Course on Stereochemistry
Prof. Amit Basak
Department of Chemistry
Indian Institute of Technology Kharagpur
Mod07 Lecture 29
Conformation and Reactivity

Okay, let us just continue with what we have said last time we have just said about this ketone effects 2 alkyl ketone effect, 3 alkyl ketone effect and then I said there is 4 alkyl ketone effect too also, and, but I did not elaborate on that 4 alkyl ketone effect.

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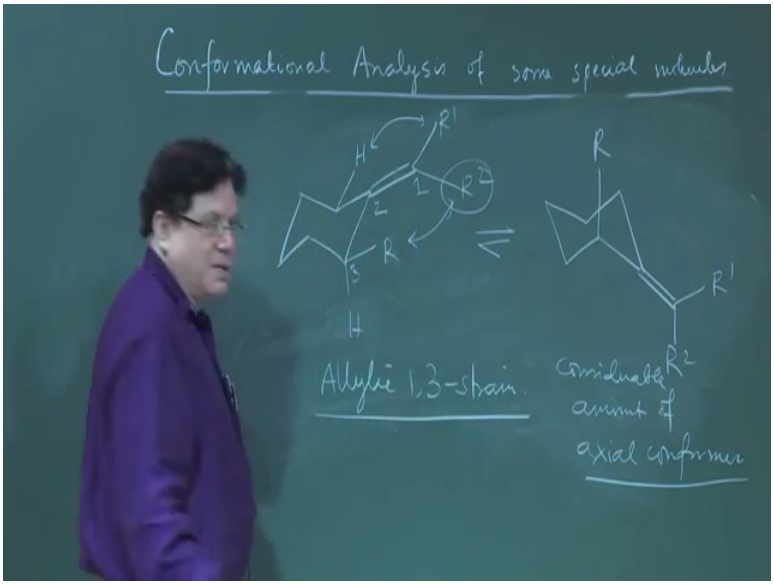

in other systems, another interesting system is instead of a ketone if you have a double bond here, suppose and this double bond will have substituent at this position, but in that case, it will be also very similar, because of this double bond now these equatorial hydrogen will be equatorial hydrogen will be will be eclipsing this one that is no dought, but this is quite close to this R2 on this side and the equatorial hydrogen here that will also be quite close to R1, but if it is hydrogen, it does not suffer much interaction, but suppose this is not hydrogen, if the R, I place here and if the hydrogen is here than what happens? There will be steric compression between R and R2, okay and that steric compression we reduce if it goes into this form, if it flips and goes into this is R2, R1, but now this R is in the axial position where this type of steric interaction is not present.

So this is cyclohexane alkyl (())(1:59) system I can make the system here for you , this is the cyclohexane cyclohex exocyclohexene. So cyclohexane attached to the exo double bond and if you see that there are, now if I put this group in the equatorial position, so what I was pointing out is , sorry this is just coming up I means, yes this is the cyclo this cyclohexane alkyleden (()) (2:41) system.

Now this is the group which is suppose R1 or R2 and this is the equatorial group at C2, okay. So you see how close are they. So they are now satirically crowding each other, okay. Now if you invert it if you now do the flipping, so you see, this is the double bond going away from this group. Now because this group is in the axial position. So axial orientation you do not have this strain, because far apart. The groups attached to this exocyclic carbon is no longer in proximity with the axial alkyl group, okay.

Now this is what is called, so this systems also we will have considerable amount of considerable amount of this type of this axial (())(3:40) axial conformer and like your 2 alkyl and 3 alkyl ketone effects this has also a name, this is called allylic 1,3 strain why, because this is your suppose this, because the strain is between the substituents at attached to C1 then 1,2,3 and attached to C3. So it is the strain between the substituents attached to C1 and C3. So this is called allylic 1,3 strain, okay. These are some interesting features. They are very important while dealing with reactivity of molecules, okay.

