Essentials of Oxidation, Reduction and C-C Bond Formation
Application in Organic Synthesis
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Lecture -10
Dess-Martin periodinane oxidation

Hello everyone welcome to this lecture of today we will briefly look at what we did last time before we proceed further with the oxidation reactions. In the last class that I took was I introduced a way of converting 1, 2 ketone transposition and we introduced the sulfur based chemistry and the second transformation that we discussed was 1, 3 enone transposition.
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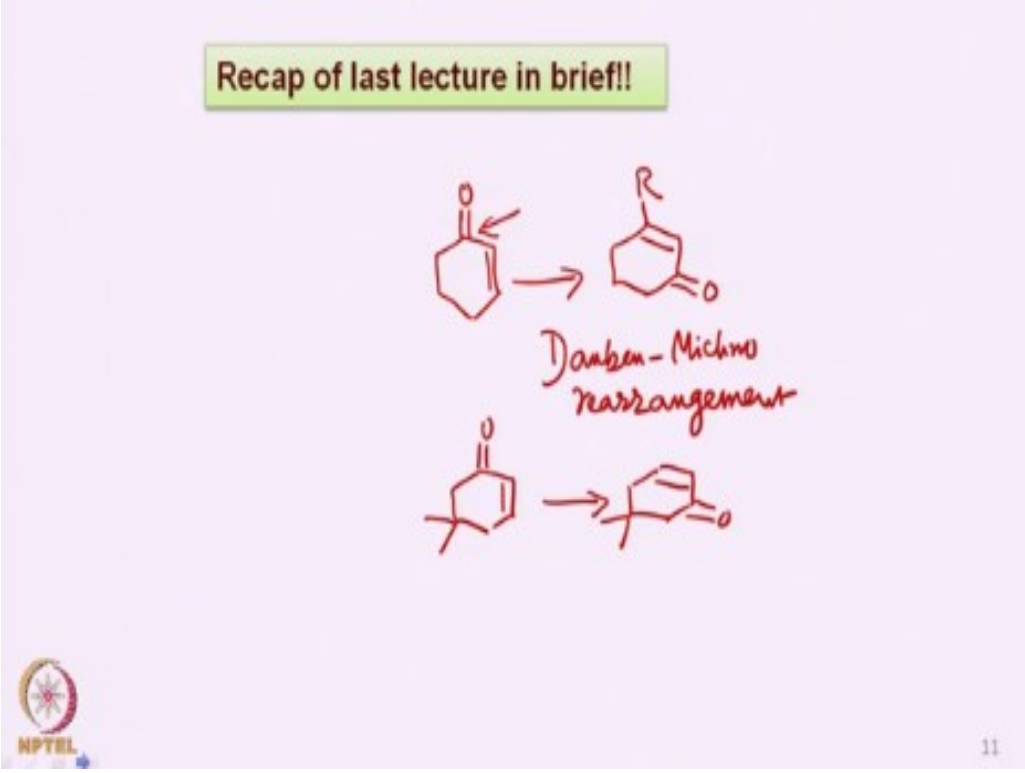

Where we took two different types of substrates and, those substrates where we had an enone of this kind and we transposed into an enone of this kind by introducing an R group here at this position. This was one method that we discussed using Dauben rearrangement, Dauben-Michno rearrangement. The other method that I introduced was simply a conversion of say for example, you have an enone of this kind and then with the help of selenium based reagents we converted this into this.

So this is without the introduction of an R group whereas this one was with the introduction of the R group.
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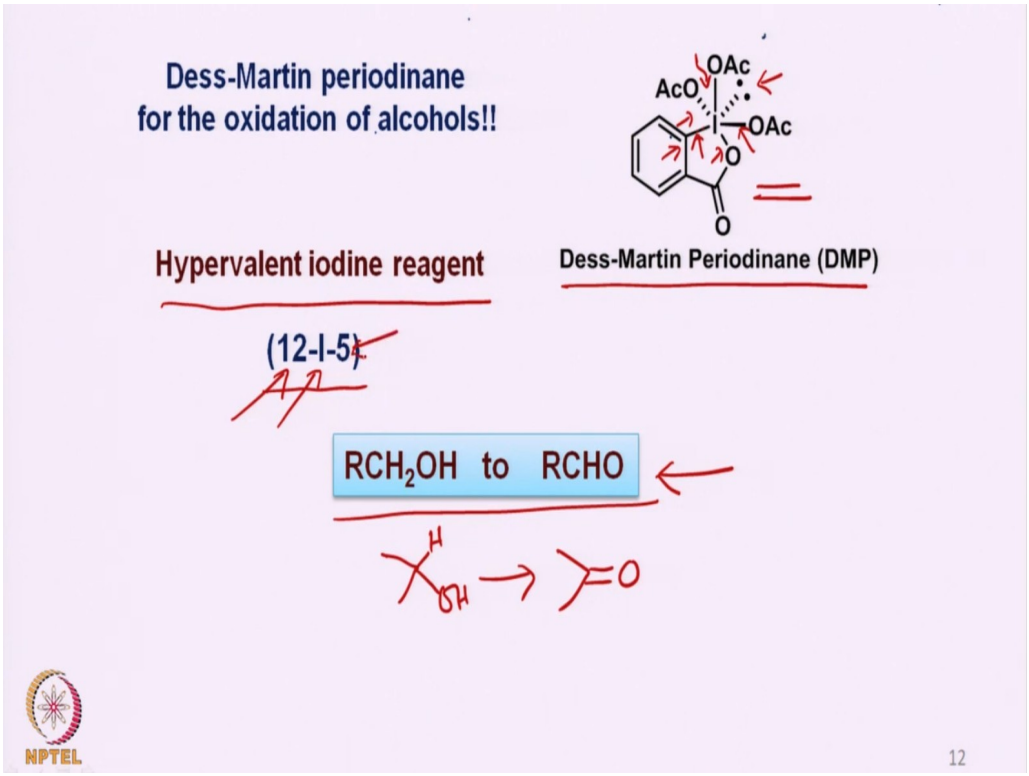

