Introductory Organic Chemistry
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Lecture - 09
Conformational Analysis of Cyclohexane_Part – 2

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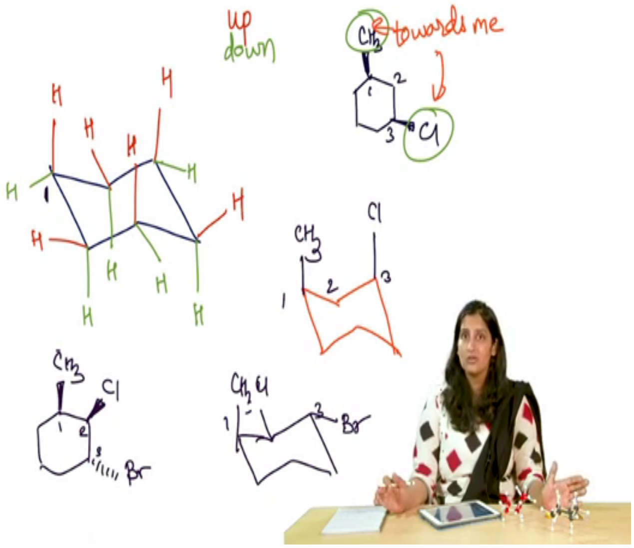

Now, these two chairs that I have drawn here are not the most stable representation of this particular chair conformer. In fact, the chair flip could be more stable and we are going to look at that now. So, how do I convert one chair to its chair flip?

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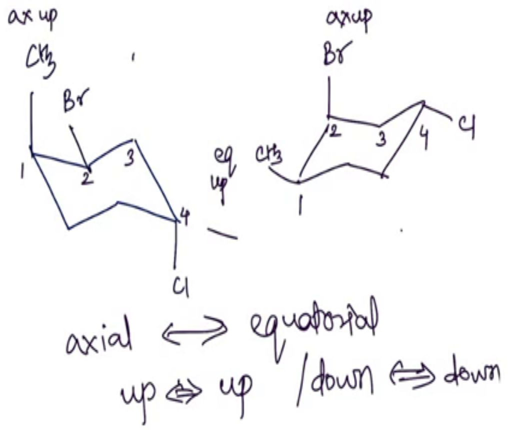

Okay, so now what I have here is this particular chair and I want to convert it to its chair flip, okay. So, I have drawn the chair flip such that I have drawn the mirror image of that chair and remember this is carbon number 1, 2, 3 and 4. So, I have substituents on carbon number 1, 2 and 4 and as the chair flips, the head becomes the leg and the leg becomes the head; we have gone over that. And we also saw that as the chair flips, the axial becomes equatorial and equatorial becomes the axial.

So, methyl here is axial up and as it flips, it is going to go equatorial up. So, this is axial up and the methyl will be equatorial up in the other chair. Remember that I started numbering in the clockwise direction on the first chair. So, I will also number in the clockwise direction in the other chair.

Now, on carbon number 2, you have a bromine that is going equatorial up, okay. Now up should remain up and equatorial should become axial. So, on carbon number 2, you have this bromine going up okay. So, this is axial up. On carbon number 4, you have an axial down. So, as this chair interconverts and the leg becomes the head, the axial down chlorine will become equatorial down chlorine, okay. So, as the chair interconverts, you have axial going on equatorial; the axial interconverts between equatorial, but up will remain up and down will remain down. So, that is something you always want to remember.

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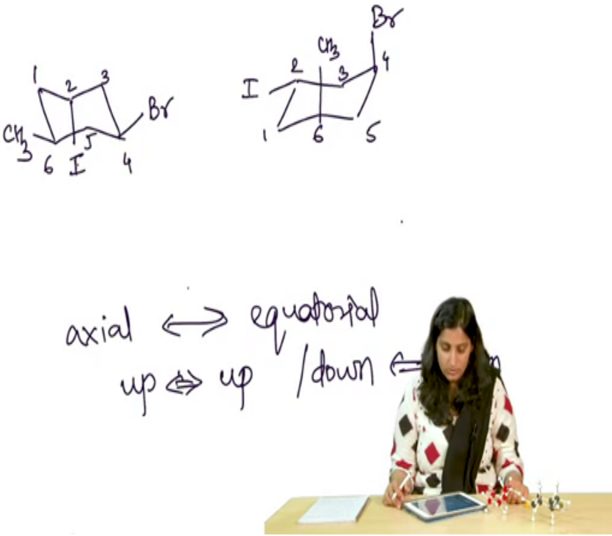