So we have seen, so far we have just been dealing with the preferred conformation of different, first we did acyclic system and then we studied the some other acyclic systems then the cyclic systems and special cyclic systems like cyclohexanone or alkyleden (())(4:55) cyclohexane that means cyclohexane with exocyclic double bond and we have seen that according to the situation, the preferred conformation varies, okay.

The factors that need to be considered while drawing the preferred conformation are first of all the torsional strain, then the steric strain. Torsional strain is also the eclipsing strain is similar to the torsional strain and then the steric strain that is a size (())(5:25) effect then you have the hydrogen bond effect, you have dipole-dipole repulsion. So these are the things which we need to consider while arriving at a conclusion to draw the prefer conformation of a molecule, okay.

Now this stereochemistry, what we have learned so far is what is called static stereochemistry means we have only check the conformation and we have only check the energy differences between the possible conformers and that is it we did not say anything about the reactivity of these molecules reactivity of these molecules means this conformation analysis has two aspects, I gave you the definition of conformational analysis, one is conformational analysis deals with the variation of energy, as you rotate the system, as you rotate around carbon-carbon bonds, as you flip a system like cyclohexane then how the energy changes that is what is what is call the. There is one type of conformational analysis with respect to energy. There is another type of conformation analysis which is the verses which is which takes care of the reactivity that means how the reactivity pattern of a molecule changes, with different conformations of a system, okay. Now this is what is call dynamic stereochemistry.

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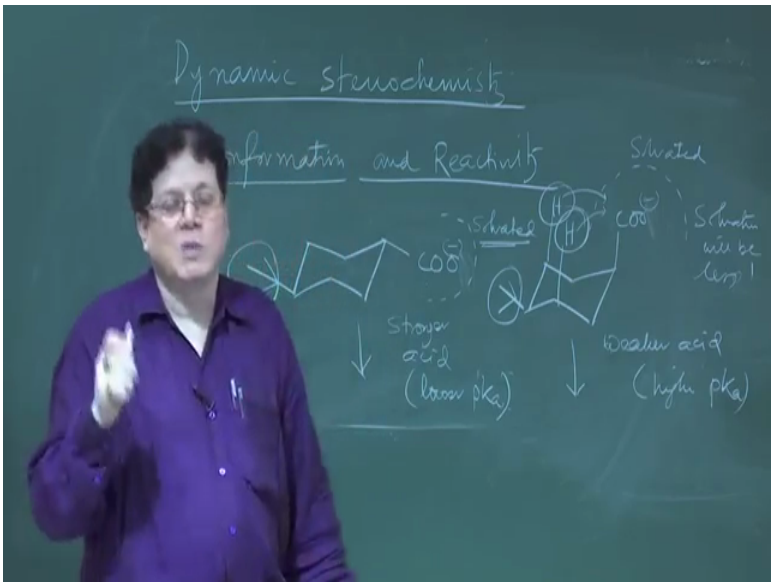

So now the topic is going to change, now dynamic, so what we have seen so far is static stereochemistry. So the molecules are just seen in isolations. There is no partner to react with we just check the energy and the different types of interactions that are present in the system. Now the next question is how these different types of interactions and different types of conformers are going to affect the reactivity of the system. So this is what is called dynamic stereochemistry. Dynamic means what is the, the other way to tell it as conformation and reactivity.

So now the reactivity that means the reactivity issue is brought in (())(7:43) that how does the different conformers affect the reactivity of a system, conformation and reactivity. Now this conformation and reactivity concept that actually conformation also dictates the reactivity was put forward by a British scientist very elaborately, his name was sir Direct Barton, he was that imperial college and he wrote a paper, in a journal call experiential that was very famous those times earlier. So he wrote the conformational analysis of conformational analysis verses reactivity of cyclic system, when there are different types of number when the number of cycles varied. So he studied the cyclohexane, the decalin and then even the bigger ones like steroids and (())(8:41), because they have similar kind of decalin systems okay. His name was Barton.