So now today we will look at another reagent system which is called as Dess-Martin periodinane of this kind which allows oxidation of alcohols to the corresponding aldehyde of course it can also allow secondary alcohols oxidation to the corresponding ketone. But this is especially very important for primary alcohols to the corresponding aldehyde.

Because with other reagents such as chromic acid Jones oxidation or many other oxidation in which the primary alcohol gets oxidized to the corresponding acid, so there is an always over oxidation and also this method is fairly mild as we go along we will see how important is this method from the point of view of dealing with sensitive substrates. Now this is called Dess-Martin periodinane basically it is based on hypervalent iodine reagent.

For example; this reagent here where the iodine is having hypervalency. So this is called as 12-I-5, 12 means, now there are 12 electrons which are around two from this bond and two from here, two from here, two from here, two from here and another pair of electrons here. So that indicates 12 and iodine and there are 5 bonds which are attached because 3 iodine acetoxy bond and 1 iodine this aromatic carbon bond and one iodine oxygen bond. So this is what indicates the 5 that means 5 bonds are around.

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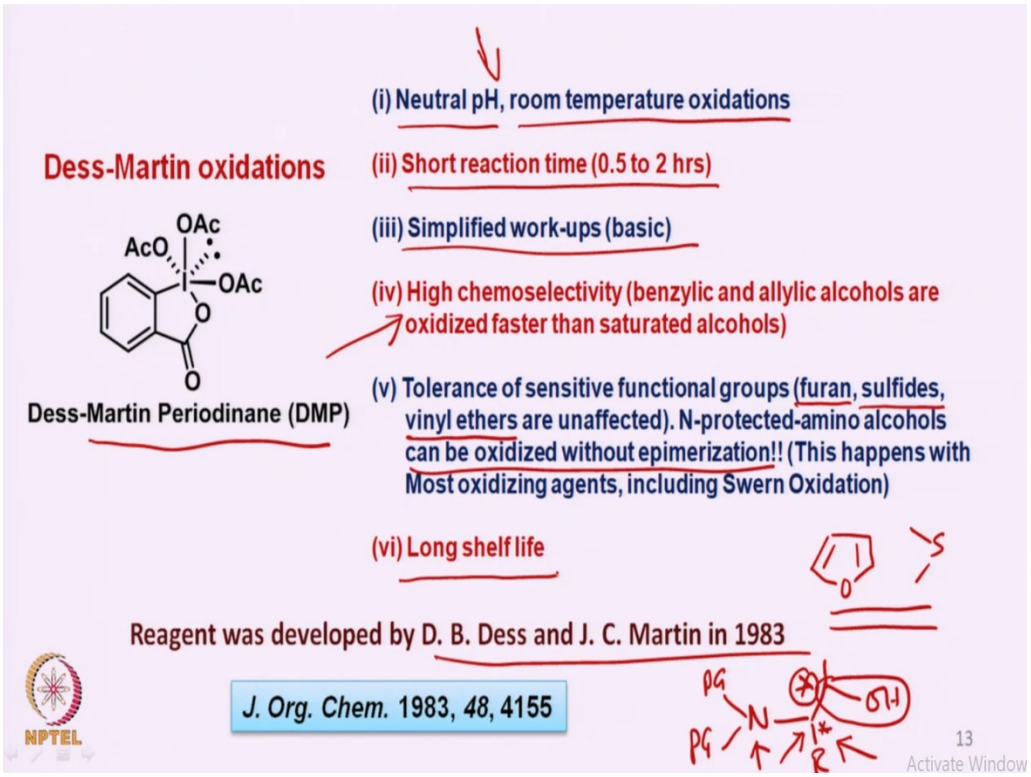

Now this particular, Dess-Martin periodinane ox reagent this particular reagent is called DMP was developed by Dess and Martin in 1983 and has got tremendous application and use in the literature. So it is a reagent that works at neutral pH at room temperature and short reaction times. Many times you will see that many of the oxidizing agents such as Swern oxidation is carried out at very low temperature -78 to -65 or something like that.

And maintaining that low temperature is somewhat difficult and of course involves an expansion of energy, plus this particular reagent system involves a simplified workup a simplified basic workup we will see later on how the mechanism allows this reaction to occur and what comes out of the reagent is only acetic acid which is a mild acid. This allows high chemoselectivity particularly benzylic and allylic alcohols are oxidized faster than saturated alcohols or non benzylic non allylic alcohols.

So that is chemoselectivity this also tolerates a number of functional groups such as furan sulphides. Now for example, if you have a few round ring and you have a sulfide group here they both can be affected by many of the chromium based oxidizing agents. However, here the iodine is fairly mild reagent this Dess-Martin periodinane containing iodine is a mild oxidizing agents. Therefore the furan, sulfides, vinyl ethers are unaffected.

