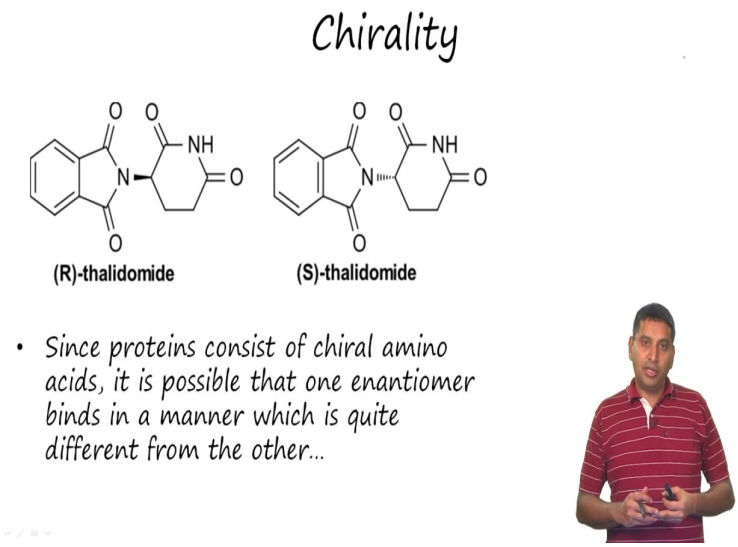
Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institute of Science Education and Research, Pune
Stereochemistry and Conformation

(Refer Slide Time: 0:15)

Alright, so we have so far looked at the major types of receptors and how ligands bind to receptors and the kind of mechanism that are involved in signal transmission inside the cell and we have also looked at some quantitative methods that we used to understand agonist, antagonist and so on and so we are now in a position to figure out how to evaluate a new compound whether it is an antagonist or a agonist and how we want to a proceed in terms of trying to understand the mechanism by which the molecules acts.

But one thing that we are limited by is that we do not still know how exactly the molecule interacts with the receptor, so if you are to break it down into various parts, of course the structure of the molecule is very important we already looked at hydrogen bonding and another weak interactions that occur, but the molecule itself has many aspects that we have not considered so far.

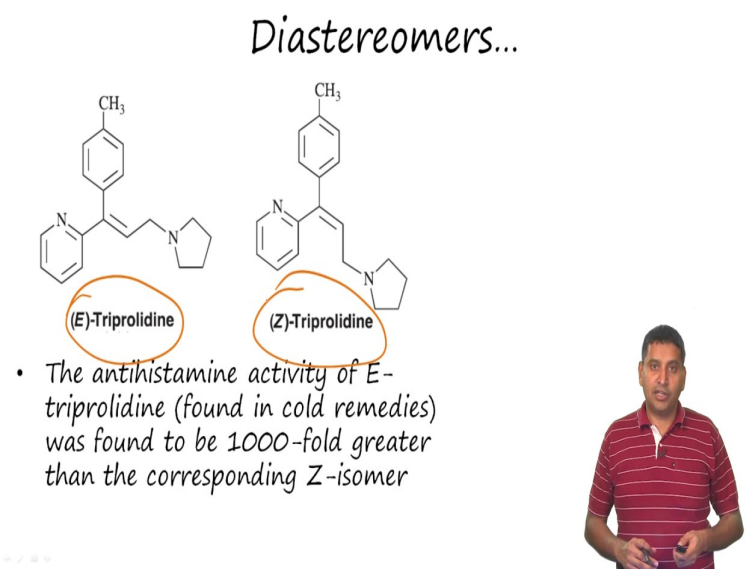
(Refer Slide Time: 1:26)



Ok, so obviously the first thing that we looked at look at is Chirality, so since the proteins which constitute the receptor are themselves Chiral, it is possible that one enantiomer of your a drug binds better or binds you know has better efficacy than another enantiomer. We have already looked at an example of this in the previous classes where because the binding pocket is designed in such a way that one of the key interactions is not possible for one of the enantiomer the binding does not occur.

Of course we have also looked at this case of thalidomide which in which one of the enantiomers is a drug while the other one can lead to very bad side-effects, so Chirality as a concept of is very important.

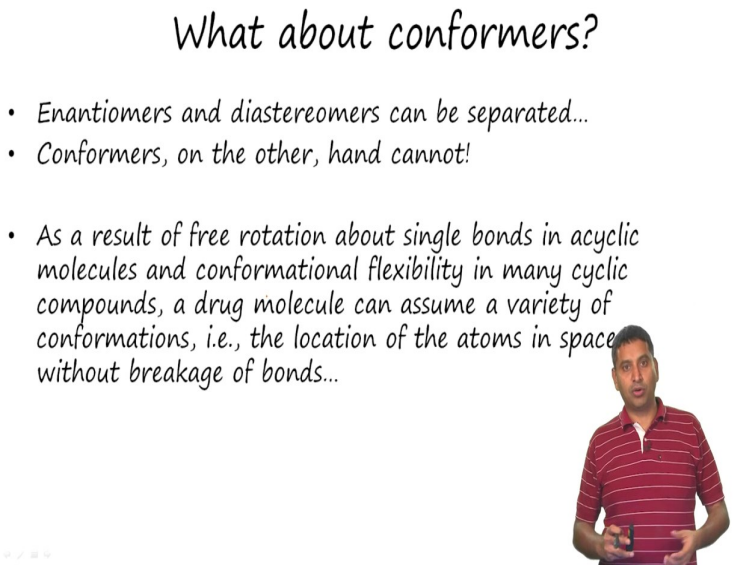
(Refer Slide Time: 2:17)



Okay, so next thing in terms of stereochemistry is diastereomers, so let us take this example of a triprolidine, so this compound has antihistamine activity and the E–isomer which is shown here has is used in cold remedies and it has a very good effect and it is 1000 fold greater in efficacy compared to the Z– isomer, so what this tells you is that the spatial orientation of molecules and these it keep in mind are frozen that is once it is a configuration of the molecule that means R configuration versus the S configuration can be discriminated by the receptor or by the target.

Similarly the E-isomer and the Z–isomer can also be discriminated and have very different activities, so therefore understanding stereochemistry is a very important component of trying to figure out what is going on in this drug receptor interaction.