Now Barton before Barton, there was another professor from Norway. He first pointed out, so if Barton has elaborated the whole concept, that the whole things started with a person called odd Hassel. He was a (())(9:07) scientist and he was studying the pKa values of cyclohexane carboxylic acids, okay. Now cyclohexene carboxylic acids if you put a tersary butyl suppose I am not very shure whether this was a example, but the essence of his study is a can be described with the help of these molecules. So he was studying the pKa of cyclohexane carboxylic acids. He took one molecule where the carboxy is in the equatorial position and he took another molecule where the carboxy is in the axial position, but in order to lock the system, see you need a locking group, I already told you tersary butyl is a locking group. It prevents the molecule to flip. So there is no inter-conversion between actual carboxyl verses equatorial carboxy here (()) (10:02).

So he was trying to measure the pKa. Now interestingly what you observe is that the pKa of the two compounds are first of all not same. So this is very interesting that where the electronic effects obviously will be similar in the both the cases, the electronic effects will be the similar, because the connectivity is same. So and the (())(10:32) butyl group is far away. So its inductive effect electron donating effect cannot reach. This carbon even if it reaches the carbon, he reaches this carbon to the same extent like this molecule in this molecule also. So there is no electronic effect that can say that there will be a pKa difference, but he found a pKa difference and what he found is that this as, this is a stronger acid than this one. So this is a weaker acid.

So weaker acid means higher pKa. So this is a higher pKa and this is lower pKa, okay. So this is stronger acid. So that is the starting point of conformation and reactivity concept. So that means

the property of this molecule, the reactivity the reactivity as an acid of these molecules depend on the conformation, whether it is adapting an equatorial CO2H or an axial CO2H. This was studied by odd Hassel (())(11:40). So then he what was the explanation? The expalation was that the pKa is measured by the dissociation constant. So it dissociates into the carboxylate. Now the more the carboxylate you have that means more dissociation you have that means the acidity will increase, okay. Now this is the carboxylate in the equatorial position, this is the carboxylate in the axial position. Now you know that there is a huge role that is played by the solvent in stabilizing this anionic species (())(12:12), okay. This carboxylate, so this carboxylate will be solve (())(12:16) will be solve (())(12:18) will be stabilized by salvation and this will also be solvatent (())(12:24).

Now the problem is the solvation of this axial carboxy will be little bit hindered, because of the presence of these hydrogens, okay. So because of the presence of this hydrogen salvation will be less here that means salvation stabilization through salvation will be less here. This on the other hand the, because it is in the equatorial phase, so there is no such interaction can be consider ((())) (12:56), because there is no 1,3 diaxial interaction. So salvation will be more here that means stabilization to salvation will be more here, that means dissociation of the corresponding acid to the carboxylate that means the equatorial acid to the carboxylate will be more than the dissociation of the axial carboxylic acid to this carboxylic acid. So that is due to the problem of salvation in a axial carboxylate, because salvation means size increase and size increases means more or greater steric repulsion, okay.

So that is why this dissociates more that means the equatorial carboxy and that became the that has got the higher acidity that means small pKa. So that is the starting point of the whole story, but this is a thermodynamic a parameter that pKa. What about the what when the reactivity we say, this is kind of thermodynamic parameter pKa that is the acidity, but we have to also bring in the kinetic parameter, in order to in order to study the reactivity of these type of molecules which can exist in different conformations, okay.

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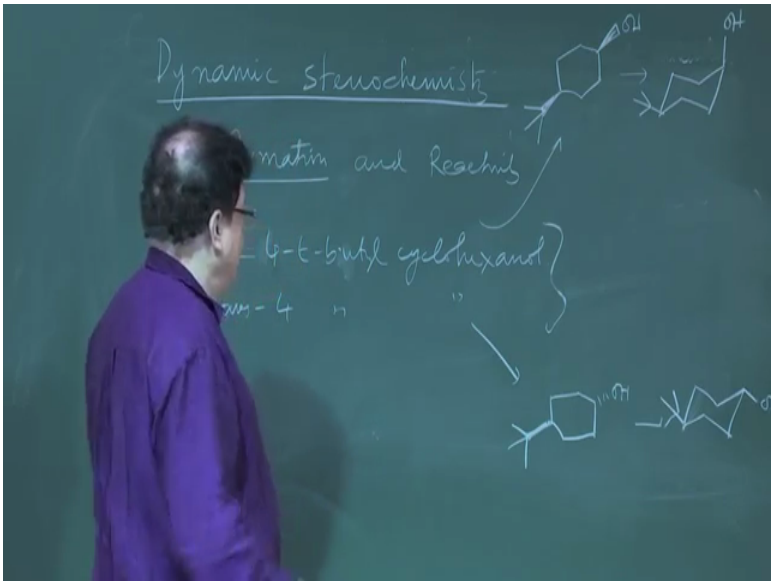