So, let us do one more example, going to draw a chair; on this chair I am going to draw the following groups. So, this is the chair that I have and if I want to draw a chair flip, what I am going to do is first I draw the mirror image of the chair. So, I draw the skeleton. Now again start numbering such that you keep it consistent. I like to start numbering from the head carbon. So, this is 1, 2, 3, 4, 5, 6, but remember you can start numbering from any carbon. The trick is to just be consistent and in the same direction go on numbering; otherwise you can really start from any carbon, it does not matter. This is 1, 2, 3, 4, 5, 6 on the same chair flip.

Now, the sixth carbon is going equatorial up, right. So, on the chair flip as the carbon flips, the equatorial up position will become axial up. So, on the sixth carbon I am going to draw this axial up. On the second carbon, the iodine is going axial down, right. So, on the second carbon here, it is going to go equatorial down. Carbon number 4 which is bromine is going equatorial up; so, in this case it is going to go axial up, okay. So, as you can see as the chair interconverts, axial interconverts to equatorial and equatorial interconverts to axial, but up still remains up and down still remains down, okay.

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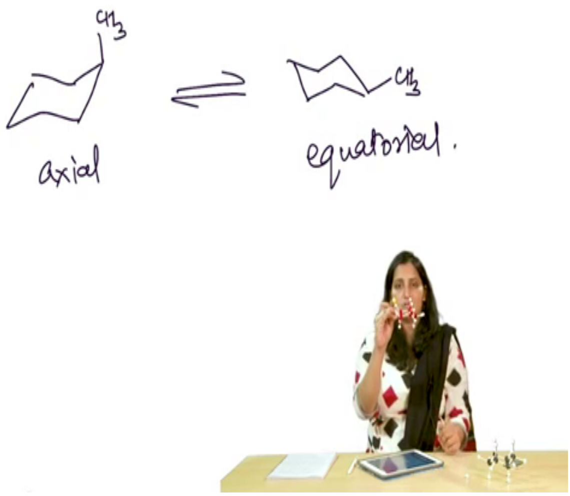

So, now let us again look at the cyclohexane chair and imagine that there is a substituent something other than hydrogen is present here. I want to debate whether this particular substituent is stable such that it is in the equatorial position or as the chair flips, it becomes more stable in the axial position, okay. So, as you can see as the chair interconverts, I am going to change the position from equatorial to axial right and I do not know which one amongst these is more stabilizing for the molecule in the sense, which one is more an energy that will be unstable, right.

So, what we are going to do is we are going to start with methyl cyclohexane and we are going to see whether it is more or less stable when it is in the axial versus equatorial position. So, I have a methyl cyclohexane, I am going to put it in the axial opposition here. As the chair interconverts, it goes from one form to the other; going to go from axial to equatorial.

One of the things to notice, such that, when it is in this axial position, it is sharing the same space as that of these two hydrogens, right. So, what happens is that it has to accommodate itself in this particular space. So, if the group is really bulky; so, we are talking about methyl now, but if we really imagine a very bulky group like a tertiary butyl group for example, what is going to happen is that it is going to have a clash for space with these two hydrogens here.

On the other hand, as I move this to the equatorial position, see that it is not occupying; all of these other bonds are going in different orientations and they are not in pointing in the same orientation as out of this particular group. So, this group has much more space in the three dimensional view of this particular molecule. This particular group has, is much better stable when it is in the equatorial position than when it is in this axial position, right.

