Course on Stereochemistry
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Mod06 Lecture 28

Conformational Analysis of Systems with Preferences for Axial Groups

Okay, welcome back to this course on stereochemistry and during the last few lectures we have been discussing the conformational analysis of cyclohexane systems, the mono-substituted, the di-substituted and then we went to a bicyclic systems that was the decalin system, okay.

today we will discuss conformational analysis of some special molecules. Why are they special, because they do not follow the rules that we have seen so far that is in a cyclohexane system, the groups always tend to prefer the equatorial orientation if it is available, sometimes there may be competition between groups, but it is the bulkier groups then we will occupy the equatorial position and, but there are certain molecules where these type of simplified concept may not hold, okay.

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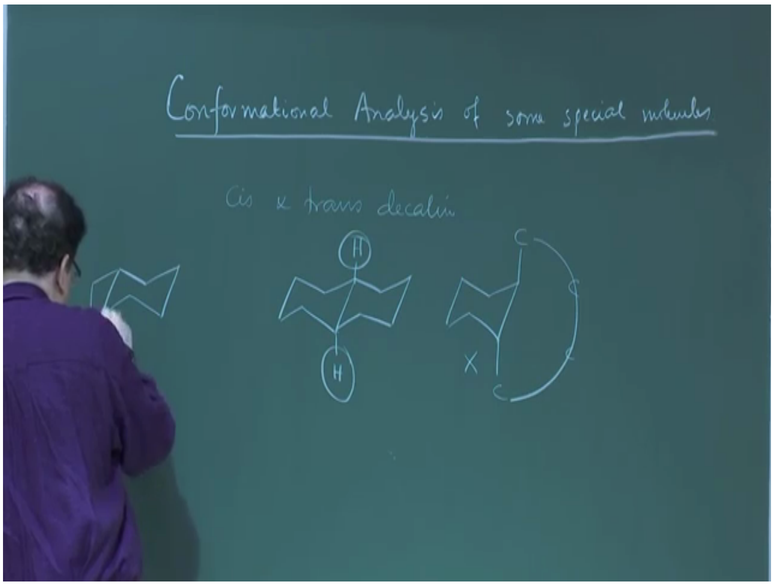

Now before going into the this some special molecules let us again just have a quick revise it of what we ended up a last time that is we were discussing the conformational analysis of Cis and trans decalin that is a bicyclic system and we have seen that the trans isomer is a rigid molecule, which cannot be flipped, because the hydrogens at the ring junction has to be they have to be always in the axial position with respect to both the rings, okay.

So they are axial and the ring bonds are equatorial. The reason for this rigidity is that if you want to flip then it will not be possible the hydrogens will occupy the equatorial positions and it is not possible to make a cyclohexane out of 2 axial carbons, okay. So it is not possible to connect these two carbons with only two carbons in hand, okay that is why flipping is not allowed whereas in the Cis decalin system, you have flexibility and so it can flip from this form to another form, which was the we have shown like Cis 1,2-dimethyl cyclohexane that will be the mirror image of this form and so that makes it a non-resolvable dl-pair, we have also seen the energy difference between the two.

There are three additional gauche between interactions in this system, so that making it unstable by an amount of 2.7 kilo calorie per mol. So that is all about the bicyclic system. If we find time later on we can work out some problems on the bicyclic involving the conformations of bicyclic cyclohexane like decalin, okay.

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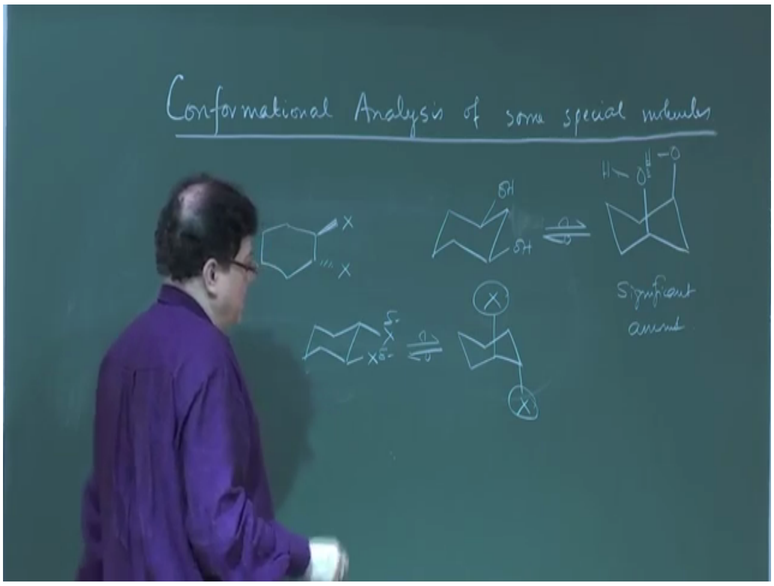

Now let us consider systems where the groups occupy not to equatorial preferred equatorial position, but we will go to the axial position, because of some other factors okay. One example I have given to you and that was that if you have this molecule a Cis 1,2-diol Cis 1,3-diol diol that is Cis cyclohexane 1,3-dol. Now this the expected conformer is this one, if you want to maintain the beta orientation then it should be placed here and the other one should be placed here, okay. So this is the expected preferred conformation, but what happens, because of the presence of possibility of intra-molecular hydrogen bond. So this molecule flips and the (()(4:49) now will be in the axial position, okay. So one O-H (())(4:54) here and the other O-h (())(4:57) will be here.

So now you see there is hydrogen bond between this hydrogen and the oxygen or the other way around (())(5:05). So this is now significant present in significant amount. Another system I told last time, I think I so far as I remember, it has been told that if you have 1,2-dihalo compounds then also 1,2-dihalo compounds then due to dipole-dipole repulsion in the trans compound, the preferred conformation if it is methyl, if x is methyl, this will be the preferred conformation, but if x is halogen then, because of the repulsion between these two delta negatively charged x. So it will now tend to flip and we will represent in substantial amount in this form. Okay where the 2xx are far apart.

So these are examples where the groups occupy significantly or the conformation where the groups are in the axial position are present in significant amount and there are certain other driving force, earlier we have seen only the steric and the torsional strain. Now we are bringing in some other parameters like intra-molecular hydrogen bond or dipole–dipole repulsion that stabilizes or that dis-stabilizes the sometimes dis-stabilizes the di-equatorial system, sometimes stabilizes the diaxial system, okay.