So before we will discuss some of the some of the issues that Barton had dealt with , one of them is conformation and reactivity, one example is, suppose I want to oxidize two compounds, one is Cis 4 tersary butyl cyclohexanol and the corresponding trans compound. The trans 4 tersary butyl cyclohexanol. If I want to, so what which one will oxidize, so oxidation profile that means which one will be oxidized more or at a faster rate. Now we are bringing in the kinetics, okay. At a faster rate than the other, okay. Now you know that this is an alcohol. Alcohols can be oxidized by chromic acid suppose, we are using chromic acid in fact Barton was studying the chromic acid oxidation of this Cis and trans 4 tersary butyls cyclohexanol, okay.

Now in order to arrive at a (())(15:25), so what we need to **to** do we have to first draw the molecules. So the so this is your Cis tersary butyl cyclohexanol and the trans one is, this is the alpha OH, okay. Now from the planar system you cannot actually arrive at a conclusion. So what we have to do? We have to draw the correct conformation at these systems. Now these are locked systems, okay. One good thing is that they are locked system. So there is no question of flexibility in this molecule. They are lock, because of the tersary butyl. So there will not be any inter-combustion between the equatorial OH or the axial OH, okay. So this Cis compound has an axial OH and the equatorial compound will then have an a this trans compound will have an equatorial wedge, okay. So these are two conformations.

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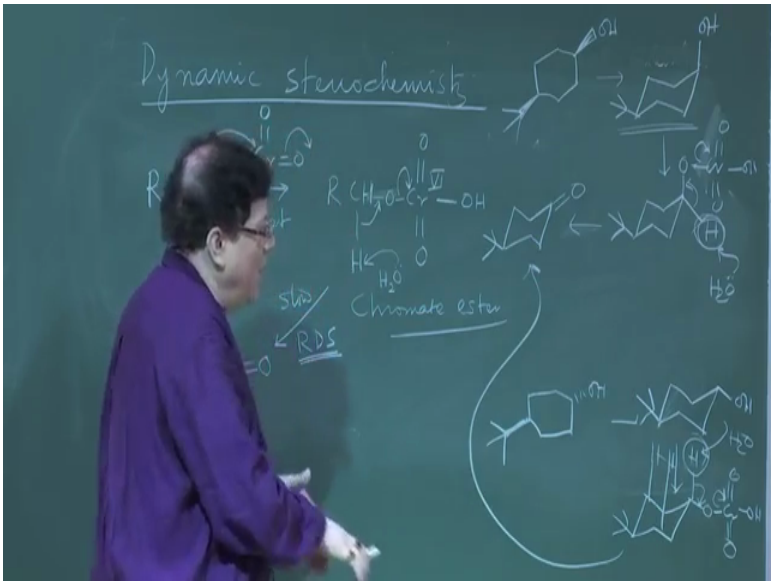

Now if we know that the chromic acid oxidation, or if you do not know let me tell you that the chromic acid oxidation actually takes place via formation of, so this is the chromic acid the anhydrite CrO3. So the first step is that wedge attacks the chromium and these goes to the, so this is in the plus 6 state sorry, okay. So first the OH attacks the chromium and it becomes RCH-Cr-OH, because it is done in sulphuric acid, so there will be lot of propene sources double bond O and double O, okay.