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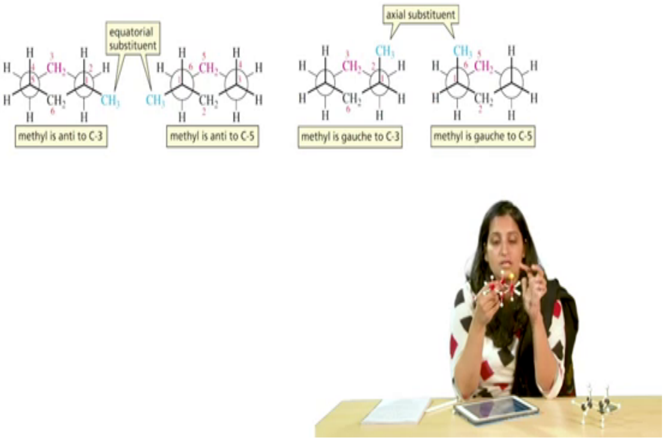

In order to show it more systematically, we are going to look at the Newman projections. So, again we are going to have a look at this particular molecule such that we are going to look at it from this end and you will see this particular Newman projection as drawn here on the screen. You will see that this particular methyl group here is such that it is staggered with all other carbon hydrogen groups, right.

So, as you can see in this particular case this methyl group is such that it is anti to this particular carbon here. Now let us try to put this position of methyl in the axial position. As you can see now it has multiple gauche interactions; first it is gauche with this particular carbon.

So, what you can see is that it is kind of destabilizing. In fact, there is a quantitative way in which we can predict how much of a one conformer is preferred over the other. So, now, we are going to have a look at that, okay. A convenient way to establish whether a particular substituent is favoured in the axial or equatorial position is to look at the diaxial interaction that particular substituent has.

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Now, when we say diaxial interactions, we are talking about 1, 3- diaxial interactions. So, for example, if I have a substituent on this particular carbon, what are the interactions it has with these other axial groups which are going in the same direction. So, for this particular carbon number 1, what are the interactions with the groups on carbon number 3 and 5, okay?

We are going to have a look at that. Because of these diaxial interactions, there is going to be a steric strain in the system. So, for example, if there is a bulky group here, it's going to place a steric strain on the group on this particular carbon and they are going to fight for space. As a result of which this group might be favoured such that it goes in the equatorial position.

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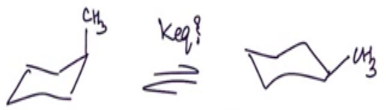

$$K_{eq} = [P]/[R]$$

$$\Delta G^\circ = -RT \ln k_{eq}$$

$$-1.8\ \text{kcal/mol} = -1.987\ \text{cal/mol/K} \times 298 \ln k_{eq}$$

$$\ln k_{eq} = \frac{1800}{1.987 \times 298} = 3.03$$

$$K_{eq} = 20.69 = \frac{[P]}{[R]} = \frac{20.69}{1}$$

Now, if I really want to do this kind of calculation for methyl cyclohexane so, I am going to take very simple methyl cyclohexane, okay. I am going to start from the methyl group going up and we know that the chair keeps interconverting. So, it is going to go from that axial up to the equatorial up.

Now, the question we have is which of these two conformers is favoured and if I really click a picture of this cyclohexane molecule which conformer which will I find in majority. So, remember there are a lot of molecules. So, if I have to say, at any given point of time, If I click a picture, how many of these molecules will be in the first form versus the other form?

We have some idea we have said that in the axial position there are these 1, 3- diaxial interactions whereas, in the equatorial positions you do not have those. So, in the axial position, there are those gauche interactions as well. So, in order to avoid those, the molecule interconverts to have the methyl group on the equatorial position.

But now if I have to quantitatively state, how many molecules are in that equatorial form as compared to the axial form; I am going to look at this particular process as a process of equilibrium. So, the Keq for this particular reaction will be, or not a reaction, but process will be concentration of products over concentration of reactants that is Keq. We also know that,

$$\Delta G^o = - RT \ln Keq$$

So, that is the Van't Hoff equation.

