alcohol gets oxidized first and then the alcohol attacks onto the aldehyde to form this lactol. This lactol then gets oxidized and this is mainly because of the cis junction here or the cis junction of the cis orientation of the 2 hydroxy and hydroxy methyl groups.

We can compare this with this example which we discussed earlier here oxidation does occur of the allylic alcohol faster. Because that; leads to the formation of the corresponding lactol and to the lactone. On the other hand here the oxidation occurs only when the 2 hydroxy groups are cis to each other. Now we look at the mechanism of this reaction there is reversible chemi absorption of the alcohol on the surface of oxidizing agent with the electrons of O of the oxygen forming a bond with silver ions.

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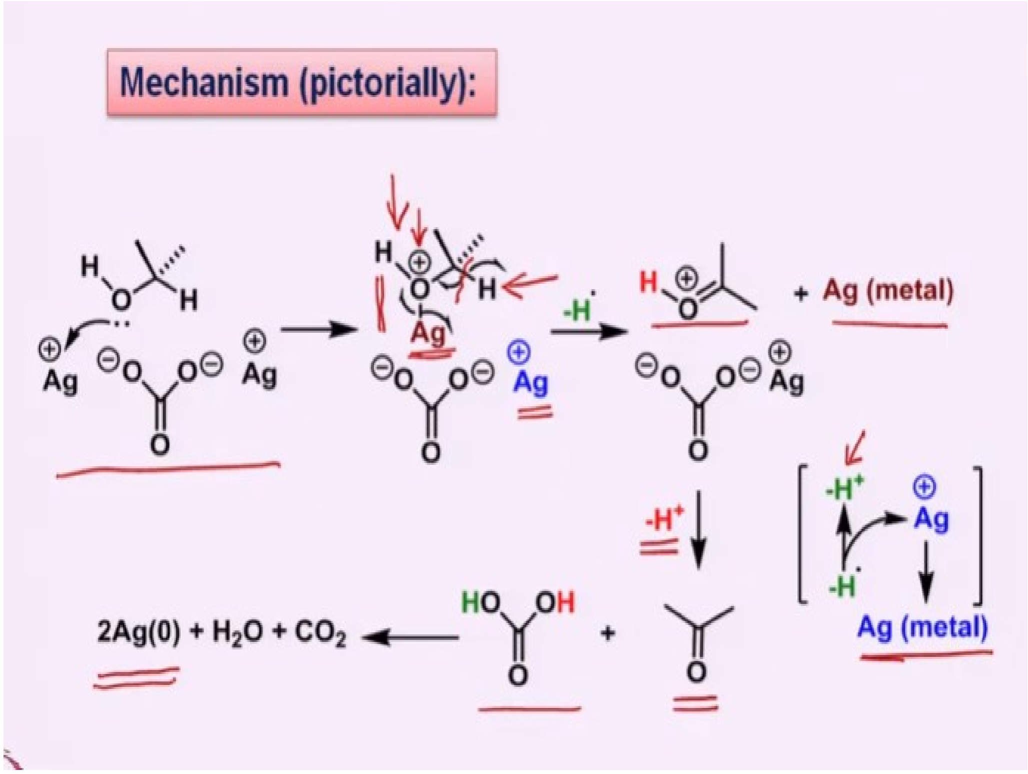

Mechanism (pictorially):

Now I can show this in the next slide here like this is how it is going to be forming. We have the oxygen of the alcohol then forms a bond with the silver in this fashion. So there is a chemi absorption RCH2 storage on the surface of the oxidizing agent with the electrons of O forming a bond with the silver ion. Oxidation of this CH bond occurs so the CHOH is coplanar and perpendicular to the silver carbonate celite surface.

This is exactly how it is shown here that the hydrogen here oxygen here and this hydrogen here they are in the same plane and they are perpendicular to the silver carbonate and celite surface. Then there is a concerted irreversible homolytic shift of electrons to generate reduced silver cations. And hydrogen ions and a protonated carbonyl group that are formed this is how it is here.

So you have silver metal formed here this oxonium ion that is formed here and that then loses the proton to form the corresponding carbonyl group. And the homolytic cleavage that has taken here leads to the formation of a hydrogen radical this hydrogen radical, then donates an electron to the silver here forming silver metal and of course a proton which is here. So this is exactly what is written here the concerted irreversible homolytic shift of electrons to generate reduced silver cations H^+ ions and protonated carbonyl group are formed.