Similarly one can oxidize N-protected-amino alcohols. So if you have an N protected amino alcohol you have a nitrogen here and you have here say an alcohol which one wants to oxidize and there is a protecting group here PG, some sort of protecting group. Now this nitrogen is not affected, so the oxidation of this alcohol occurs readily with this particular DMP Dess-Martin periodinane oxidizing agent and the nitrogen is not affected.

So many of the functional groups which are there they are not affected plus for example, if there is an asymmetric center here at this particular position or there is another asymmetric center here so you have an R group here and you have here an asymmetric center although this asymmetric center will get destroyed because of the oxidation that we are going to carry out. But then this asymmetric center here which has a hydrogen at this position can get affected by the carbonyl group here.

If the; reagent conditions are either acidic or basic. But since here it is a neutral pH, it is a neutral reagent system this at particular symmetric center does not get affected and there is the oxidation that happens without epimerization. Now this epimerization not occurring with DMP is something that has been observed in with many other oxidizing agents. So there are many plus points of this Dess-Martin periodinane oxidation and this reagent this DMP is having also a long shelf life.

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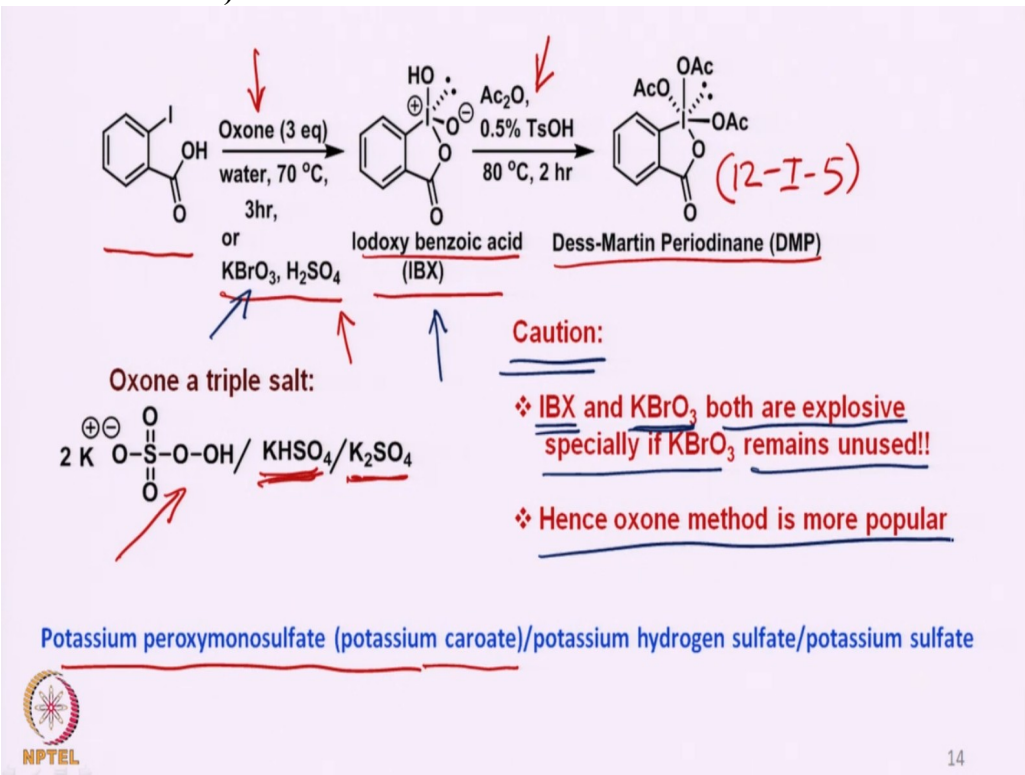

So considering these aspects of the reagent that we are discussing there is a lot of scope for the utility of this Dess-Martin periodinane or DMP reagent or DMP oxidation. How this reagent is made you start with ortho iodo benzoic acid and react it with oxone is nothing but a triple salt. Basically the oxidizing agent is this potassium peroxy monosulphate is the actually is also called potassium carotid and these are only added to which stabilize the shelf life of these oxone.

And also help in kind of maintaining the reagent in a proper way. So this oxone is reacted with this ortho iodoxy benzoic acid, but you can also use $KBrO_3$ potassium bromide and sulfuric acid, but there is a little problem with this particular reagent system that I will tell after some time. So this undergoes oxidation to form this iodoxy benzoic acid and this absolute iodoxy benzoic acid is then acetylated under acidic conditions to form Dess-Martin periodinane.

Now here as I mentioned earlier it is a hypervalent iodine base reagent, so that is the 1 that is the 12-I-5 that is the reagent that is formed. Now in we need to exercise a caution in this particular preparation and that caution is that both IBX this is the intermediate that is formed which is a stable intermediate and this IBX this is called iodoxy benzoic acid and potassium bromate that is starting material that we have used, if we use oxone then there is no problem.

But if we use potassium bromate then of course you both of this IBX and $KBrO_3$ both are explosive, especially if $KBrO_3$ remains unused. So it is little tricky and little dangerous if one uses $KBrO_3$, however still people do use but it is recommended that oxone method is used for preparing this particular Dess-Martin periodinane reagent.