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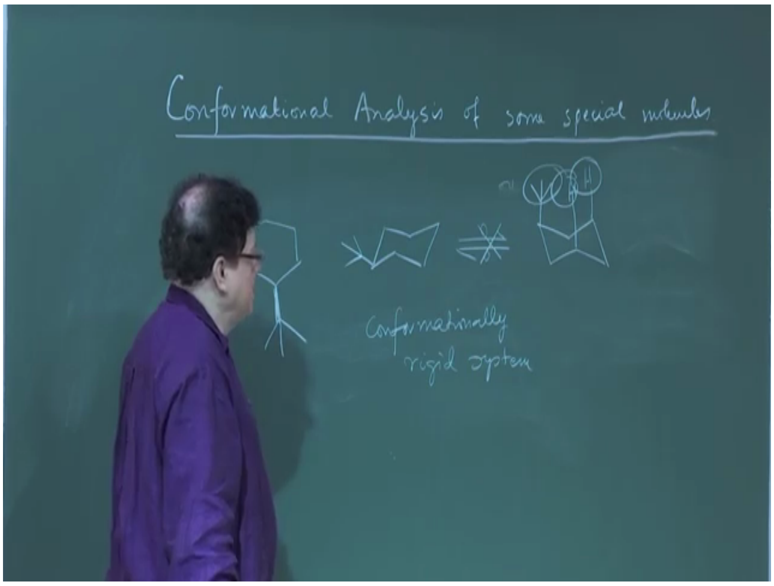

Now these are some of the examples. There other examples like suppose I have a tersary butyl group which is which we know that it is a very bulky group, a tersary butyl cyclohexane. Now we know that in tersary butyl cyclohexane the only possible conformer is this, because it is the big group tersary butyl and it will occupy the equatorial position. Now this system is also regarded as a conformationally rigid system. Why, because if you want to flip it what is conformationally rigid where flipping is not possible, okay.

So if you want to flip it, the problem is that this will now occupy an axial orientation which is not possible, because of enormous steric interaction with this 1,3-diaxail hydrogens. So this is not permissible in case of tersary butyl cyclohexane. So this is a nice way to lock the conformation of a cyclohexane in the chair form, okay.

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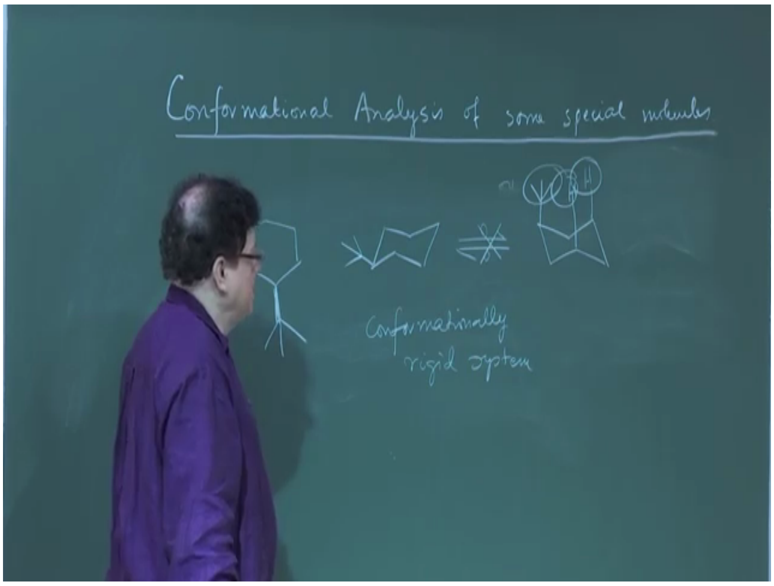

Now, suppose I have di-tersary butyl, now instead of 1 tersary butyl of I have a di-tersary butyl 1,4 system like this and this is the trans form, okay. This is the Trans di-tersary butyl cyclohexane. So this is beta that is alpha. So what will happen now? This there is no problem here, because both the tersary butyl group can occupy the equatorial positions, because this is beta that is this one and this is alpha that is this one. So that is the most stable and this is also conformationally locked system, but if I change this into also the Cis form, so suppose I consider the conformation of the Cis form then the problem is I have no other choice, but to put one of the ternary butyl in the axial position, okay.

So both are beta so one is 1, 4 beta means 1 is equatorial and other axial. So that is not now that problem is I said that you cannot put a tersary butyl in the axil position, because of enormous 1, 3-diaxil interaction. So this will not stay in this chair form. So this is one of the few examples where it will be present not in the boat form, but in the twist you know that twist boat form is another conformation available, another conformer available for the system and so for we have not consider the twist boat, because most of the molecules that we have (())(9:46) remain in the chair form.

Now this is a molecule where because of their steric dis-position, because they are Cis and, because you are forced to put 1 tersary butyl in the axial position. If you adopt a cyclohexane chair then it prefers not to do that and rather have a twist boat conformation where, both the di-tersary butyl groups occupy the equatorial position at the flagpole carbon. So remember these are the flagpole carbons, these are the flagpole hydrogens, we know that in the boat form or in the twist boat form there is this eclipsing interactions between these between these carbons and these carbons, because this is the if you look through these carbons you see that these are, these carbon is eclipsing, this carbon-carbon bonds. This carbon-carbon bond is eclipsing this one and this carbon-carbon bond is eclipsing that one.

So because of the eclipsing interaction, the boat or the twist boat is less stable than the chair form, but here that in stability is overcome by the instability of the 1, 3-diaxil interaction involving tersary butyl. So this prefers the twist boat conformation. This is Cis (())(11:16) if you want to correctly draw this then you have to do the inverted means in order to make the beta, because the way I have drawn it is alpha now, but actually this molecule birth are beta. So better put this is the correct diagram, both are same because they are they are symmetric. They have a plane of symmetry passing through the 1 and 4 carbon atom. So it does not matter whether you write this or (())(11:43), but since you have both we have put both the tersary butyl in the beta position, so I **I** can draw it in this fashion also, remember these two occupying the equatorial position, leaving the flag pole hydrogens in (())(11:57). So this is a molecule where boat form is boat form is the (())(12:04)one, okay.