So then so this is what is call the, sorry this is O-CHO-Cr, so R-CH2O, this hydrogen will be lossed after the neuclofilic (())(17:30) attack O-Cr-OH and O-Cr double bond O-Cr. This is what is called chromato-ester. Why ester because this is the basically chromic acid and then alcohol, so that makes the chromate-ester. So the next step, so this is not the oxidation, remember chromium is still in the 6 oxidation level. So in the oxidation chromium will be reduced. So this is the first step and the second step is that a base, which is most likely to be the water that is present, little water that is present in the system, so it comes or it could be bysulphate also if there is sulphuric acid. So that comes and takes this hydrogens as a proton. This comes here and now the chromium is reduced and gets the two electrons on to its ((()))(18:22). So chromium gets 2 the 4 plus 4 state and then it can be and then it disproportionate into plus 3 and plus 6, okay but that is the more important issue is that there are, this gets oxidized, okay. There is a creation of a double bond O in the system. So this gets oxidized and the that means the rate of chromic acid oxidation now, it involves two steps.

Now which is the rate determining step that is the very important issue here, okay. Now what has been found that this is a very fast step and this is the slow step? So if this is the slow step that means the breakdown of the chromato-ester is the rate determining step. So breakdown of the chromate-ester is the rate determining step, okay. So this is on the side. So we know that first this will form a chromato-ester. So R- Cr double bond O , R-Cr double bond O-OH and then this H equatorial H has to be taken up by the base to form the cyclohexanone and in case of the axial OH, a equatorial OH, sorry that was we started with the axial OH, the axial chromato-ester. Decomposition of the axial chromato-ester and that will give to the tersary butyl cyclohexanone. These will also lead to a tersary butyl cyclohexanone, but via an equatorial chromato-ester O-Cr double bond O-OH and then double bond O and then this axial hydrogen has to be picked up by the base which is water here and this is the mechanism. So you have tersary butyl.

So that goes to the same compound. So final product is same. So now the question is which one will be oxidized at a faster rate. First it was first Barton gave an explanation, which relied on the abstraction of this equatorial hydrogen verses axial hydrogen. So he argued that the axial hydrogen will be more difficult to pick up because the water has to come I showed from this side, but you see there are axial hydrogens. So basically if the water approach of the water to abstract the hydrogen will be more difficult, because this phase is satirically hindered than the approach of water to abstract the hydrogen from the equatorial side that was Barons explanation. So he said, the equatorial the essence is that the axial hydroxy the axial hydroxy that means the Cis compound Cis 4 tersary butyl cyclohexanol should be oxidized faster at a faster rate, because it involves the abstraction of an equatorial hydrogen which is a more (())(21:47), okay.

And this is oxidized ta a slower rate, because it involves the abstraction of a hydrogen at the axial position; however later on, it was found we are not going into very big details, but later on it was found that these type of explanation was not correct, the actual explanation after studying several other compounds different substituted cyclohexanes (())(22:15).

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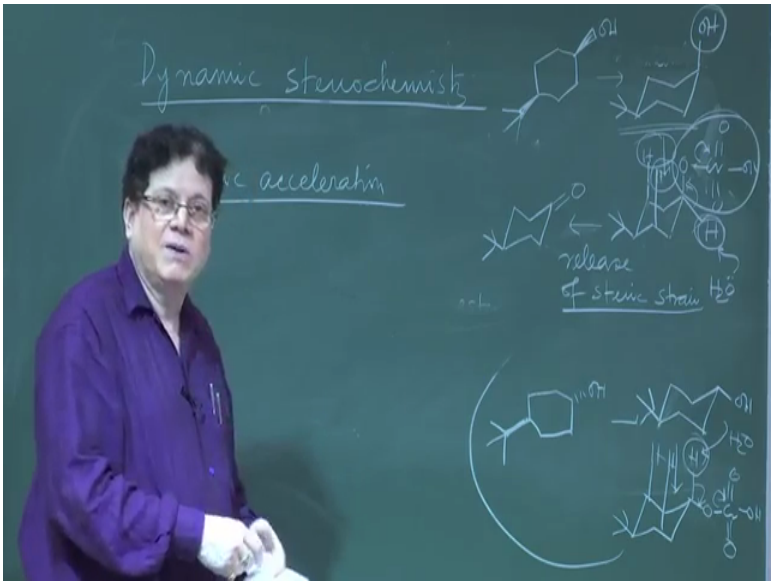