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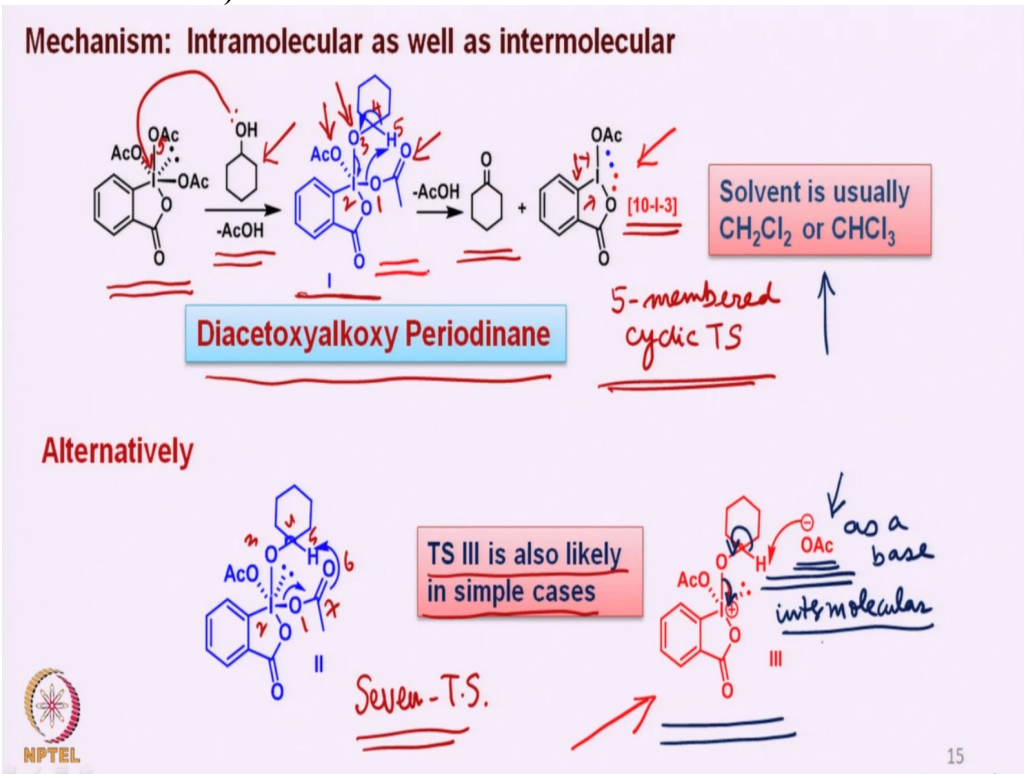

Now how does the reaction occur? So if one takes say you take this particular cyclohexanol. For example, here for oxidation to the corresponding cyclohexanone it is a simple example just to illustrate how the reaction occurs. So if this particular alcohol lone pair of electron attacks onto this one of the acetate group will go and of course you will have the preparation of the intermediate I.

Now this is basically having two acetoxy groups here, one here and one here that is the reason why it is called as diacetoxyalkoxy periodinane. So your alkoxy group is coming because of the alcohol that we are going to oxidize it and there are two acetoxy groups which are already present in the reagent system. So basically what is happening is that alcohol replaces one of the acetoxy groups from the starting reagent.

By the laws of acetic acid and forms this intermediate which is what is called diacetoxy alkoxy periodine and then that undergoes and is a possibility that this involves 1, 2, 3, 4 and this 5, 5 membered cyclic transition state. So you have 5 membered cyclic transition state that allows the

oxidation to take place and of course you are left out with this iodine containing byproduct which is 10-I-3.

So you have 3 bonds here and of course you have 2 to 4 to 6 to 8 into 10 electrons and we have this iodine in between. Now other possibility is that you carry out the oxidation starting from one 1, 2, 3, 4, 5, 6 and 7. So this is a 7 member transition state, so these both are intra molecular this 5 membered transition cyclic transition state and seven member cyclic transition state both are intra molecular transition states that allow oxidation to take place.

But there is also possibility of a third transition state which is possible in simple cases such as this where you have a possibility of simply an inter molecular you have an inter molecular oxidation with the help of the acetate. So when the alcohol is reacting with the reagent then what you have is a possibility of there should be this intermediate can break this intermediate which is number 1 can break and form an intermediate of this kind.

Where there is a positive charge on the iodine and the acetate has lost has come out this acetate can act as a base and remove the proton from here and in this fashion the oxidation can occur and that gives the corresponding ketone. So this is an intermolecular way by which the oxidation occurs with the help of the acetate ion which can come out from the intermediate which is either 1 or 2.

And they form a third intermediate which allows inter molecular oxidation to take place. Now these reactions are generally carried out in solvents like dichloromethane or chloroform and of course as I mentioned at room temperature. Now why are we talking about these type of transition states such as 1 and 2 when we can easily think about that, such inter molecular transition state can occur readily to form the oxidized product.

And reagent gets reduced to the corresponding byproduct which is what is here. What is the need to invoke the intermediates or the transition states of this type.