Collapse to product with carbonate ions acting as an H^+ ions acceptor to form; carbonic acid that collapses to water and carbon dioxide. So this is exactly what is shown here that the alcohol interacts with the silver plus and the carbonate species will be just around with other silver plus and the silver plus of the first one interacts with the oxygen lone pair forming this intermediate. And then of course as I explained that eventually it is going to form this carbonic acid which looses carbon di oxide and water and in the process we get 1 silver metal from here.

And then another silver metal from here that is how there are 2 silver metals which are released from it.

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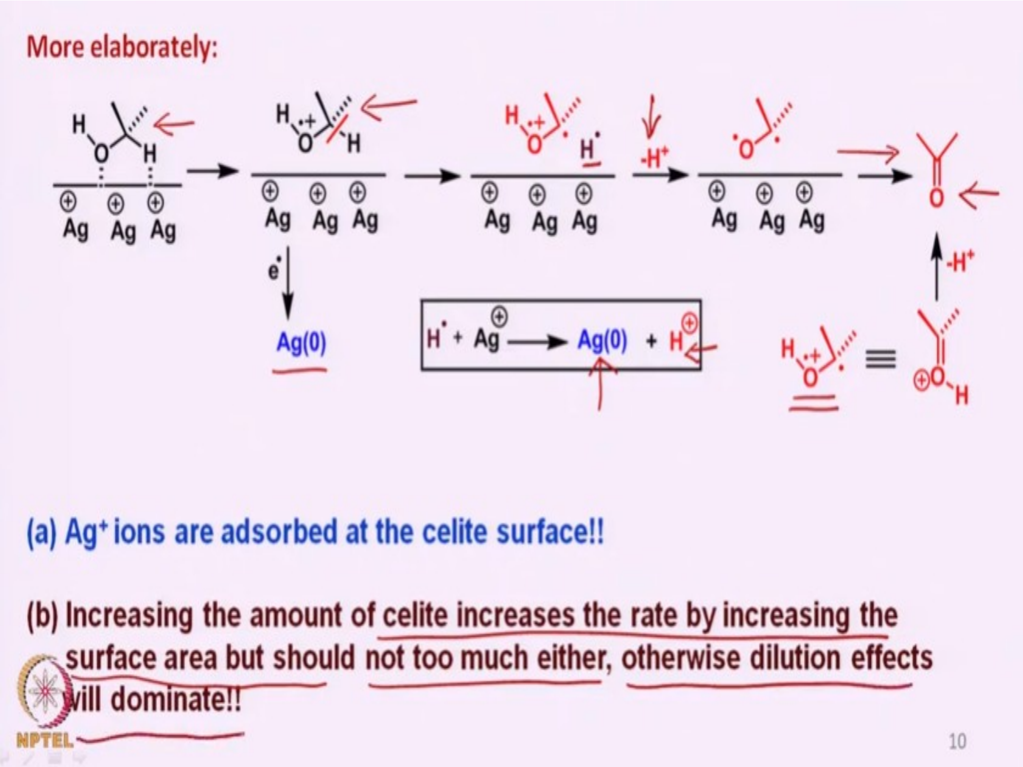

More elaborately:

(a) Ag+ ions are adsorbed at the celite surface!!

(b) Increasing the amount of celite increases the rate by increasing the surface area but should not too much either, otherwise dilution effects will dominate!!

Now we can also see in a slightly differently that we have this substrate which is the alcohol it is absorbed onto to the surface of the silver carbonate celite reagent. And then we can think about transferring an electron from the oxygen to the silver plus forming a silver metal here and this radical cation. This radical cation then undergoes a homolytic cleavage here forming hydrogen radical and this radical where then proton is lost from here we generate this di radical which collapses to form the ketone.

Now this hydrogen radical which is ejected from here reduces another Ag+ to form second silver metal and of course you release a proton from here. Now there is a loss of proton from here which eventually give the ketone. So essentially it has the similar mechanism which I have showed earlier it is slightly more elaborate manner. So, silver ions are absorbed at the celite surface now increasing the amount of celite increases the rate by increasing the surface area.

We can increase the amount of celite which allows more surface area to be formed. Therefore the rate of the reaction increases but it should also not be too much otherwise dilution effects will dominate and that leads to the reduction in the rate of oxidation.