Another scientist he gave what is called an explanation based on what is called steric acceleration? I think you will be amaze to know this word, because I am shure so up till now what you are told that steric factor is always a very bad thing which slows down the reaction slows down the reaction, but this is an example where (())(22:44) is telling. He is (())(22:46) scientist. He said that the reason that this is oxidized at a faster rate is what is called steric acceleration that means here the rate determining step is the second step that means decomposition of the chromato-ester. Now the chromato-ester, this is very big, but axial group was earlier OH when it forms the chromato-ester, it becomes big and now it is suffering from enormous steric compression; however formation of the chromato-ester is not the rate determining step. If that was the rate determining step then this would have been slow, but this is a very fast step and so it is formed irrespective of whether if there is increase of steric compression or not.

Now the steric compression has increased, so now do decomposition, in the decomposition state that means decomposition is chromato-ester. Now the chromato-ester will decompose very rapidly in the axial chromato-ester, because there is release of enormous release of steric strain. So this is what is called he called as steric acceleration that means the steric factor or steric compression is accelerate in the next time that is the oxidation, okay, the loss of the hydrogen.

So it is note the that the hydrogen is more accessible. Now accessibility of the hydrogen is not the factor. It is the release of the steric strain which is much more in the axial compound, axial chromato-ester than in equatorial chromato-ester where it does not suffer from such type of strain. So this there is no steric strain release in this case. There may be some, but much much to the extent in the axial that is present in the axial isomer. So now this will be that is the reason due to steric acceleration, this equatorial this axial OH is oxidized at a faster rate, (())(24:47) okay.

There are again very similar examples where there is a difference. So I have given you a difference between the pKa of the carboxylic acid when they are in the axial and the equatorial positions. Next I have talked about the rate of oxidation of an axial alcohol, verses an axial a equatorial alcohol.

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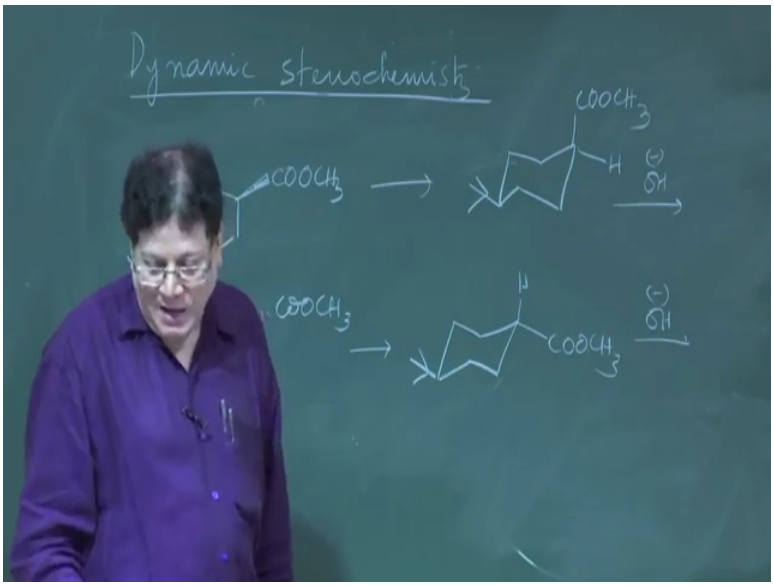

Now I will tell you the third example, which is the saponification of an ester molecule in a cyclohexane system. If the ester is in the axial position or in a equatorial position. So what is the rate? So again I take two compounds, the tersary butyl is always required, so that equilibration between the axial and the equatorial does not take place, because we are comparing the rates of the axial and the equatorial systems. So the whole thing will be will become complicated if there is equilibration between the two. So to stop that equilibration you have to put the tersary butyl group.