(Refer Slide Time: 3:20)

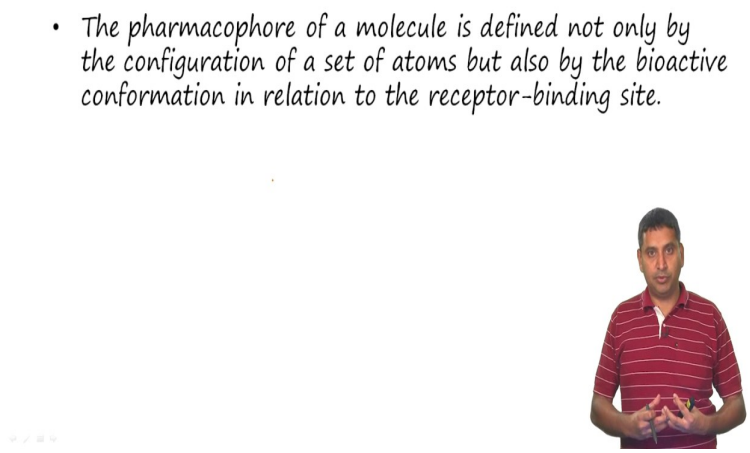


But the question that we want to ask today is what about conformers., Since enantiomers can be separated we have already looked how if you have the racemic mixture you can convert the racemate into the corresponding diastereomers and the diastereomers may be separable and therefore and there once we cleave it, we can get back the two single enantiomers in high enantiomeric purity.

Of course diastereomers by their inherent nature because they have differences in physical and chemical properties they can also be separated, but conformers on the other hand cannot, these are basically conformers are structures which are formed as a result of free rotation about carbon carbon single bonds or other single bonds and a acyclic molecules there is large degrees of freedom and so there is they could be a number of conformations that could be adopted.

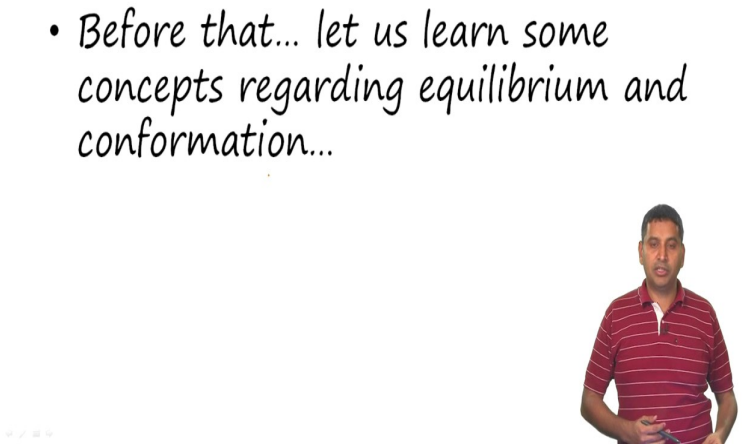
While the conformation flexibility in many cyclic system also may be high and so the drug molecule can assume a huge number of conformations when it is interacting with the receptor that is the location of the atoms in space where there is no breakage of bonds is very important.

(Refer Slide Time: 4:35)



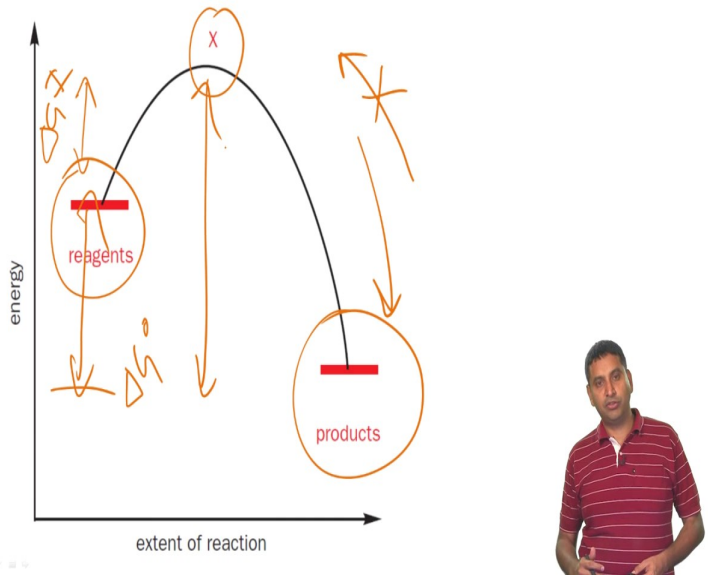
So we have looked at this concept of pharmacophore. Pharamacophore is basically the structure which interacts with the a receptor or the enzyme, the pharmacophore of the molecule is defined not only by the configuration that is how the atoms are connected but also by the bio active conformation that means we need to know what is the conformation that is most effective in binding to the receptor.

(Refer Slide Time: 5:02)



So before we get into that lets learn some concepts regarding equilibrium and conformation, so since confirmation is a reversible process, equilibrium or thermodynamics comes into picture.

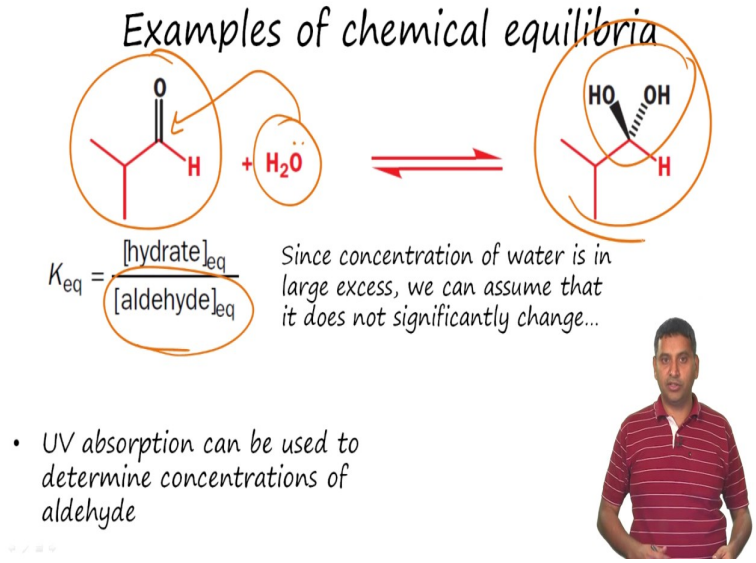
(Refer Slide Time: 5:14)



So let us take a hypothetical reaction, we have a set of reagents and we have a set of products and of course there is a transition state in this reaction, so if this is an equilibrium you will have a delta G double dagger and there is also delta G.