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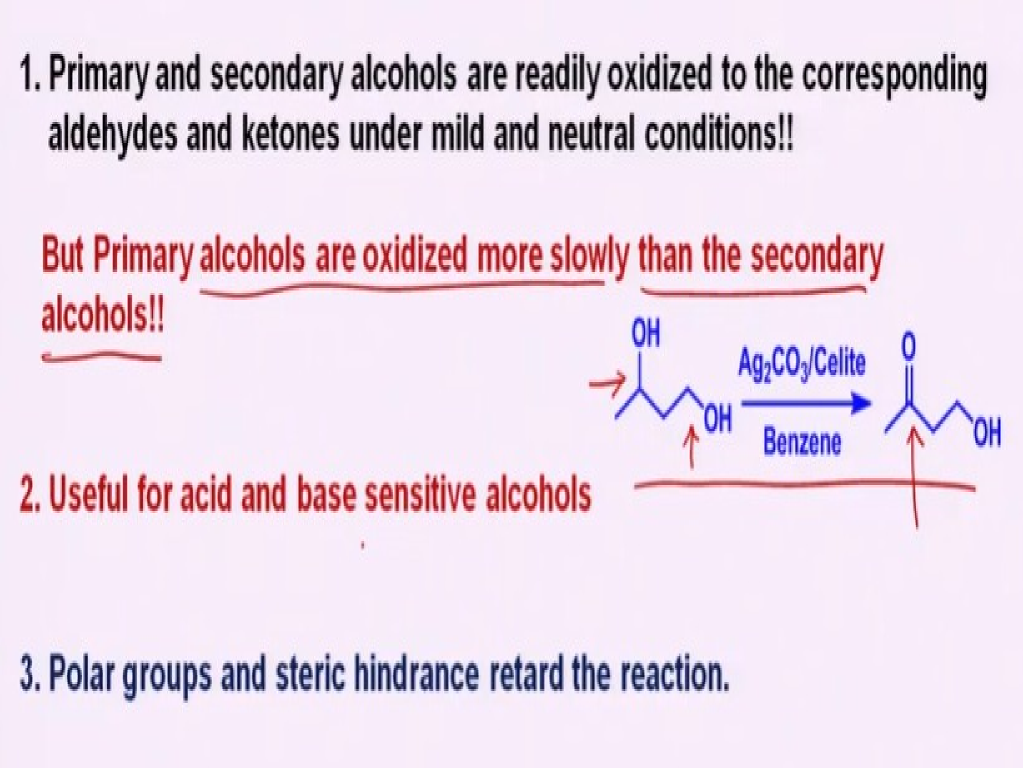

1. Primary and secondary alcohols are readily oxidized to the corresponding aldehydes and ketones under mild and neutral conditions!!

But Primary alcohols are oxidized more slowly than the secondary alcohols!!

2. Useful for acid and base sensitive alcohols

3. Polar groups and steric hindrance retard the reaction.

As I mentioned earlier primary and secondary alcohols are readily oxidized to the corresponding aldehydes and ketones under mild and neutral conditions. But primary alcohols are oxidized more slowly than the secondary alcohols at the same time as I explained earlier allylic or benzoic alcohols are oxidized faster than the non-allylic or non-benzylic alcohol. And the reason for that is obviously very clear that we have the formation of a radical which is here and that is more easily stabilized when the position would be allylic or benzylic.

This is an example where there is a primary hydroxy group as well as there is a secondary hydroxy group. When the reaction is carried out there is a preferential oxidation of the secondary hydroxy group over the primary hydroxy group. It is useful for acid and base sensitive because it is a relatively mild reagent and therefore the conditions are easily useful for acid and base sensitive alcohols. Polar, groups and steric hindrance retard the reaction I already about the steric hindrance.