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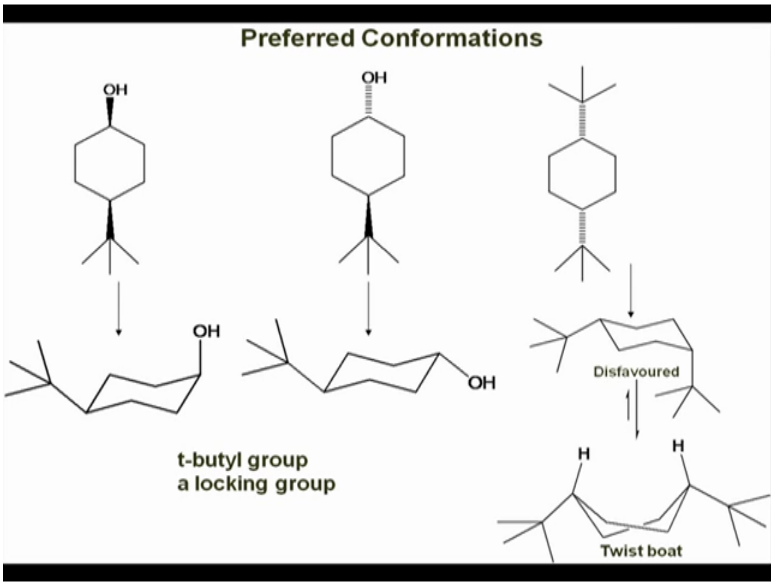

Preferred Conformations

t-butyl group
a locking group

So I think I have some examples where a conformationally rigid systems like here is an example of, if I want to draw the conformation of tersary butyl cyclohexanol 4 tersary butyl (())(12:25) will be 4 tersary butyl cyclohexanol, this is a number one carbon. Now this is Cis compound, so you have to put te first you draw the chair form, the way to do it is first you draw the chair form and then put the tersary butyl in the equatorial position and beta. So that is one of the position you can select, you can select other position, but this is the common practice that you put the tersary butyl at this end.

So it makes it beta as well as equatorial (())(12:53). Now this is your number 1 carbon, so you are now force to put the hydroxyl to make it beta, you are force to put it in the axial position, okay. So this is how to draw the conformation of this and then if you want to draw the conformation of the trans one what you need to do is the just put the (())(13:13) in a equatorial that is the outside (())(13:15) okay.

This is the example I was talking about if you have di-tersary butyl 1,4-di-tersary butyl cyclohexane, then you are forced to put one of the tersary butyl groups in the axial position. So instead it adopts, this is the other way to **to** draw the twist boat conformation, I think this is a better way of drawing it , but this is also perfectly okay if you write twist boat, okay and these two di-equatorial a di-tersary butyl substituents are in the equatorial position, I said is in the flagpole hydrogens (())(13:56).

Now remember why twist boat is a conformer and not the boat, this is because in the twist boat this hydrogens are not that closed unlike in the boat form. So the boat strikely to state, so that the flagpole hydrogens a interaction is little bit less okay.

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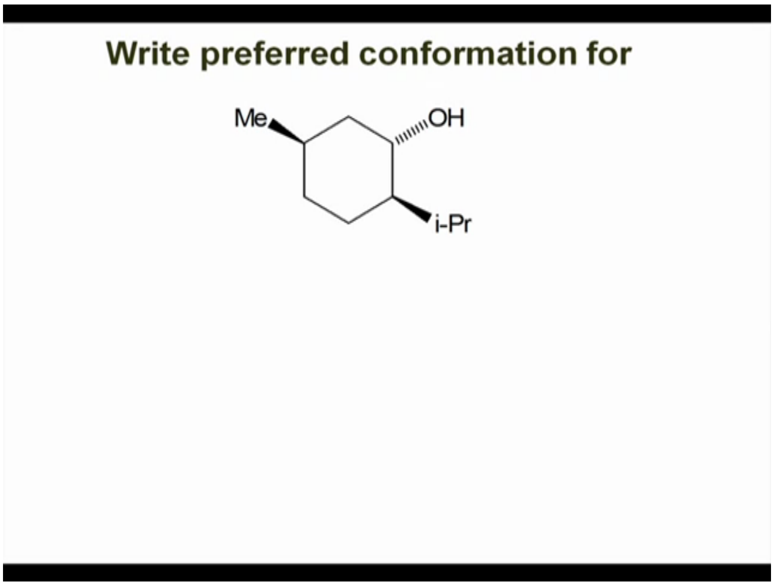
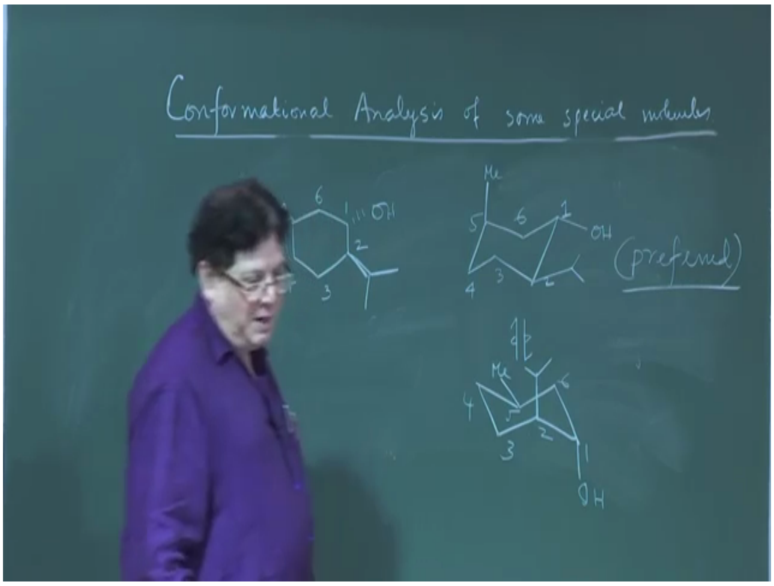
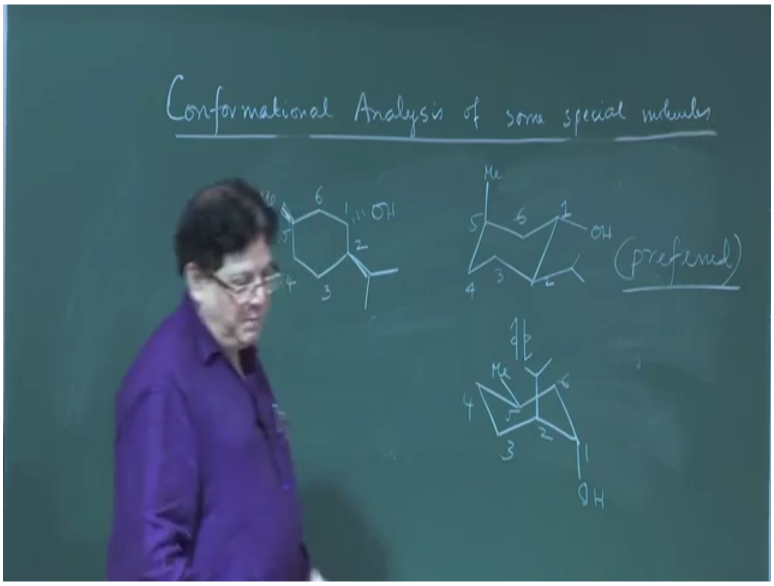
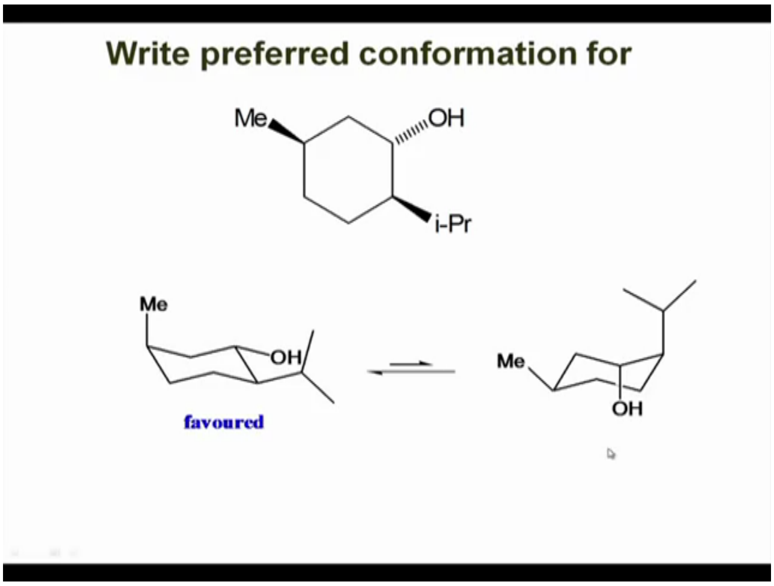