Now, we want to figure out what is the Keq for this particular process. So, right, in order to do that, I would like to assume that the temperature is at room temperature and the delta G^0 value here we have to look up in a table.

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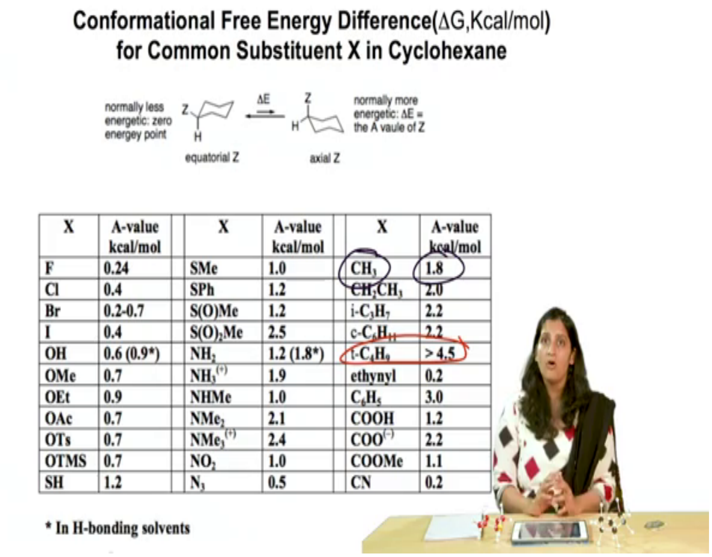

Conformational Free Energy Difference(ΔG,Kcal/mol) for Common Substituent X in Cyclohexane

X	A-value kcal/mol	X	A-value kcal/mol	X	A-value kcal/mol
F	0.24	SMe	1.0	CH_3	1.8
Cl	0.4	SPh	1.2	CH_2CH_3	2.0
Br	0.2-0.7	S(O)Me	1.2	i-C_3H_7	2.2
I	0.4	$S(O)_2Me$	2.5	c-C_6H_{11}	2.2
OH	0.6 (0.9*)	NH_2	1.2 (1.8*)	t-C_4H_9	> 4.5
OMe	0.7	$NH_3^{(+)}$	1.9	ethynyl	0.2
OEt	0.9	NHMe	1.0	C_6H_5	3.0
OAc	0.7	NMe_2	2.1	COOH	1.2
OTs	0.7	$NMe_3^{(+)}$	2.4	$COO^{(-)}$	2.2
OTMS	0.7	NO_2	1.0	COOMe	1.1
SH	1.2	N_3	0.5	CN	0.2

* In H-bonding solvents

In this particular table is called as the table for the A value which basically tells you as we go from axial to equatorial, what is the delta G^0 or how much is the free energy difference between the axial and the equatorial forms of that particular substituted cyclohexane. So, if I look at methyl group here, it looks like 1.8 kilocalories per mole difference between the axial to equatorial. So, as the group goes from equatorial to axial, there is a destabilization of around 1.8 kilocalories per mole, okay.

So, I am going to now in my equation, I am going from an axial to equatorial. So, in my calculation I am going to use it in the negative form. So, minus 1.8 kilocalories per mole right because, we have, we are looking at process going from axial to equatorial. If you look at this table, this table talks about going from an equatorial to axial position, okay.

So, now,

$$-1.8 \text{ kcal mol}^{-1} = -1.987 \text{ cal mol}^{-1} \text{K}^{-1} \times 298 \ln K_{eq}$$

So, if I simplify this, ln Keq becomes,

$$\ln K_{eq} = \frac{1800}{1.987 \times 298} = 3.03$$

$$K_{eq} = 20.69$$

But what is Keq?

$$K_{eq} = [\text{Products}] / [\text{Reactants}]$$

And so, 20.69, I can also state the same number is 20.69 divided by 1. So, if I take this particular cyclohexane and if I ask a question at that at room temperature, what is the ratio of the molecules that have the cyclo hexane methyl group in the equatorial position as that of the cyclohexane methyl group in the axial position; the ratio is approximately 20 is to 1. So, right there are 20 times more number of molecules where they have the methyl group in the equatorial position.