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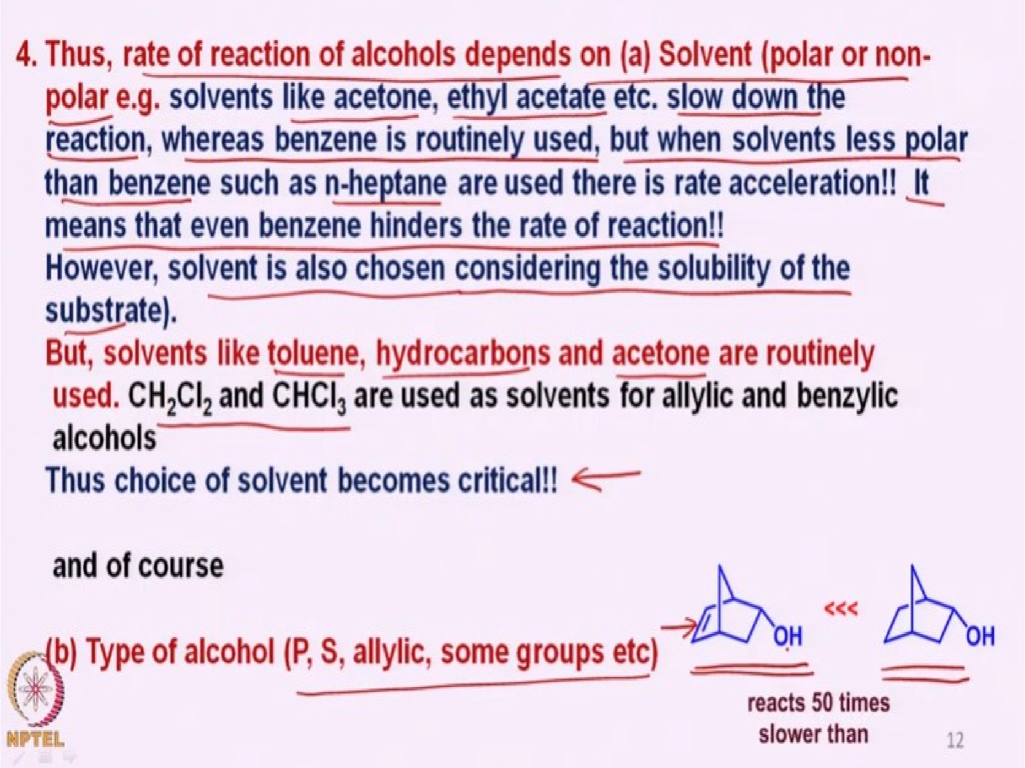

4. Thus, rate of reaction of alcohols depends on (a) Solvent (polar or non-polar e.g. solvents like acetone, ethyl acetate etc. slow down the reaction, whereas benzene is routinely used, but when solvents less polar than benzene such as n-heptane are used there is rate acceleration!! It means that even benzene hinders the rate of reaction!!

However, solvent is also chosen considering the solubility of the substrate).

But, solvents like toluene, hydrocarbons and acetone are routinely used. CH_2Cl_2 and $CHCl_3$ are used as solvents for allylic and benzylic alcohols

Thus choice of solvent becomes critical!! ←

and of course

(b) Type of alcohol (P, S, allylic, some groups etc)

reacts 50 times slower than

Now let us see the polar effects the rate of reaction of alcohol depends on solvent polar or non-polar. For example solvents like acetone ethyl acetate slow down the reaction because there is a comparison there is a competition between the oxygen of the acetone and the ethyl acetate with the oxygen of the alcohol to attach on the surface of the silver carbonate celite system. Now benzene is also used routinely but it was found at when solvents which are less, polar than the benzene such as n-heptane are used the rate is increased.

It means that it is simply means that even benzene hinders the rate of the reaction because it as Pi electrons. And therefore there is possibility of having a competition between adsorption of the benzene onto the surface of the reagent versus the adsorption of the alcohol onto the surface. Of course alcohol will get adsorbed faster but still there is little hindrance from the benzene so you one has to choose the solvent based on also the solubility of the substrate.

But solvents like toluene hydrocarbons and acetone are routinely used and so are dichloromethane and chloroform particularly for allylic and benzylic alcohols. Thus the solvent becomes very critical for as a choice for the reaction to take place. As we discussed it also depends on the various kinds of alcohols primary secondary allylic etc., and we have here one very interesting example that this particular alcohol reacts 50 times slower than this alcohol.

One can see that the presence of the double bond makes the difference between 2 substrates where the oxidation. That means this Pi-bond like benzene can also compete with the alcohol for the adsorption at the surface of the silver carbonate celite reagent system. So we will stop it at this stage and continue with the reaction of different types of alcohols with Fetizon’s reagent in the next class. Meanwhile you can read and try to understand what I mentioned and discussed in this class thank you.