Now what we are talking about? The problem is that we are talking about the hydrolysis of a of an ester when it is in the axial group verses the hydrolysis of an ester when it is in the equatorial position, okay. Let see because I said equatorial, because I know that if I want to draw this into the perfect in the conformation in the puckered conformation. So this will be the equatorial and this will be the axial, okay. The question is which one will saponify Faster? The saponification means hydrolysis in a basic condition, okay. So if I hydrolyze it under a basic condition that means OH minus is the nucleophile (())(26:49), okay. So which one will hydrolyze at a faster rate? Now this is interesting, unlike the axial alcohol verses equatorial alcohol. Now it is the other way around. The equatorial acetate that the equatorial ester will be hydrolyzed faster as compared to the axial ester.

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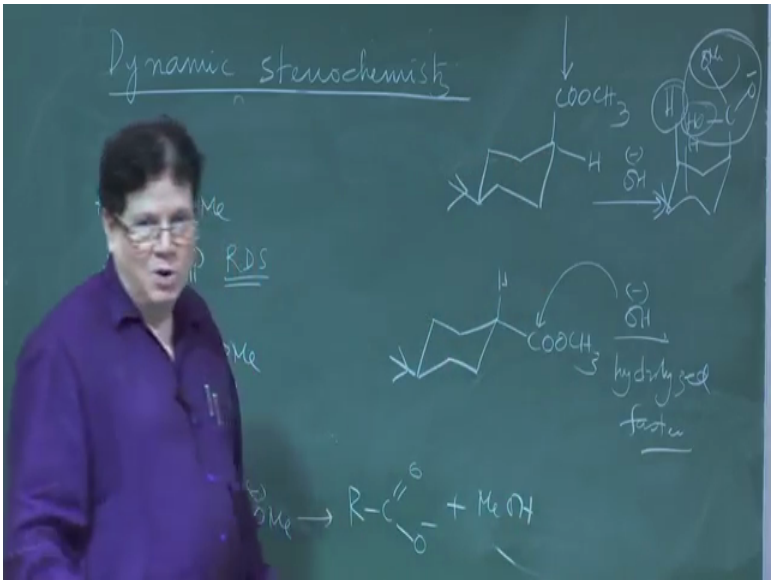

Now what is the reason here? The reason is that again the mechanism has to be brought in that what is the mechanism of saponification take a very general case R-C-O-O say OMe and if you add alkali (())(27:30), so the first step is this attack this goes back. So R-C-O minus then OH then OMe. So this is a tetra hydral intermediate and then so this is the first step and the second step is expulsion of this O-Me, so you get R-C double bond O-OH plus OMe minus and then there is mutual exchange of the hydrogen, because this is a stronger base and this is, so that we abstract the hydrogen from here and this is the weaker base. So it will be the carboxylate plus methanol. So that is the mechanism.

Now this is a very fast step. This is also very fast step. The rate determining step is the is this one to the attack by the OH minus. So this is the slow step that means this is the rate determining step. So what happens in the rate determine step that will guide the process. So when OH minus attacks I again remind you that is the rate determining step. So there will be increase of steric bulk in the axial (())(28:39), O minus OMe and then OH okay. Then there will be hydrogens. So there is this increase of steric strain I due to the OH minus attack and that is the first step that is the rate determining step. So this will be slower as compared to the attack by this OH minus into the carboxylate into this ester carbonyl, because there is even in the size increases, there is no increase of steric strain here, but there is increases of steric strain here. So this will be slow and that will be fast. So here interestingly the breakdown of this stator intermediate is not the rate determining step and that is why this whole result has gone just the reverse way.

Now the equatorial ester is hydrolyzed faster, because the step where the steric side increases that is the rate determining step. In chromato acid oxidation the step where the steric bulk reduces that becomes the rate determining step. So that is why we see different results in (())(29:56) all these systems. Thank you.