So, if you really calculate this, this comes to be that there is more than 98 percent of the molecules that are there in the, such that they have their methyl group in the equatorial position. So, you can see that if I click a picture 100 times let us say, 98 times I may find that the methyl group is in the equatorial position; 2 times I may find that it is in the axial position.

Okay, so now let us try to solve this particular question. In this cyclohexane you have substituents that are tertiary butyl and two of the methyl groups, what we are going to do is we are going to draw the chair flip of this cyclohexane and then we are going to figure out the Keq for this equilibrium between the two conformations. And what we are also going to do is with the help of this Keq, we are going to predict if the products dominate or the reactants dominate; in the sense, which one of these two conformers really in the majority.

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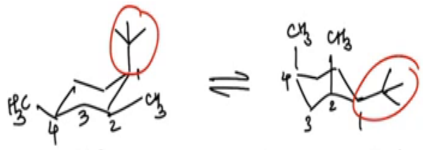

$k_{eq} = \frac{[P]}{[R]}$ $\Delta G^\circ = -RT \ln k_{eq}$

ΔG° tbutyl axial - eq $-4.5 \frac{kcal}{mol}$

methyl eq - axial $1.8 \frac{kcal}{mol}$

" " $1.8 \frac{kcal}{mol}$

net $\Delta G^\circ = -0.9 \frac{kcal}{mol}$

So, let us now try to draw the chair flip. What I am going to do is I am going to first number the carbons; this is very important to not make mistake, right. So, I am going to number the carbons and now I have this particular chair flip, I know that the head becomes the leg of the chair when the chair flips. So, now, this tertiary butyl which was going axial up will now go equatorial up on the chair flip.

Now if you look at this is 1, I have gone clockwise in this particular numbering. So, I will also go clockwise when I am numbering the flip 1, 2, 3, 4. On the second carbon, I have a methyl group that is going equatorial up. Now when the chair flips, it is going to go axial up. So, what I have here is a methyl group that goes axial up. On carbon number 4 again, I have an equatorial up methyl which is going to go axial up on carbon number 4 in the flip; I just complete this right. So, what I have here are the 2 chairs which are the chair flips of each other.

Now, let us try to calculate the Keq for this flip. So, we know that Keq is equal to concentration of products over reactants. We also know the Van't Hoff equation which states that ΔG° is -RT ln Keq. So, let us figure out the Keq with the Van't Hoff equations and then figure out if products predominate or the reactants, okay.

So, now I am going to calculate the ΔG°. Now in the last question, we had just one methyl group that was going from axial to equatorial. Now we have three groups right, how do we go about when we have multiple substituents on the cyclohexane?

First what we do is, we start looking at which group is going from axial to equatorial. So, in this case, I have a tertiary butyl group right; going from axial to equatorial. This is going to be an instantaneous or a favourable reaction or a favourable flip. So, this is going to have a negative delta G of around 4.5. So, I have referred to the table minus 4.5 kilocalories per mole, that is going to be the ΔG°. But I also have a methyl that is going from equatorial to axial and remember, we said that when you have groups that are axial, they have these flagpole interactions. So, they are not favoured.

So, in this case this particular ΔG° is going to be positive. So, which is going to be 1.8 kilocalories per mole. The same way I have another methyl group going equatorial to axial; another 1.8 kilocalories per mole right. So, if I sum it up together, the total net ΔG° of this particular reaction, what is it going to be? It is going to be minus 4.5 plus 1.8 plus 1.8, getting to close to minus 0.9, right. So, this is minus 0.9 kilocalories per mole.