Write preferred conformation for

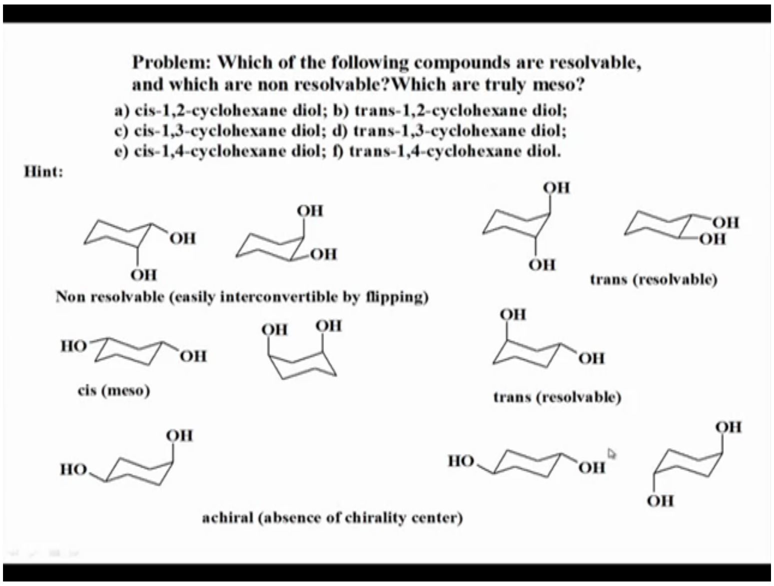




Conformational Analysis of some special molecules



Write preferred conformation for



Problem: Which of the following compounds are resolvable, and which are non resolvable?Which are truly meso?

a) cis-1,2-cyclohexane diol; b) trans-1,2-cyclohexane diol;
c) cis-1,3-cyclohexane diol; d) trans-1,3-cyclohexane diol;
e) cis-1,4-cyclohexane diol; f) trans-1,4-cyclohexane diol.

Hint:

Non resolvable (easily interconvertible by flipping)

trans (resolvable)

cis (meso)

trans (resolvable)

achiral (absence of chirality center)

There are other molecules I can show you. So this is the locking group write the preferred conformation. So there is a problem of this molecule. This is a also called neomenthol, okay. Neomenthol, but the name is not that important, let us do this problem, okay. The problem is that how to draw the preferred conformation of this molecule, okay, again I look at the molecule. So this is methyl beta then you have a hydroxy alpha and you have a isopropyl you have a isopropyl at the beta position, okay. So suppose this is 1, this is 2, this is 3, this is 4, this is 5 carbon, this is 6. So now to draw the conformation of this you draw the chair form, okay you put the if you **you** put the groups, suppose this is 1, this is 2, 3, 4, 5 and 6. So look at the one carbon, so there is a hydroxyl and that is alpha. So the hydroxy now has to be alpha equatorial, at the 2 position there is this isopropyl which is in the beta orientation, okay.

So this is also equatorial and now at the 5 position you have a methyl which is beta. So you have another option that you put the methyl group at the axial position okay. So this is one of the conformations. Now if you flip it you always try to write the flipped form and if you flip it, so it will undergo a mirror, it will undergo this type of chair. So it will be converted to this type of chair which is the mirror image chair and then you have to be careful put the number where the carbons ended up after flipping this is 1, there this 2, that is 3, that is 4,5, and 6.

Now at one OH is alpha equatorial, now it is alpha axial, (())(16:14) it is beta isopropyl, (()) (16:20) beta equatorial. Now it is beta axial and the methyl will be beta equatorial. So you can see that you can from the or looking at this two conformations carefully you can tell, which one is more preferred, because this contains, this bulk here isopropyl in the equatorial position as compared to the methyl that is number 1 and this also puts the OH in the equatorial position.