Okay, so this is just to recap the concepts of equilibrium with you. Okay, if it is an irreversible process then once its goes here the products do not go back that means that this barrier reverse barrier is significantly higher than the forward barrier, but for the purposes of this discussion we shall assume that these are equilibrium processes that means that both the barriers are accessible at room temperature or the temperature at which we are doing the experiment.

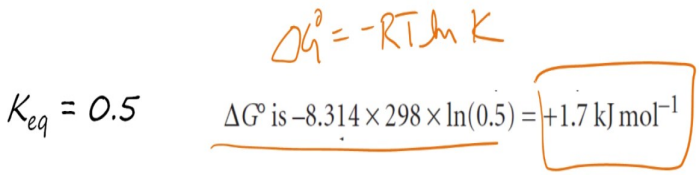
(Refer Slide Time: 6:07)



So let us look at some examples of chemical equilibria so one of the simplest experiments that one could do is to take an aldehyde and reacted with water. Okay so you take an aldehyde you added into water then because these aldehydes are electron deficient one could expect that water adds to this and form a geminal diol. Okay, since the concentration of water is at large excess we can assume that it does not significantly change. One of the ways in which we can carry out this experiment is to use UV absorption. Okay, since the aldehyde as fairly good absorption in the UV region because of the presence of this double bond you will see a good signal in the UV region.

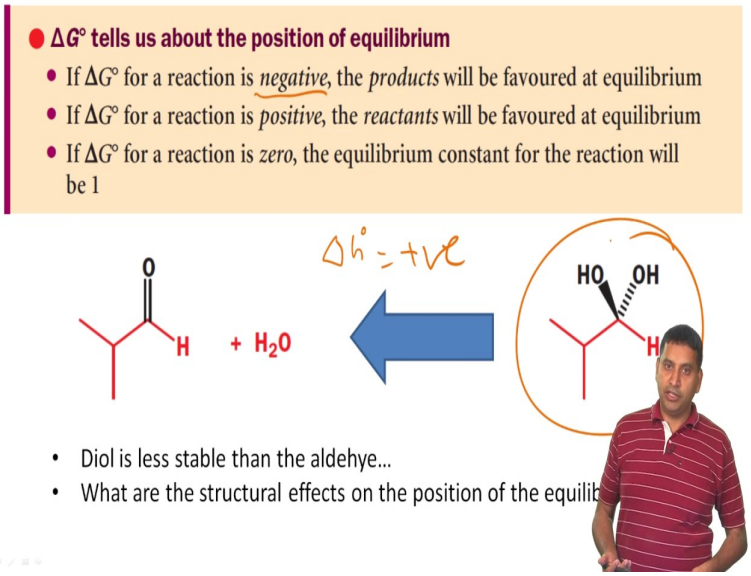
Now, once its forms the diol, the signal would go down and so measuring the absorption can give us an idea about the concentration of the aldehyde that is the equilibrium and since we know how much of the aldehyde has been added subtracting out the concentration the aldehyde from the one in equilibrium will give us the amount of the hydrate, so this K equilibrium is a measure of how much of the diol is present in solution with respect to the aldehyde and we assume that (water) water's concentration does not change.

(Refer Slide Time: 7:30)



And let us say the equilibrium constant is 0.5 if the equilibrium constant is 0.5 you have already looked that delta G not equal minus RT ln K right, so the R is 8.314 temperature is let us say 25 degree to 298 Kelvin and the equilibrium constant is 0.5 and so if you do the math you get a value of plus 1.7 kilojoules per mole.

Refer Slide Time: 8:04)

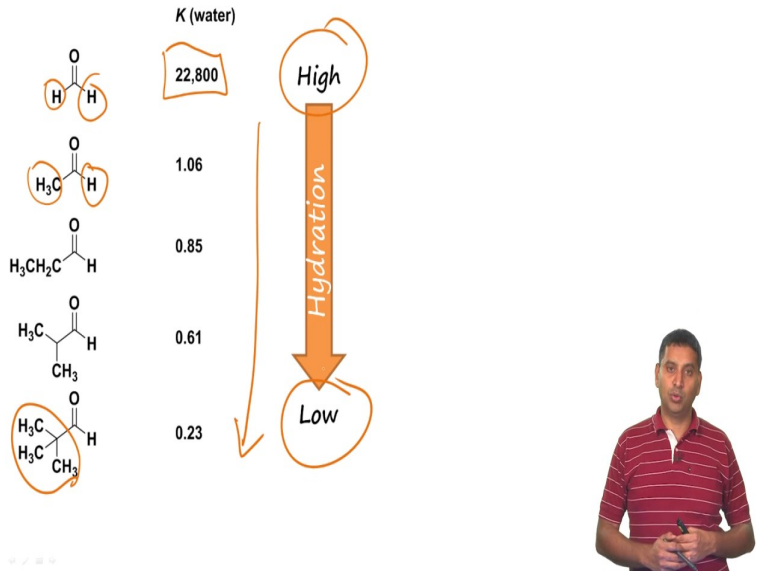


Now let us look at what this means, right delta G tells us about the position of the equilibrium, so if delta G not is negative then the products will be favoured, if delta G not is positive then the reactance will be favoured at equilibrium and of course if delta G not is zero

the equilibrium constant is one and you will have equal amounts of the starting material and the product.

In our case the delta G not value is positive which means that the diol is less stable than the aldehyde. Okay, so the concentration of the product is less than the concentration of the reactant. Okay, now let us look at some of the structural effects on the position of this equilibrium.

