Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-Solving Approach

Professor Amit Basak
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture 20

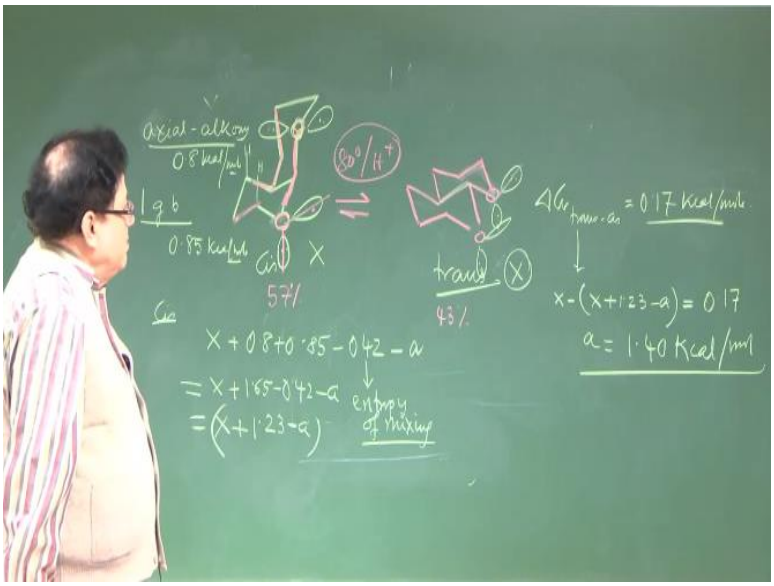
Examples of Anomeric Effect and Stereoelectronic Effect

Hello, welcome back to this course on Structure Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-Solving Approach, last time you have been introduced a new concept which is called the stereoelectronic effect and a subset of stereoelectronic effect what is called the anomeric effect which is basically the genesis of the stereoelectronic effect. The anomeric effect was explained to you and that how the anomeric effect originates and then how to calculate the number of anomeric effects that are present in a system and then also we have seen that there is something called stereoelectronic requirement for many reactions, for any reactions there is a stereoelectronic requirement.

Basically, the stereoelectronic effect guides the molecule to adopt a perfect conformation in order to minimize the electron electron repulsion or maximize the electron electron overlap and also while doing the reaction it tries to adopt a transition state where there is maximum overlap of the interacting orbitals.

Now, let us talk about that how this anomeric effect was evaluated, was determined because the amount of anomeric effect, the extent of anomeric effect is important to know because if you want to calculate the ratio of 2 isomers, equilibrating isomers having 2 types of anomeric effects then this value of this anomeric effect is important. So, somebody was curious to determine that what is the extent of anomeric effect, is it really sizeable effect, means more than one kilo calorie or less, last, in the last lecture I told you that it has been evaluated to be about 1.4 kilo calorie per mole, the question is how was it done, okay.

(Refer Slide Time: 2:32)



It was done by studying a bicyclic acetyl compound, okay, bicyclic acetyl, a cis and a trans, this is one compound which is an acetal as you see, there is a carbon here which is attached to this oxygen, so this is a cis compound and there is a you can have the trans compound, the transversion of this and that is, okay, and that is the oxygen I put here, okay.

So, this is the, these are the 2 compounds, 2, your 2 acetyls, bicyclic acetals they have been cis and trans can equilibrate at 80 degree in presence of an acid, so if you equilibrate, allow them to equilibrate and you can determine the ratio of the 2 how much is the percentage of this, this was found to be 57 percent and this was found to be 43 percent.

Now, if that be the case that means contrary to the expectation, here the trans compound is less stable than the cis compound, that means the trans compound has more energy than the cis compound and the energy difference between the 2, the trans minus cis if you calculate from this ratio and utilize your formula minus rtlnk is equal to del g, so you will find out that the del g will be around 0.17 kilo calorie per mole. Now, so from them, from that value and by studying these molecules and adding some interaction energies you can actually determine the value of the anomeric effect.

So, let me try to do that, now these 2 molecules are basically isomers they have the same molecular formula, so they have the same number of carbons, hydrogens, oxygens etcetera. So, they are just the heat of formation coming only from the carbon, from the molecular formula basis will be suppose X, so that X energy is already inbuilt in both because they have the same molecular formula.