In this conformation the bulkier group is in the axial position and OH is also in axial position. So this will be the preferred conformation, okay. this will be in (())(17:10). So there are molecules where the methyl takes up the axial position and the reason I brought this is a this will also is a practice session that how to draw the draw the conformation of a particular system. So this is the slide that represent the favored one is this and the unfavored one is the one where the isopropyl is in the axial position, more over here the OH is also in axial position. So you have a double benefit here. This is equatorial and the OH is also equatorial.

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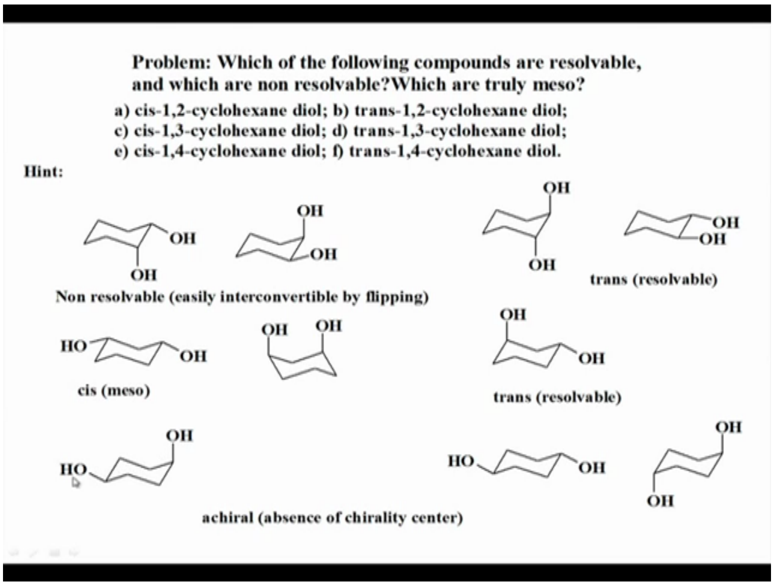

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Hint:

Non resolvable (easily interconvertible by flipping)

trans (resolvable)

cis (meso)

trans (resolvable)

achiral (absence of chirality center)

Now this examples, I think we have already worked out some of these some of these problems that Cis 1,2 cyclohexane diol then trans 1,2-cyclohexcane diol, so if you are ask to draw the preferred conformation and which one is reversible a resolvable and which one non-resolvable which one is truly a meso compound, which ones are optically active. So what you have to do? You have to draw the conformation; this is like the very similar to your 1, 2-dimethyl system. So they will exist in this two forms, but interestingly this is the mirror image of the other one and the relationship is that they are easily convertible by flipping.

So they are non-resolvable, they remain as non-resolvable dl-pair, just like here Cis compound. This is the trans compound that trans (())(18:44) obviously this one is the is the major conformer, because both the hydroxyl groups are in the equatorial position and **and** there is a possibility of hydrogen bond of course between this oxygen and the hydrogen on this oxygen and this hydrogen.

So this is the trans compound. It is a optically active compound. Here the mirror image is non-super imposable with this at the origin. So they are resolvable and if you take the trans compound the trans 1,3 system as, I told you in trans 1,3, this has got (())(19:18) considerable amount, this also exist where the both the hydroxyl are in the diaxial position, because of eth intra-molecular hydrogen bonds that also exist significant proportion and this is the 1,4 system ,4 system you can have to either the trans or the Cis obviously in the trans will be more stable, because the OHs are both in the di-equatorial position and this one is the flip form of this, but because of the two hydroxy gropes are axial, so that is not the fevered one

(())(19:55) this is the favored one and here only one option (())(19:58), so you have a one axial one equatorial even if you flip this.

Now this will become equatorial and that will become axial, but these two will be identical. Now how can I very quickly say that they are identical, because there is a mirror plane passing through C1 and C4 and containing this oxygen (())(20:16), okay. So a vertical plane of symmetry is there passing through 1 and 4. So you cannot generate a non-identical molecule by having the mirror image. So mirror image has to be same, as this one and the flipped form will be the same as this one, because one is axial and one is equatorial. So in the flipped form the same relationship is there, okay.

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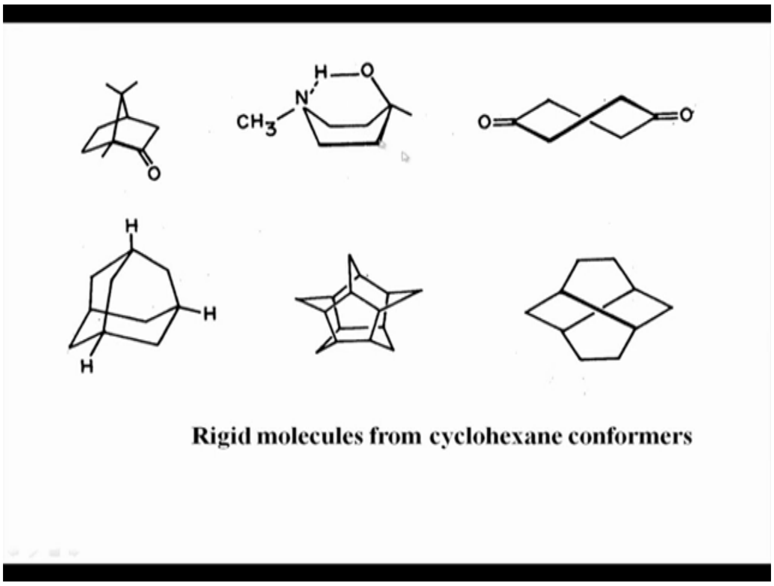

Rigid molecules from cyclohexane conformers

So this is now there are certain other molecules which are special importance like which remain in the boat form like this molecule. This is call the adamentaon (())(20:54) molecule in (())(20:57) okay. This is of course in the , these are all in chair conformation and this is the special attraction where because of intra-molecular hydrogen bonding. This is a nitrogen substituted compound that means this is call (())(21:13) if you reduce (())(21:14) in, you have the 6 numbered ring with the nitrogen in the present in the as a **as a** ring atom and then if you have a OH at the 4 position. So then because of this intra-molecular hydrogen bonding it exist in the boat conformation, okay. It exists in the, so you can say a boat or the twist boat conformation to be correct, okay. It exists in the twist boat conformation.

So there are rigid molecules I have just for example, I have shown certain rigid molecules. These are these are all locked in their conformation, okay. They cannot do any moment (())

(21:55) okay, because the one try to once they try to move around or rotate around bonds, the bonds started breaking up, okay. So rigid molecules (())(22:07).