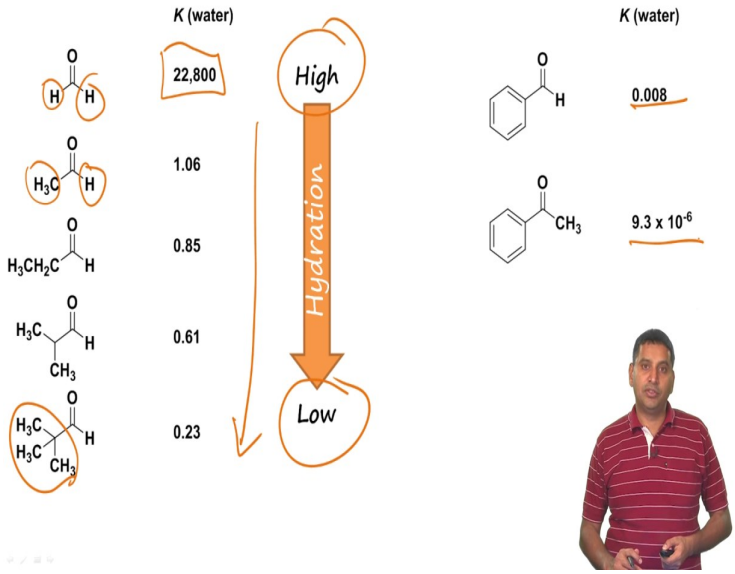
(Refer Slide Time: 8:57)



So if I do the same experiment across various substituted aldehydes I find that the equilibrium constant for formaldehyde which has two hydrogens is 22,800 acid aldehyde which is as a methyl group and hydrogen is 1.06 and so on and so forth, so you will see a trend here that as the size of the substituent increases the equilibrium constant goes down in value.

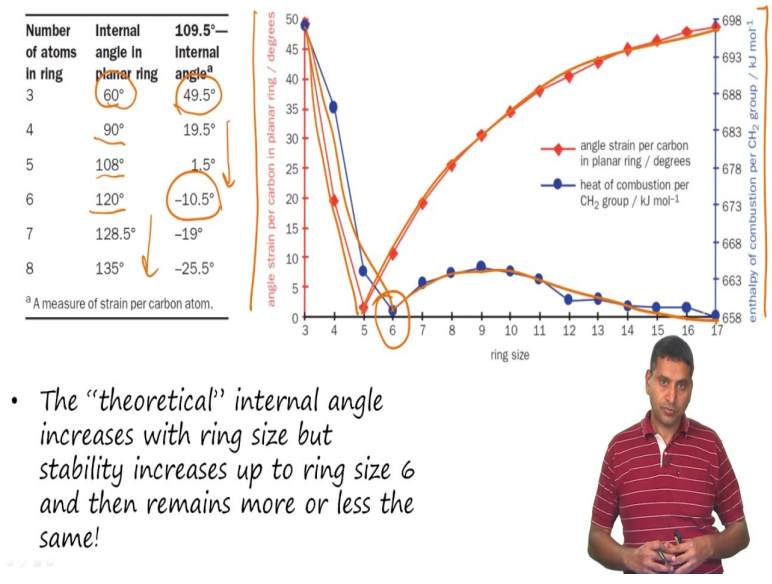
Right, so what it means is that by doing this experiment of hydration what we can understand is the effect of the substituent on the stability of the hydrated species versus the stability of the aldehyde, so in the case of formaldehyde hydration levels are extremely high and therefore the equilibrium constant is quite high whereas in the case of tertiary butyl aldehyde you find that the concentration of the hydrated species is extremely low which perhaps means that the aldehyde is more stable than the hydrated molecule.

(Refer Slide Time: 10:04)



Similarly if you do an experiment with Benzaldehyde you get a value of 0.008 and with acetophenone the value is it 10 power minus 6, so what does this clearly means is that if you go to a aromatic aldehyde or a ketone you find that the stability of the carbonyl compound improves with respect to the hydrated species.

(Refer Slide Time: 10:32)



Okay, now let us take a different concept we look at the number of atoms in a ring. Okay, so we have already looked at in detail in previous organic chemistry courses that there is a concept of an internal angle in a planar ring and we have also looked at how the you know

hybridisation and so on and so we know that the sp^3 hybridised compound should be the angle should be 109.5.

So if I take a three number ring and if it is planar than the angle internal angle is 60 degrees and if it is four number ring it goes to 90, five is 108, six is 120 and so on; right, now since I know that the carbon or since we are theoretically we estimate that the angle or it should be 109.5, I can subtract these two numbers that is the internal angle versus the expected theoretical angle and get an estimate of (how the) how much strain is there in the system.

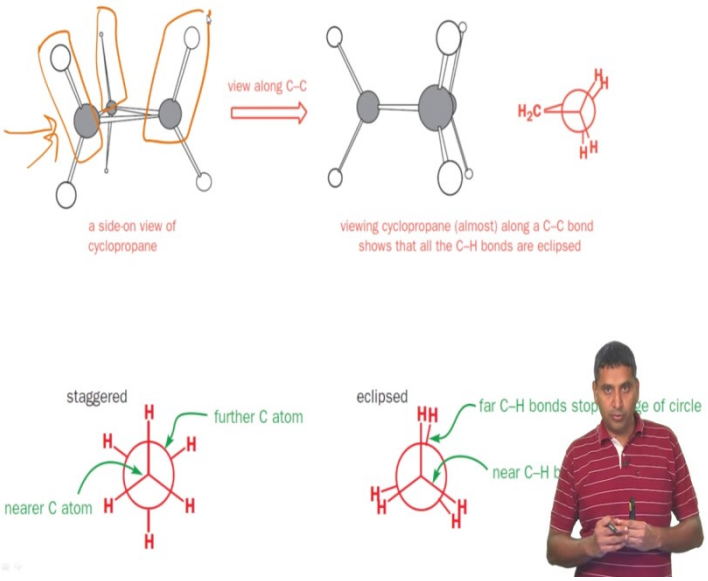
So for example, (if I subtract) if we subtract 109.5 from 60 we get a value of 49.5 and so if you do the same thing for a four number ring and a five numbered you will get a values of 19.5 and 1.5, in the cases of six number ring, since the value internal angle is now exceeding 109.5 the value becomes negative and as this ring size increases the value becomes more and more negative.

So what we have done in this plot here is that if you plot the angle strain per carbon in terms in the planar ring and if you look on the other side is the enthalpy of combustion which we have looked at using by measuring the enthalpy of the combustion, then you would expect the trend to be in the following manner that means it goes down, the angle strain per carbon goes down and then it starts to increase.

Okay but in reality when we do the experiment, we find that indeed the value goes down up to six and the six a numbered ring appears to be extremely stable and after that again it goes up and then as the ring size become larger and larger the value goes down.