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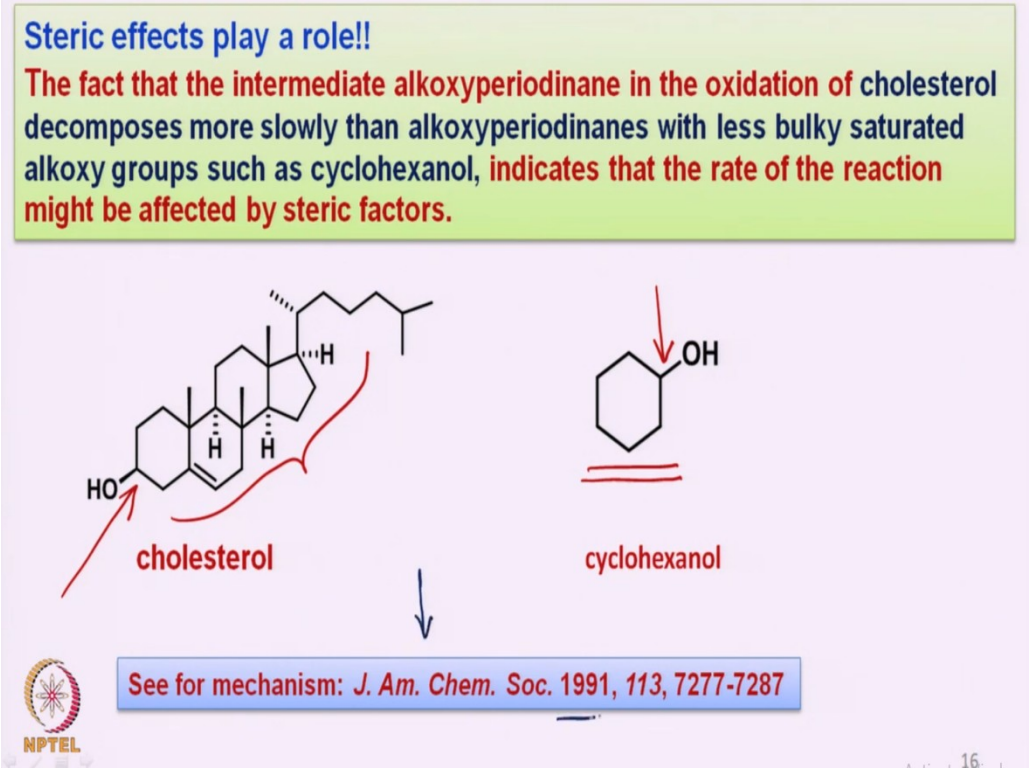

Now there is a reason the steric effects play a very important role the fact that the intermediate alkoxyperiodinane in the oxidation of cholesterol decomposes more slowly than alkoxyperiodinane with less bulky saturated alkoxy groups, such as cyclohexanol indicates that the rate of the reaction might be affected by steric factors. So say for example, if one takes a case of cholesterol.

Now this alcohol here you compare this alcohol with this alcohol here, here you have a bulk of the cholesterol that we have whereas there is not much of bulk of this. If the reaction was occurring according to this mechanism here where it is an intermolecular removal of proton or the oxidation takes place in intermolecular fashion then there should not be much difference in the rate of cholesterol versus the normal cyclohexanol.

But it is seen that this reacts very slowly compared to cyclohexanol indicates that there is a role of steric effects that plays and if one invokes intermediates of type 1 or type 2 I am talking about intermediates because they then undergo a transition state involving 5 membered or a 7 membered ring. So these intermediates of 1 and 2 kind which allow intramolecular oxidation to take place via a 5 membered or a 7 membered transition state would then be affected by the steric factors obviously.

Because it will be a compact 5 or 7 membered transition state and therefore there will be a possibility of steric hindrance and that is the reason why these type of mechanisms or these type of transition states involving 5 and 7 membered ring are introduced and there is a very nice description of these mechanistic aspects in this particular paper which is published in 1991.

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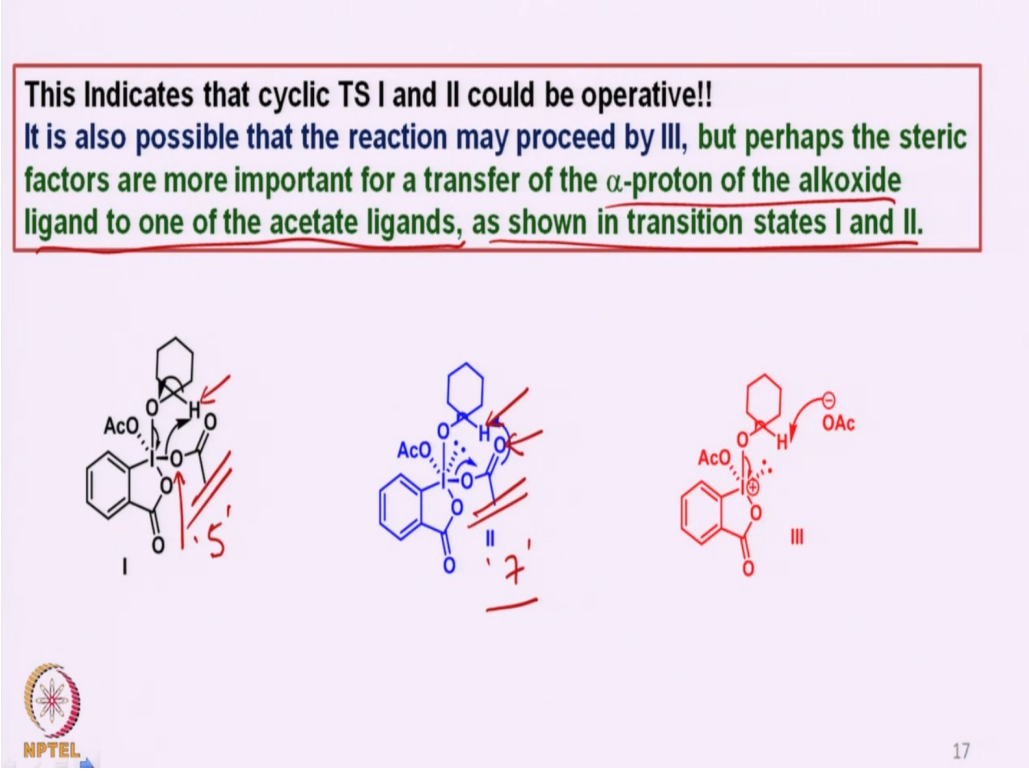

So these type of experiments when they were conducted clearly it shows that steric effects can be important. So what they have concluded this this indicates that cyclic transition state 1 here and 2 could be operative it is also possible the reaction may proceed by transition state 3. But perhaps the steric factors are more important for a transfer of the alpha proton of the alkoxide ligand to one of the acetate ligands as shown in transition states 1 and 2.