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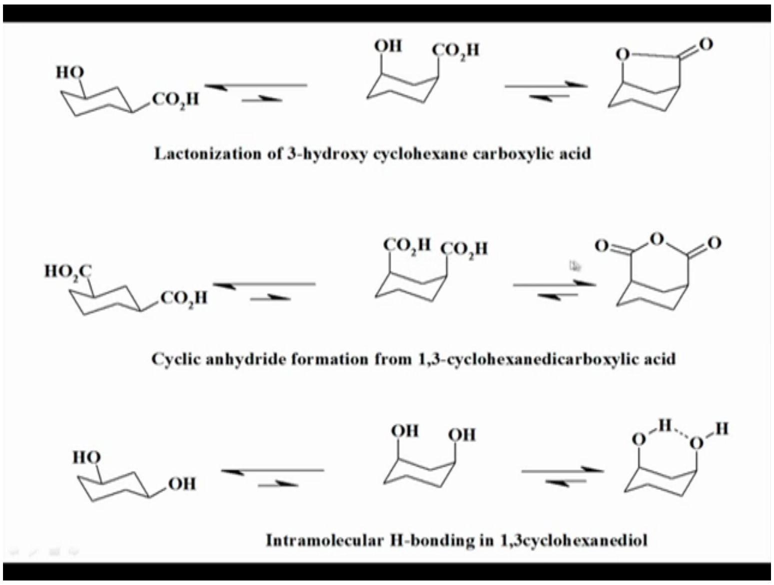

Lactonization of 3-hydroxy cyclohexane carboxylic acid

Cyclic anhydride formation from 1,3-cyclohexanedicarboxylic acid

Intramolecular H-bonding in 1,3cyclohexanediol

This also I have this molecule exist in this di-equatorial form. This is a compound cyclohexane carboxylic acid with the 3 hydroxy grouped and if you want to do the lactonization between the OH and the CO2H remember, this lactone means intra-molecular esterification if you try to do then this molecule has no other choice, but to flip into the axial formation and we will form this lactone, okay.

So I think I gave you told you about this that if you one to form an anhydride out of a Cis 1,3-cyclohexane dicarboxylic acid then what happens? If you want to make try to make the anhydrate which has to the only option, this has is to flip into the diaxial position diaxial flipped into the form where the dicarboxylate carboxylic groups are in the axial position and then they can form the (())(23:03), okay and this I have already shown that this is present at the intra-molecular hydrogen bond, okay.

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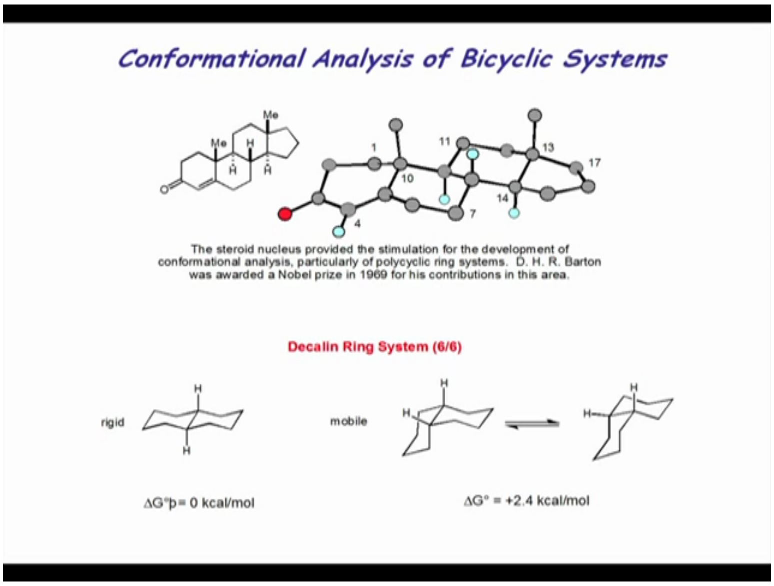


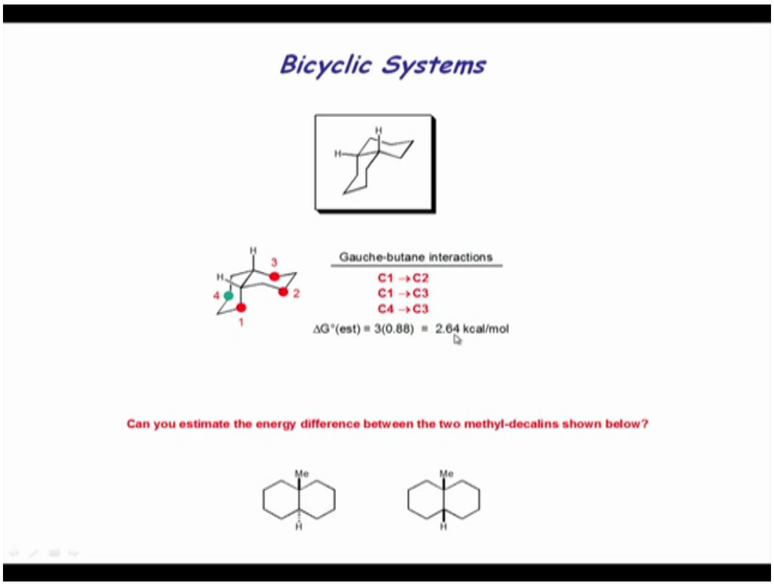
Conformational Analysis of Bicyclic Systems

The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)

$\Delta G°_{p} = 0$ kcal/mol

$\Delta G° = +2.4$ kcal/mol



Bicyclic Systems

Gauche-butane interactions

C1 → C2
C1 → C3
C4 → C3

$\Delta G°(est) = 3(0.88) = 2.64$ kcal/mol

Can you estimate the energy difference between the two methyl-decalins shown below?

I think we have done on this conformational bicyclic systems we could have gone very far, because there are we can have 2 rings, 3 rings, 4 rings, but that makes a complicated and as beginners I think we should stop at the decalin stage and that exactly what I need. The decalin have a quick (())(23:31) up, but there are this extra 3 gauche butane interactions that are present in the Cis form and thus the energy difference between this 2 is to 0.7. Here it is around 2.64, but actually if you take it 0.9 then that will be 2.7 kilo calorie per mol, okay.