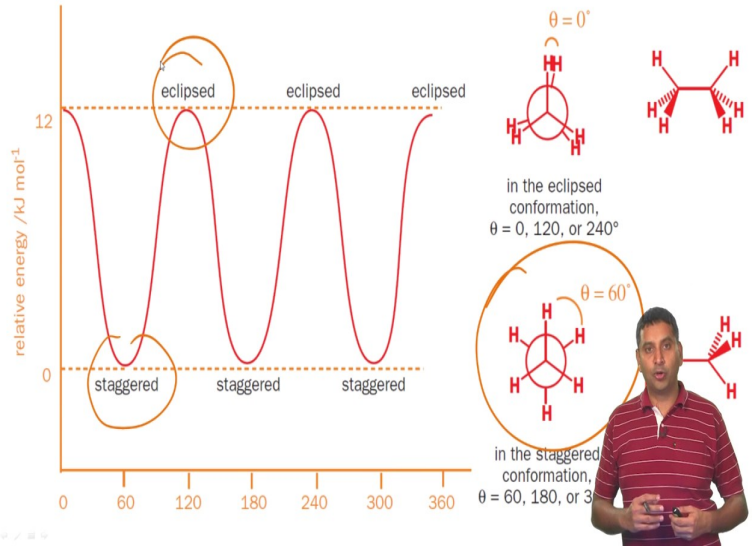
Okay, now (this is also) this is some of these concepts have already been looked at in previous organic chemistry courses but it gives us an important a prospective that a six number ring is extremely stable.

(Refer Slide Time: 13:06)



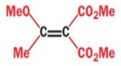
Okay, so if you want to understand this we need to look at a the concept of conformation and how this conformation affects the or a strain and how this strain affects the stability, so let us look a three number ring which is cyclopropane and if you view along each of the carbons you will find that there are eclipsing interactions in all the cases that means if you look from here you will find that this CH is eclipse with the CH, the similarly if you look along this carbon you will find that this CH is eclipse along with the CH and you already may know from basic organic chemistry that eclipsing interactions are not very favourable.

(Refer Slide Time: 13:52)



Okay, a just to recap if you take a ethane molecule and look at how the relative energy varies with bond angle with degree of rotation you will find that a plot like this, so the staggered conformation which is shown here is extremely stable while the eclipse conformation is going to be quite unstable and so if we were to do this rotation n number of times you will a get similar observation that the eclipse is more unstable compared to the staggered conformation, once you can put this in perspective the cyclopropane has only eclipsing interaction in it, contributing to it's instability.

(Refer Slide Time: 14:32)

Compound	E_a, kJ mol^{-1}	Approximate k, 298 K/s^{-1}	$t_{1/2}$ at 298 K
	12	5×10^{10}	0.02 ns
	45	8×10^{4}	10 µs
	70	3	0.2 s
	108	7×10^{-7}	11 days
	180	2×10^{-19}	ca. 10^{11} years[a]

[a] The age of the earth = 4.6×10^{9} years.

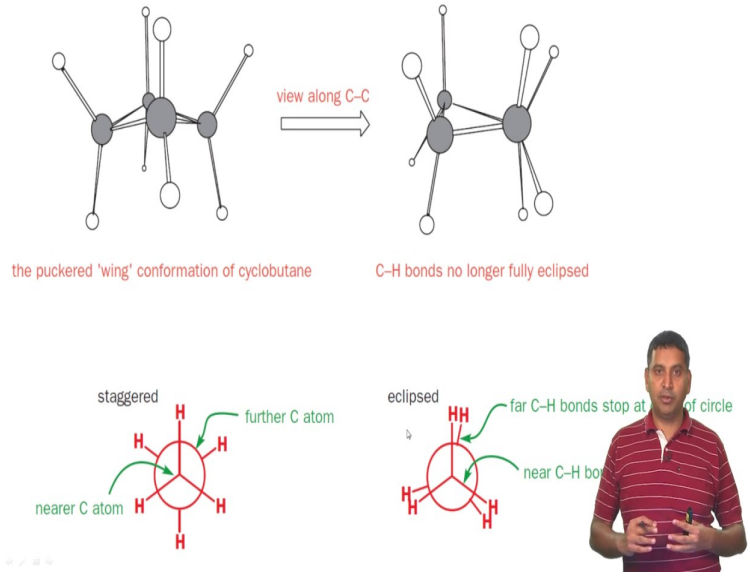
So, if we were to put this to understand it in terms of how fast the carbon (carbon) bond can rotate if you were to calculate the activation energy, the activation energy for ethane molecule turnouts to be around 12 kilojoules per mole and as you increase the size of the substituent on the electronegativity for example by using tri-chloro or hexa-chloro ethane you find that the energy of activation goes up and in the case of a of an amide this carbon nitrogen bond which is rotating has significant amount of double bond character and so the activation energy goes up even further.

And of course in the case of an olefin you will find that its really impossible to achieve at room temperature and you the barrier is about 108 kilojoules per mole and lastly in the case of stilbene the barrier estimated barrier energy is 180 kilojoules per mole.

If you have to look at the rate constant for this reactions, the rate constant is 5 times10 power 10 per second for ethane which is extremely fast and the half-life is 0.02 nano-seconds and if I have to contrast this with a stilbene the half-life is about 10 power 11 years.

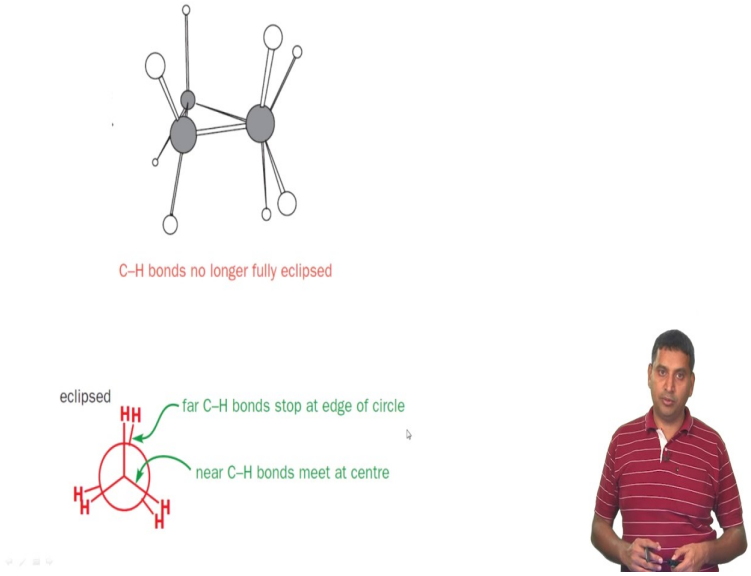
Okay and this is important to understand in prospective of the age of earth which is 4.6 times10 power nine years, so it would take a very long time for stilbene to actually rotate, for cis stilbene to rotate and form trans-stilbene in the absence of any other stimulus.