So basically what is happening is this acetate group here or this acetate group here allows the abstraction of a proton whether via this oxygen, over this oxygen that allows the removal of the proton here via a 5 membered transition state or a 7 membered transition state. This is exactly what they are saying here alpha proton of the alkoxide ligand to one of the acetate ligands as shown in transition states 1 and 2.

And because of the experiments that suggest that sterically hindered cholesterol reacts slowly compared to the non sterically hindered alcohol such as cyclohexanol these transition states of cyclic transition state involving intramolecular hydrogen bonding is introduced.

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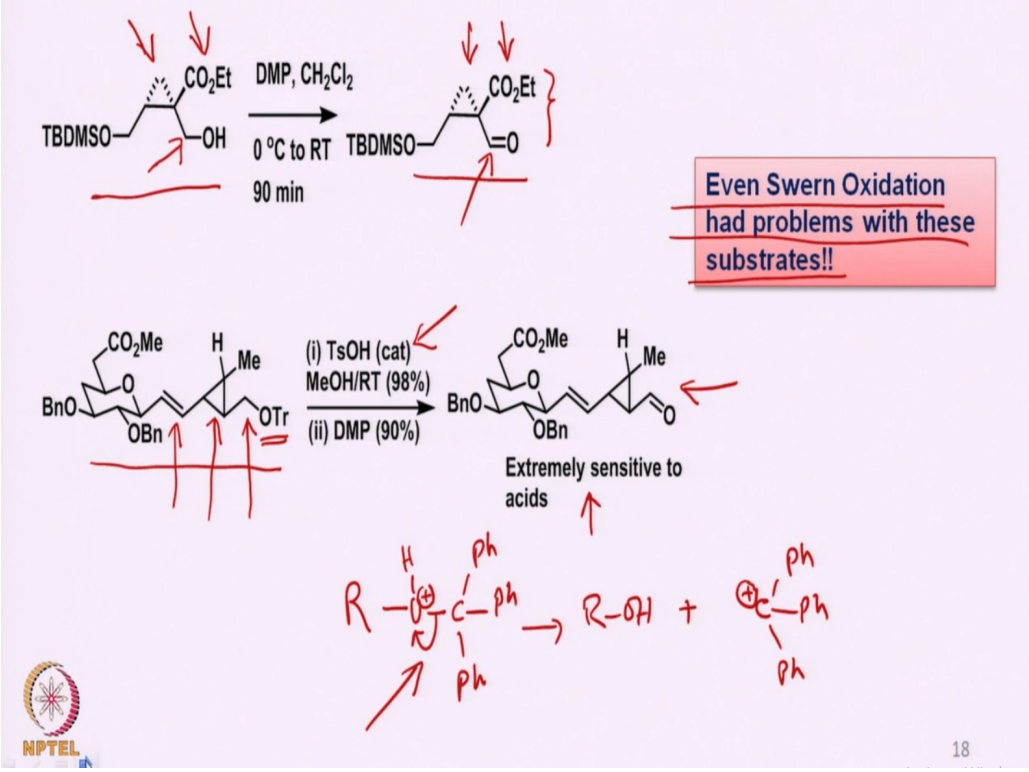

Now you see the example now here for example, here you have a very sensitive substrate where there is a cyclopropane ring here and there is an ester group here and there is an alcohol here. When this oxide gets oxidized what you have now done is got a substrate product where there is a cyclopropane ring there is an ester group here and then there is a aldehyde group here. So that means the cyclopropane ring is adjacent to 2 electron withdrawing groups.

And therefore the cyclopropane ring can easily be opened by any nucleophile if the reaction condition is either acidic or basic or particularly under acidic condition. So when people had carried out oxidation, using Swern oxidation using this kind of substrate they had problems because if you recall under the Swern oxidation condition hydrochloric acid is also one of the byproducts that comes off.

In a similar fashion if you take a substrate of this kind which is very complicated substrate having a double bond which is in conjugation with a cyclopropane ring and then of course you have the allylic alcohol which is protected as trityl. Trityl protection is nothing but this kind of group where it can easily if you treat this particular protecting group where there is an R group here, then if you use simply tosic acid in a catalytic fashion.

Then this protonates the O group here the ether and then this opens up to generate the alcohol and of course you generate a highly stable tertiary cation in this fashion. So there is a very strong driving force to keep 3 of this bond under acidic condition this is what is done by this tosic acid here and this methanol room temperature it gives 98% it releases the corresponding alcohol here and then that reacts with DMP Dess-Martin periodinane in reagent to form the corresponding aldehyde which in 90%.

This is extremely sensitive substrate for the acids this can easily get protonated and this bond can open in many ways and therefore this is a very important substrate which clearly indicates that DMP is very useful for this kind of oxidation involving as acid sensitive substrates.