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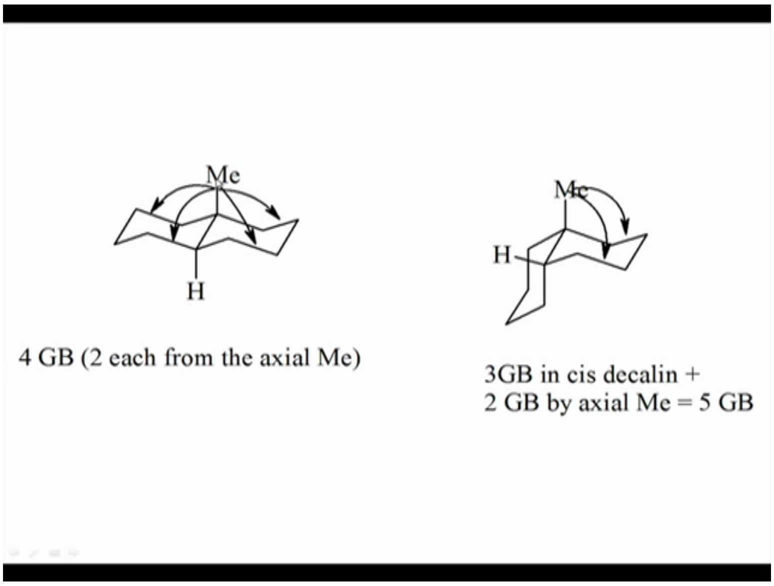

4 GB (2 each from the axial Me)

3GB in cis decalin +
2 GB by axial Me = 5 GB

If you have put a methyl at the ring junction. This is the trans compound and you can as a practice you can calculate how much energy it has over two cyclohexane chair forms, because this is axial to both the rings. So it will 1 axial methyl introduces 2 gauche butane interactions. So this will be one this methyl will definitely put, because of these are up to chair forms and with respect to both the chair forms. This is axial, so it will produce 4 gauche butane interactions and here, in the Cis form, this is the this is axial to 1 of the ring that is this ring, but it is equatorial considering the other. So it will have , because it is a Cis form, first of all, it has got this 3 gauche butane interactions that is present in inbuilt in the Cis decalin plus due to this methyl at the axial position with respect to this ring, the right hand ring. So it has got 2 extra gauche butane interactions. So it has got 5 gauche butane interactions.

So now the energy difference between this trans and the Cis, in case of a methyl at the ring junction of a decalin system that you see a has come down, earlier it was 2.7. Now it is only 0.9 kilo calorie per mol, okay.

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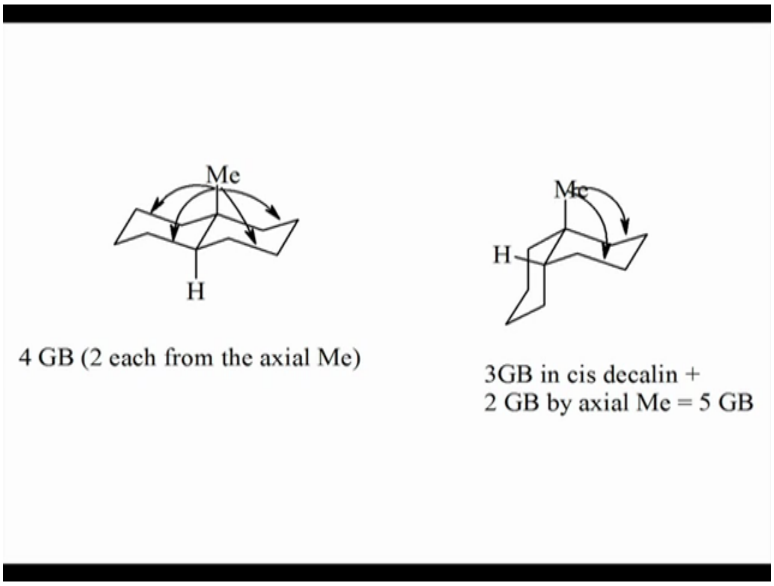
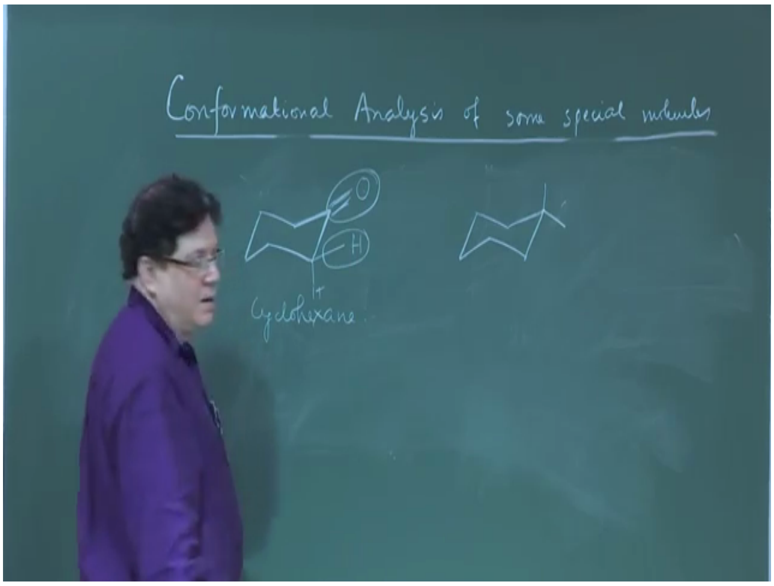


4 GB (2 each from the axial Me)

3GB in cis decalin +
2 GB by axial Me = 5 GB



Now let us, so for we have actually other, sorry before you go into the other things let us still stick to the conformation of certain other molecules where there is a axial groups is **is** present in the in-significant amount, one is one more example I gave you some example, see if you put a cyclo if you take a cyclohexane and then put a carbonyl at the ring. So it is a cyclohexanone, okay. Now this system is quiet interesting. In cyclohexanone what happens there is a flattening in figure these carbons and the carbonyl are in a plane now. In case of cyclohexane if I write the cyclohexane, so these bonds are not in plane with these two bonds, but here now, because of existence of a pi bond. So these pi bonds, this oxygen this carbon and this carbon they are in the same plane and as result of that what happens? This equatorial hydrogen is almost eclipsing this carbonyl.