(Refer Slide Time: 16:11)



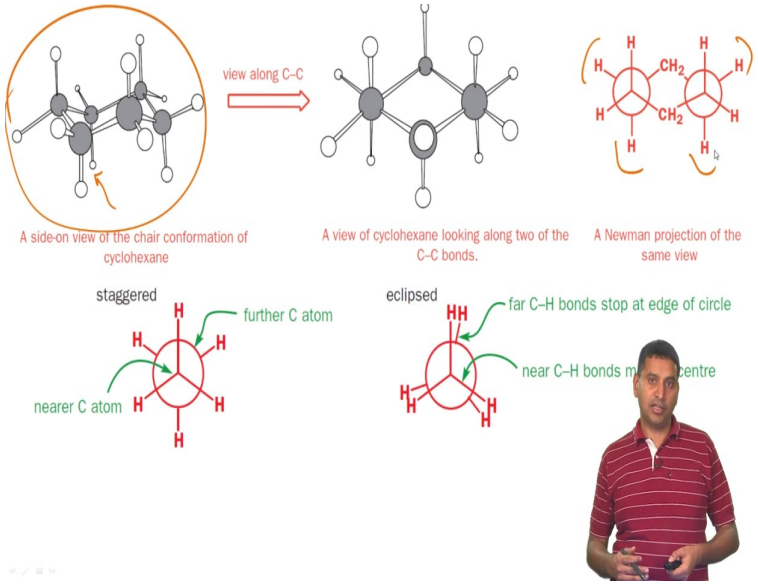
Right, now if you would move to the four number ring, what happens is that it is not completely planar and so it can assume a little bit of a pucker and so some of the eclipsing interactions can be avoided.

(Refer Slide Time: 16:24)



And so the C-H bonds are no longer fully eclipsed.

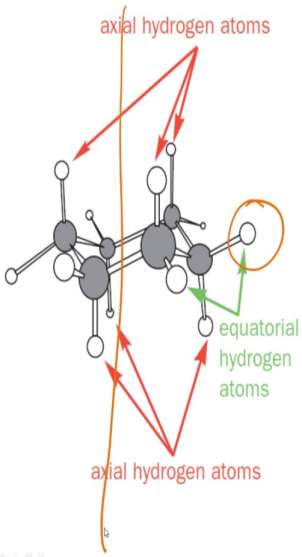
(Refer Slide Time: 16:29)

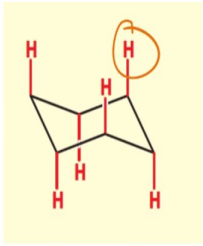


Okay, now when we move to the six number ring, what can happen is that it can adopt a conformation wherein you will see that it is a chair type conformation and the chair type conformation has no eclipsing interactions, so if we were to draw this in the chair conformation again I am recapping some of this from basic organic chemistry and if you were to view along any of this carbons, then you will find that all the interactions here are actually staggered, which means that none of the interactions are eclipsed.

So therefore you can understand how this molecule has increased stability when compared to the other molecules where there is an eclipsing interaction.

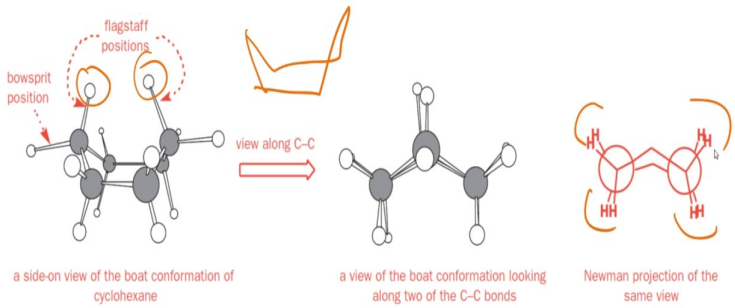
(Refer Slide Time: 17:18)





In cyclohexane you will find that there are two types of hydrogens. One is called the equatorial hydrogen which is shown here and the other one is called the axial hydrogen which is shown represented here. Axial hydrogens are nothing but those that are parallel to the centre of axis here along which you can rotate the cyclohexane and the other hydrogens are called equatorial hydrogens.

(Refer Slide Time: 17:46)

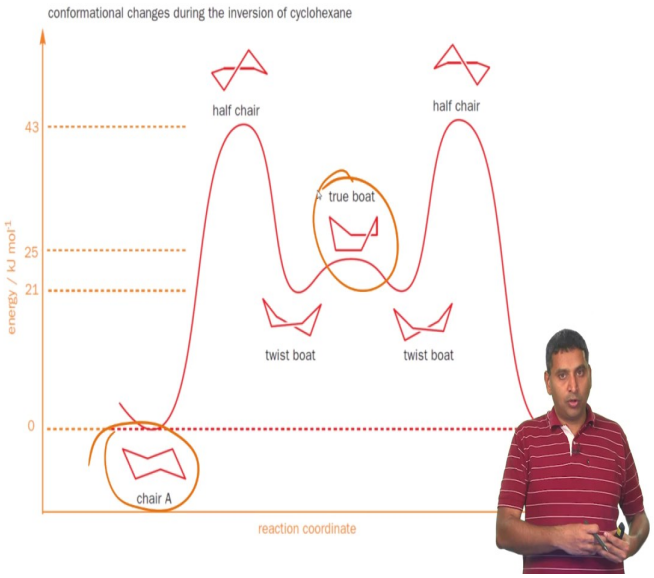


Now, there is a conformation in cyclohexane where you can have what is known as boat conformation, so the boat conformation as shown here has a position known as the Flagstaff position and it actually adopts a boat like this.

Okay, if you were to draw the Newman projection, then you will find that there are substantial numbers of eclipsing interactions in this conformation and so one would predict

that the boat conformation would be substantially less stable compared to the chair conformation.