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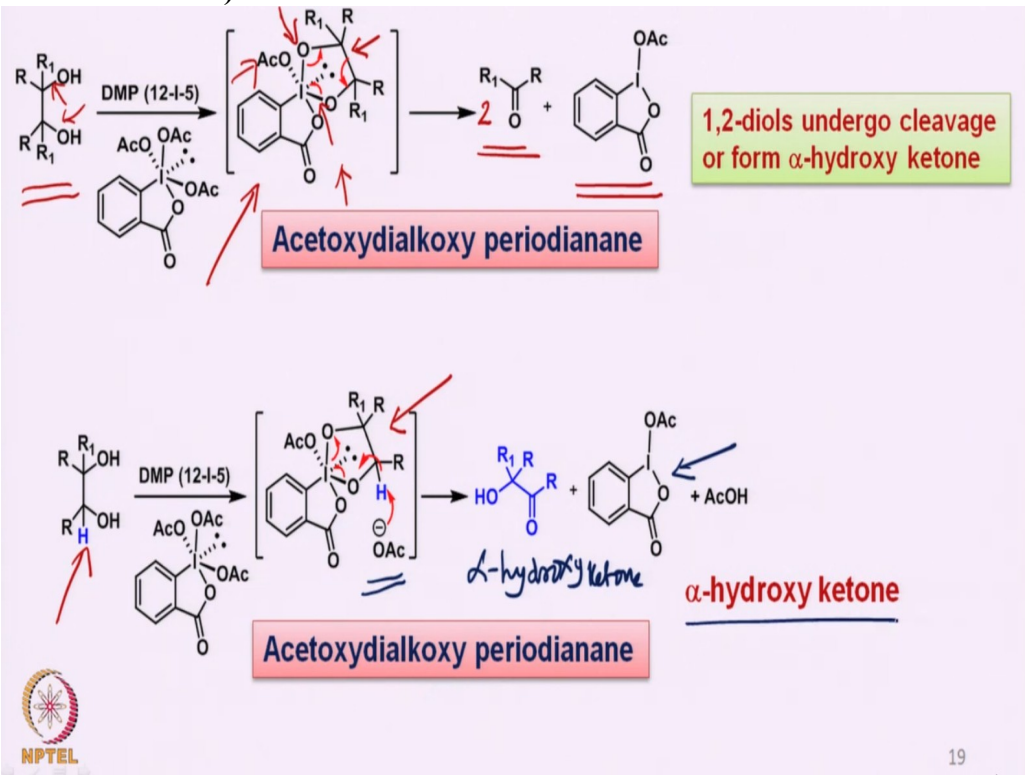

Now if one looks into the various kinds of substrates that have been utilized for this oxidation are also diols, if you have a diol which is not having a hydrogen like R and R1 are not hydrogen. So it can form an intermediate by replacing two acetoxy, two acetates from here are replaced by two alkoxy bonds of the diol that we are using one is here and the other one is here and you form this acetoxydialkoxy periodinane.

So there is one acetoxy group here and two of the dialkoxy, so this is what is called as a alkyl acetoxydialkoxy periodinane here and that undergoes a cleavage as I have shown here to cleave this particular carbon bond to form this ketone which will be of course two of them and you then regenerate the reduced species from the oxidizing agent. So this intermediate is a very important intermediate where two acetoxy groups are replaced by the two hydroxy groups of the diol.

On the other hand if we take a diol in which one of the R groups is hydrogen, then we have this type of intermediate which is similar to the one which is shown on the top, which is but then the difference between the two of them as you can see is that there is no hydrogen in this particular acetoxydialkoxy periodinane. There is no hydrogen but here there is one hydrogen. So now this particular intermediate can undergo oxidation with the help of the acetate.

This acetate ion which has come out in this reaction can take up the proton from here and one can make alpha hydroxy ketone and you generate the reduced species from the corresponding oxidizing agent. So there is an easy way of converting into the alpha hydroxy ketone or a cleaved product.

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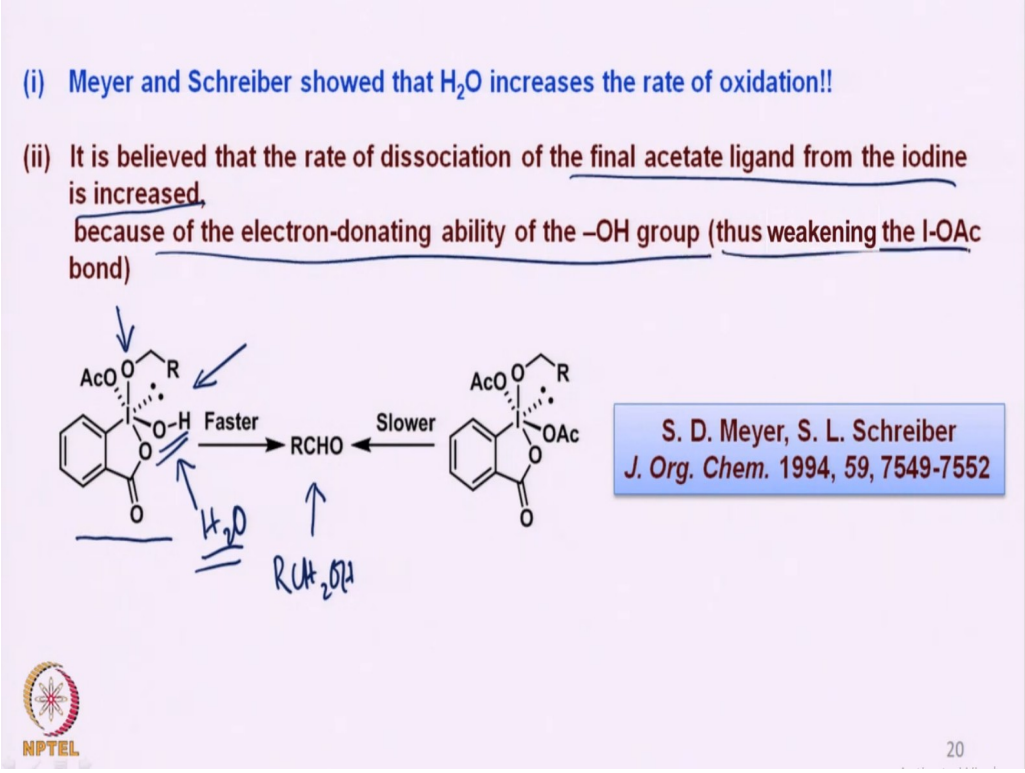