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$$-0.9\ \frac{\text{kcal}}{\text{mol}} = -\ 1.987\ \text{cal/K/mol} \times 298\ \text{K} \times \ln k_{eq}$$

$$\ln k_{eq} = \frac{900}{1.987 \times 298}$$

$$K_{eq} = \frac{4.48}{1} = \frac{[P]}{[R]}$$

$$\%[P] = \left(\frac{4.48}{4.48+1}\right) \times 100 = 81\%$$

Now, if I plug it in into the equations, I have

$$-0.9\ \text{kcal mol}^{-1} = -\ RT \ln K_{eq}$$

$$-0.9\ \text{kcal mol}^{-1} = -\ 1.987\ \text{cal K}^{-1}\text{mol}^{-1}\ \mathbf{X}\ 298\ \text{K}\ \mathbf{X}\ \ln K_{eq}$$

So, if I have to solve for ln Keq,

$$\ln K_{eq} = \frac{900\ \text{cal mol}^{-1}}{1.987\text{cal K}^{-1}\text{mol}^{-1}\ \mathbf{X}\ 298\ \text{K}}$$

So, if I really have to figure out Keq using this,

$$K_{eq} = 4.48$$

Now, Keq we also know is the concentration of products over reactants, right. So, this is divided by 1, right. So, if I want to now calculate, what is the percentage of chairs, that is in the product form or the reactant form, what I can do is, I can figure out the percentage. So, concentration of products will be,

$$[P]\ \% = \frac{4.48}{(4.48 + 1)} \times 100\ \%$$

So, this one comes out to be around ,

$$[P]\ \% = 81\ \%$$

So, as you can see when you have a very bulky group, the cyclohexane prefers to put that bulky group in the equatorial position and really avoids having it in the axial position. But of course, the chair is flipping and you have more stability for the chair conformation where the bulkier group is in the equatorial position.

So, what we are going to do now is we are going to solve similar examples in our tutorials in the coming week, but you can really revise how these particular substituents, how different substituents are favoured or disfavoured at the equatorial position and the axial position. So, this is a good way or this Keq is a good way for us to know whether a particular group is preferred in the axial position or equatorial position.

But Keq as you can see is very similar for most of the molecules. So, what I really like to look at is just the A-value. So, you can see that for a very bulky group like tertiary butyl the A-value is really-really high. So, tertiary butyl group for example, is never preferred almost never preferred such that it goes in an axial fashion. It will always be preferred to put it in the equatorial fashion because of its bulky size.

On the other hand you have other bulky substitutes like isopropyl group, then you have some other substituents here like a carboxyl group; all of these are going to occupy a lot of space. And depending on how much space this particular group occupies, they are going to decide whether it is okay to put it axially or it has to be always in that equatorial fashion. So, for really bulky groups, they always prefer to be in the equatorial fashion.

So, in the tutorial, we are going to go over many more examples of this calculation of Keq and figuring out whether an equatorial position is favoured over an axial for a particular group. As a rule of thumb if there is no other clash, you always want to state that the substituents will be favoured in the equatorial position than the axial position.

So, now we have looked at conformations in general; remember that conformations play a huge role in the way the molecules behave. So, we looked at an example where in the molecule was not biologically active in a particular conformations, but as the molecule folded itself, then that, the pheromone can be biologically active in one of the conformations only. In fact, conformations play a huge role in how these large biomolecules look.

So, for example, you may have heard that the DNA, Deoxyribonucleic acid has a ribose ring in it, right. So, the ring is 5 membered ring and this 5 membered ring is not going to remain planar in the DNA, it has a pucker. So, sugar molecules, the ribose molecules in DNA have a pucker to it and this particular pucker or the twisted form of the ribose really gives a shape to the DNA; the overall DNA. So, how each and every one of these rings is going to be conformationaly favoured is going to detect how that large bio molecule is going to look like.

Another example I can readily give where in the conformation affects reactivity is actually in the case of cyclohexanes and when we go over elimination reactions you will see this very clearly. But just to give an example, very often, we see that the cyclohexane molecules in particular elimination reactions, they do not eliminate in any particular conformation.

The molecule has to achieve a particular conformation in which the leaving group and the beta proton as we call it have to be such that they are anti-periplanar which is possible sometimes in only one conformation. So, we are going to look at elimination reactions and I am going to go over that in detail when we are in that chapter.

So, for now I just want you to remember that conformation plays a huge role in deciding the way in which the molecules react.