(Refer Slide Time: 18:23)



And indeed when we look at the profile we find that the chair here is the most stable and the boat is quite unstable compared to the chair and there is a another conformation known as the twist boat which is little bit more stable than the board and the least stable conformation is actually the high half chair which is an intermediary structure between the chair and twist boat.

Some of these concepts have been previously dealt with in detail in organic chemistry courses and so therefore we are not going to spend too much of time on this, however its important for us to understand that each or and like one of these conformations is going to interact with a receptor.

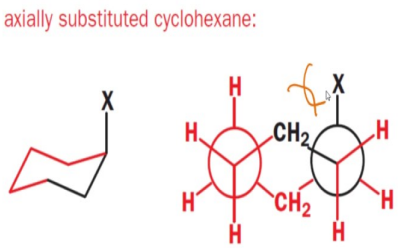
Okay, and so it need not necessarily be the most stable conformation it could be one of the conformations which is less stable and if that less stable conformation is the one that is going to have effective binding we need to understand and which (we) whether that is happening and if we can mimic that using a small molecule.

(Refer Slide Time: 19:25)

ring inversion of a monosubstituted cyclohexane
notice that the hydrogen atom shown changes from axial to equatorial

Now, since we discussed about the a conformation, if I put substituent on the cyclohexane ring the substituent can occupy what is known as the equatorial position or the axial position and if you want to flip this cyclohexane ring that is do bond bond rotation carbon carbon bond rotation, then what happens is the equatorial substituent of the equatorial position ends up in the axial position and this process is called as ring inversion.

(Refer Slide Time: 19:55)

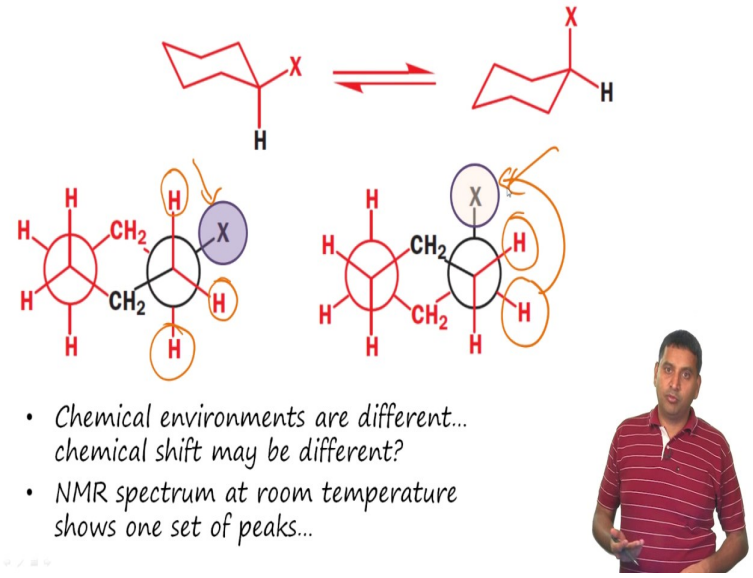


the black bonds are synclinal (gauche)
(only one pair shown for clarity)

Okay, so if you were to draw the Newman projection of this you will find that when the conformation when the substituent is the equatorial position, then you will find that the interactions are happening only with neighbouring hydrogens which are gauche in nature.

Whereas if you have the axially substituted cyclohexane you will find that there is a important gauche interaction with a CH_2 molecule; okay, and there is only one pair that is shown for clarity but you can imagine that there are two such pairs of a interactions.

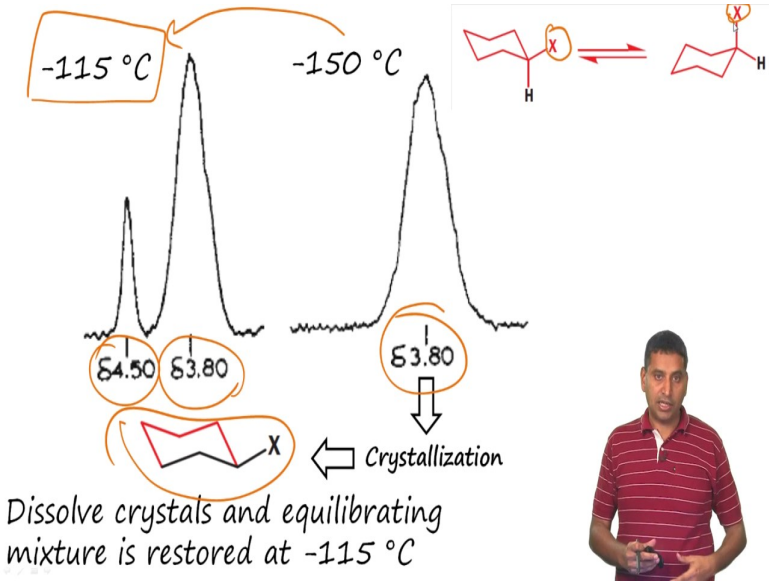
(Refer Slide Time: 20:35)



And this can be a drawn in the same slide you can see here compare the equatorial substituted one versus the axial substituted one. Okay, now a NMR is a very powerful technique which can help us understand the chemical environment around a hydrogen. Okay, so the hydrogen that is present in proximity of the substituent X may have a different chemical environment, so for example this hydrogen over here is these two hydrogens are close to this X, whereas this hydrogen is quite far away from the X.

Similarly in this conformation you have (one) only one hydrogen right next to the substituent X, whereas this hydrogen is quite far away from the X, so there was a very interesting experiment that was carried out to understand how these various conformations exist in solution.

(Refer Slide Time: 21:34)



So what they did was they took a chloro cyclohexane and measure the NMR spectrum, here we are seeing only a portion of the NMR spectrum and what happens is that at minus 115 Degree Centigrade you get two sets of peaks, so one peak at chemical shift 4.50 and another peak at chemical shift 3.80.

Okay, now when you cool it down further you get the peak at 3.80 alone and the peak at 4.50 completely disappears. Okay, so what this tells you is that there is perhaps an equilibrating mixture that is happening and as you go down to lower temperature you would expect that the more stable conformer is highly populated and the less stable conformer does not exist a in the equilibrium, or we are unable to detect the less stable conformer.