Now Meyer and Schreiber showed that water increases the rate of oxidation. Now what is happening here is if you add water in the reaction medium then there is a possibility of replacing one of the acetates by the hydroxy group and the intermediate is of this kind, that means from the reagent when one of the acetoxy groups is gone you generate this O-I bond and the other acetate is replaced by this hydroxyl group coming from the water.

Now what they have observed is the conversion of say RCH_2OH to the corresponding aldehyde is much faster if there is a small amount of water added and one of the ways that they have explained is that this particular intermediate which is formed here can easily allow the elimination of the acetoxy group which is present there and once that elimination takes place you have species of this kind.

Where; now this particular iodine oxygen bond can easily be broken up accompanied by the oxidation with the help of the acetate here. So basically what is helping is it is believed that the rate of dissociation of the final acetate ligand from the iodine is increased because of the electron donating ability of the -OH group thus weakening the I-OAc acetate bond.

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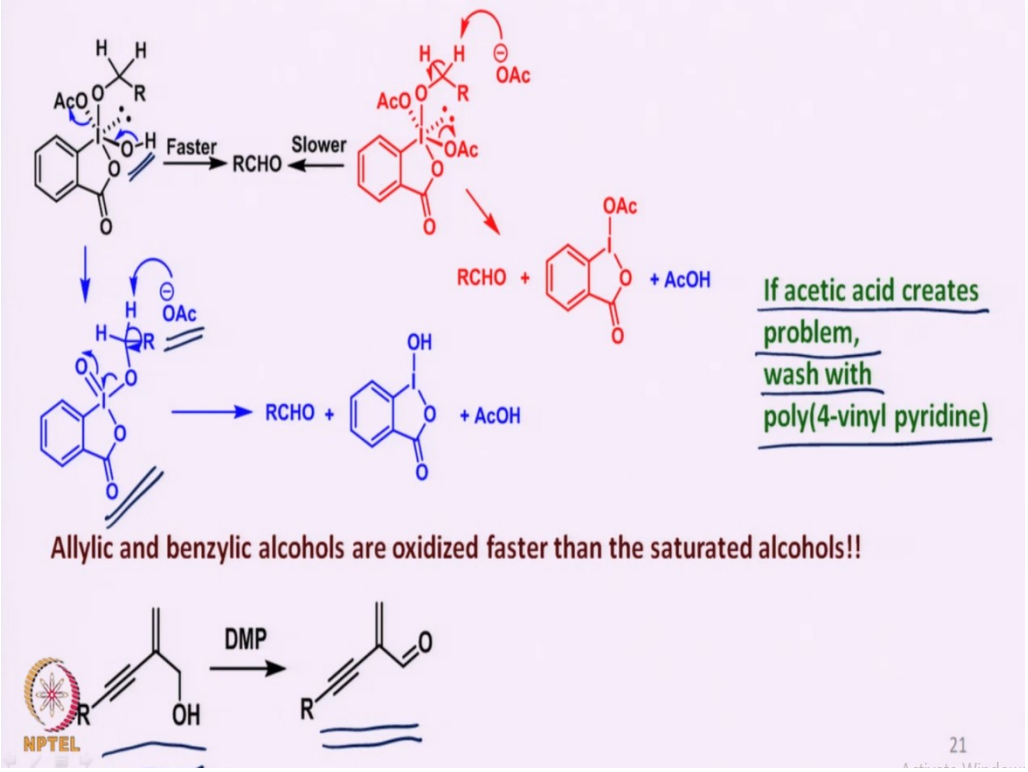

So that means what is happening is that this particular movement of electrons from the OH group kicks out the acetate at the same time there is an oxidation because this loss of acetate is much faster with this hydroxy group being present there. So that is the reason why the oxidation occurs and there is a well description of this particular aspect in this particular paper and allylic and benzylic alcohols are oxidized faster than the saturated alcohols.

Of course you can have many such type of alcohols that can be oxidized to the corresponding aldehydes which are very sensitive with the triple bond and the double bond in conjugation. If acetic acid happens to be a problem then one can wash the reaction medium with poly 4 vinyl pyridine and that allows easy workup and there should not be any problem in the reaction medium.

So we would stop it at this stage and then take up the other oxidizing agents in the next class. So I suggest that you go through these references if it is possible or whatever I have told to in today's class to go through very carefully about this Dess-Martin periodinane oxidation. So we will meet next time thank you.