So they are almost eclipsing this carbonyl, I can show you in the model, I can show you in the model that if you put a carbonyl in a cyclohexane. So this is the system, so this is the carbonyl, this is the carbonyl carbon you can see that this is these carbon-carbon bond this carbon-carbon bond and the carbonyl they are in the same plane.

Now what happens this carbonyl is almost eclipsing the CH equatorial in the adjacent carbon and same is 2 on the other side. So if it is the number one carbon 2, carbon, 3,4,5,6. So it is the two equatorial hydrogens and the 6 equatorial hydrogen they are eclipsing this carbon atom. Now what is the consequence of this? The consequence of this is that if you now put a groups name, if it is not hydrogen rather and alkyl rather and alkyl group quite be little (()) (27:37) and alkyl group much bigger than hydrogen. So what happens now? These alkyl groups and the carbonyl will suffer from the eclipsing interactions, okay. So as a result if it flips, now the group goes to the axial positions and there is no longer the eclipsing interaction.

Now the eclipsing interaction with the hydrogen, not with this alkyl group, okay. So the eclipsing interaction reduces as a result there will be significant proportion of the alkyl group in the axial conformer, okay.

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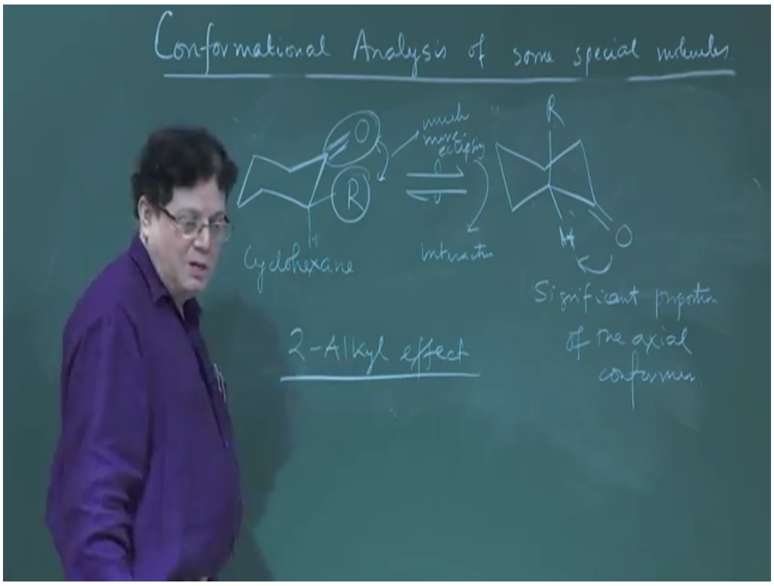

So what I am saying that if you have instead of hydrogen now if you have an alkyl group here if you have an alkyl group. So now there will be eclipsing interaction between these two, as a result of which the percentage of as a result of which it flips and the R goes to the axial position and this is the hydrogen. This hydrogen is eclipsing note out, but because of the size of the hydrogen this much smaller. So this eclipsing interaction is less. So this is much more eclipsing interaction, okay.

So as a result what happens? There will be significant proportion of this conformation, which was not expected in a cyclohexane system significant proportion of the axial conformer, okay. Now this is what is called 2 alkyl ketone effects. So what is 2 alkyl ketone effects? It is the it is because of the eclipsing of the substituent at the 2 position and the carbonyl. The substituent now prefers to adopt an axial orientation and this is what is called the 2 alkyl ketone effect.

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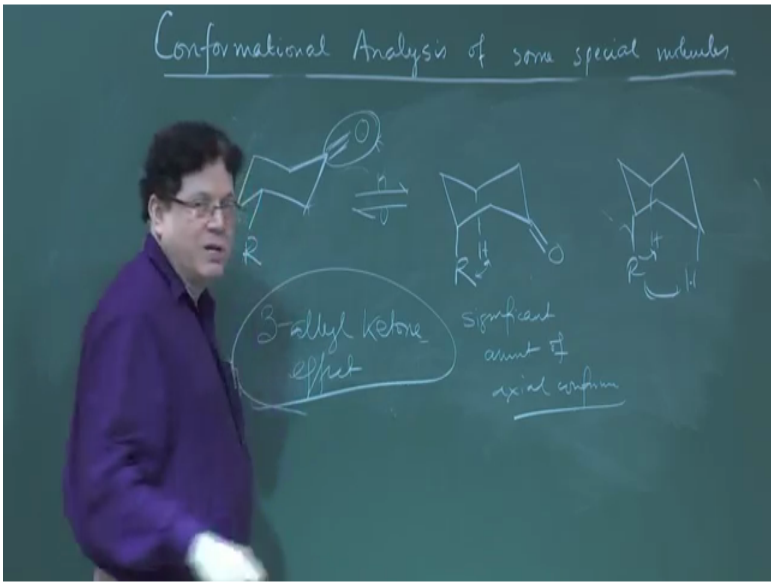

Similarly there is a like 2 alkyl ketone effect we have 3 alkyl ketone effect also. Now what is that 3 alkyl ketone effect is that if you have that alkyl group now in the 3 position and now if you inva to do the flipping. So what happens? The alkyl group, now occupies the axial position note out this is the carbonyl, but you see that now, in case of cyclohexane what happens? An axial group suffers from two 1, 3-daxial interactions this under, but 1, 3-diaxail interaction it now is no longer there, because there is no hydrogen here. This is carbonyl which is pointing towards this direction. So one of the, so now it suffers only one diaxial interaction. So as a result there will be significant amount of axial conformer at the 3 (()) (31:02) when the substituent is placed at the 3 position. This is what is called 3 alkyl ketone effect, okay. So these are very basically very same that, because due to these effects 2 alkyl or 3 alkyl, the alkyl group prefers significantly to adopt the axial orientation, okay and this is a this is applicable at the two position, also at the 4 at the 3 position and there is something which is call 4 alkyl ketone effect that is also there we are not discussing right now, we are just taking to 2 and 3 alkyl ketone effect, but remember there is a 4 alkyl ketone effect also, where it has been seen that the axial orientation (())(31:49) also gets little bit favored as compared to a cyclohexane systems.

So remember I am not saying that the axial conformer is the major conformer what I am saying compared to a cyclohexane system, the axial conformer is much more (())(32:05), okay. That is what is call effect (())(32:08) okay. Thank you.