So, using this experiment what we could understand is that A there are two conformers that are present, one where the hydrogen is at 4.50 and the other one where the hydrogen chemical shift is 3.80 and as you go a down in temperature, the hydrogen at 3.80 is the only one that shows up and if you go back upto minus 115 from here you would get exactly the same NMR spectrum which means that it is an equilibrium, an important characteristic of equilibrium is that you should be able to both the processes are going to happen reversibly.

Okay, but the key experiment that was done is at this point they crystallised the mixture or crystallised the molecule and that the x-ray structure revealed that the compound was in the substituent was in the equatorial position, that means that this dominant species here is actually the compound with the equatorial substituent.

So this experiment tells us that putting a substituent on the equatorial position is far better than putting a substituent in the axial position in terms of stability, so in a real life you will have at room temperature you will have a mixture of the substituent in the equatorial position versus the substituent on the axial position.

So if you were to synthesise a compound which has a cyclohexane structure and if there was a substituent on it you can imagine that there would be both this conformations possible and both this conformations may not interact with the receptor in the same manner and one of them can be more active.

(Refer Slide Time: 24:21)

Half-Life for Conformation Inversion for Chlorocyclohexane at Various Temperatures

Temperature (°C)	Half-Life
25	1.3×10^{-5} s
−60	2.5×10^{-2} s
−120	23 min
−160	22 yr

So in order to look at some numbers here, in terms of what they effect are in a based on temperature, if you go down in temperature from 25 Degrees to minus 160 Degrees the half -life of the conformational inversion goes up from a few microseconds to 22 years, that means at minus 160 Degrees if I am able to hold the temperature I can freezes one conformation or I can populate the mixture with one conformations specifically whereas at 25 Degrees centigrade this is very facile and so you will have a mixture of both the conformations.

(Refer Slide Time: 25:00)

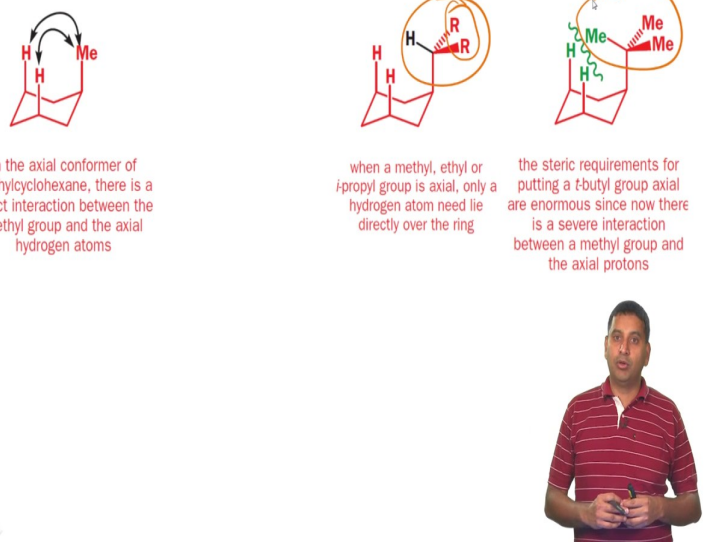
X	Equilibrium constant, K	Energy difference between axial and equatorial conformers, kJ mol^{-1}	% with substituent equatorial
H	1	0	50
Me	19	7.3	95
Et	20	7.5	95
i-Pr	42	9.3	98
t-Bu	>3000	>20	>99.9
Ph	110	11.7	99

Now, we can also understand what is a size effect on substituent much like what we did with the a aldehyde hydration experiment, we found that increasing the size of the substituent next to the carbonyl result at in the diol being less stable, we can also do a similar experiment with ring flip, so here what we do is we try to estimate the equilibrium constant when I increase the substituent, so in the case of cyclohexane then there is no difference between the two conformers and therefore the equilibrium constant is one.

When I introduce a methyl substituent the equilibrium constant goes to 19, which means the energy difference between the axial and equatorial conformations is 7.3 kilojoules per mole and if you do the math this translates to 95 percent substituent with the equatorial a methyl group that means that in a population 95 percent of the population is has the substituent in a equatorial position.

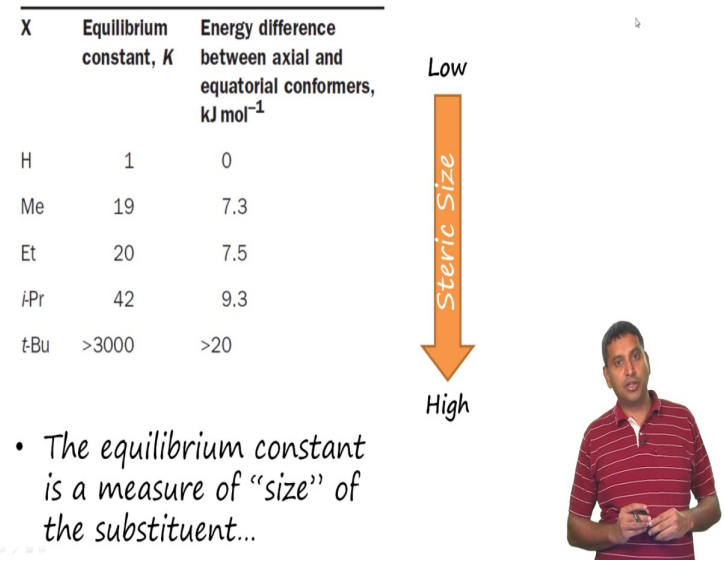
As the substituent size increases from Methyl to Ethyl to Propyl to Isopropyl to Tertiary Butyl the equilibrium constant value increases substantially and when we go to Tertiary Butyl the value of the or the population is greatly skewed in favour of the equatorial substituted Tertiary Butyl cyclohexane and in the case of Phenyl as well the similar observation is has been made.

(Refer Slide Time: 26:36)



Okay, how do we understand this as we looked at earlier the axial substituent has interactions with neighbouring CH_2 which is gauche in nature, which is not very favourable, so in the case of Tertiary Butyl when you have or in the cases of Isopropyl when you have this kind of substituent, it is possible that there are populations of the molecule where the hydrogen is close to the two methyl groups, but in Tertiary Butyl none of the rotamers are going to be a more stable and therefore this interaction is going to be quite severe and therefore it pushes it to the equatorial conformation.

(Refer Slide Time: 27:12)



So, using this equilibrium constant we can also understand or the effect of size of the substituent or we can get measure of how big the substituent is.