Now, you have to add or subtract some of the stabilizing or the destabilizing energy in the molecules, so the here, let us see what is the destabilizing force, one is this oxygen, this alkoxy oxygen which is axial to a cyclohexane, so that gives a one three diaxial interaction with the hydrogens at this positions and that amount is 0. so 13, so basically axial alkoxy is present and that gives 0.8 kilo calorie per mole.

And then there is and then you have a 1 3 diaxial, sorry, you have a Gauche butane interaction and that is this is axial to this cyclohexane ring, so that gives a Gauche butane unit, that generates a Gauche butane unit, okay, so that gives another so 1 gb and that gives 0.85 kilo calorie per mole.

So, these are the values which have to be added through X, so the energy of, so cis the energy will be X plus 0.8 plus 0.85, now there is another interesting point is that because it is a cis ring junction so it can like cis decalin can exist into 2 conformers, one is the free form of the other okay and they are present in 50-50 amount.

So, that means there will be an entropy of mixing but that gives us, that will be, that has to be deducted the entropy of mixing has to be deducted and that entropy of mixing will give a value of about 0.42, so this is your entropy of mixing, how does it arise, because the cis 1 can exist in 2 conformations, equally populated conformations. So, that is the now scenario for the energy of cis.

Now, let us consider, we have overlooked one thing, that is the presence or absence of anomeric effect. The anomeric effect again remember what is anomeric effect, the lone pair should be anti parallel to a carbon heterobot, carbon heteroatom bond, so here this lone pair is you see is just anti parallel to this one, so I can see one anomeric effect and others are not there because if you see this lone pair, this is beta to that one but this is a

carbon carbon bond, so no question of anomeric effect, if you look at the other ones also you will you no anomeric effect possible or present in the system.

So, there is one anomeric effect that is a stabilizing effect, so you have to subtract suppose, anomeric effect gives a value of a, so minus a, so if you do that that will be X that will be plus 1.65 minus 0.42 minus a, so that becomes X plus 1.23 minus a, so this is the energy of the cis form, energy of the trans form, first of all it said like a trans decalin, so there is no question of extra Gauche type interactions, that is not there only question is if there is any anomeric effect or not but there is no anomeric effect if you draw the lone pairs you will see there is no anomeric effect because there is no bond, a carbon heteroatom bond which is anti to the lone pair that is not present here, so it does not, it has only the energy X.

So, now the difference between trans and cis will be your X is the trans minus this value X plus, X plus 1.23 minus a, a is the anomeric effect and that value you know already from the equilibrium constant measurement, you can know that this is nothing but 0.17. So, that gives you a is equal to, a is equal to 1.40 kilo calorie per mole, exactly the value which I told you earlier.

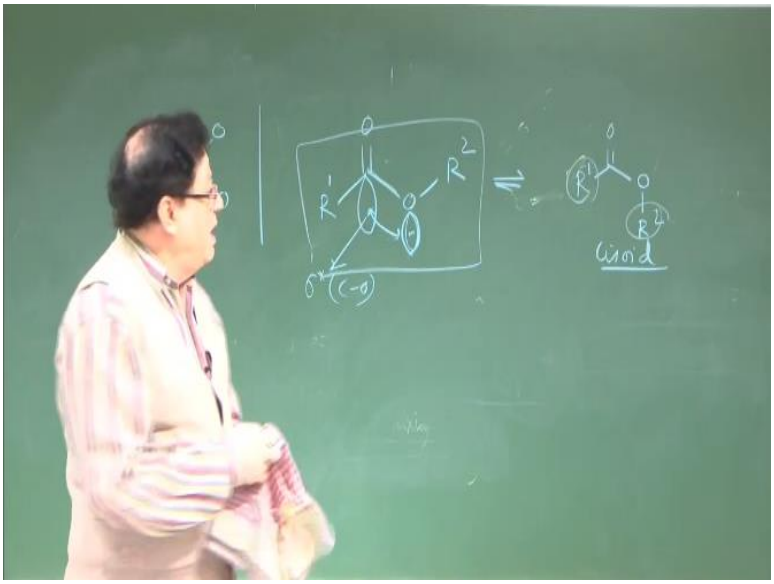
So, this is how the anomeric effect was evaluated this is, it could be little bit approximate because you are not, you are not taking into account any of these electronic electronic repulsion that may be possible in the trans system that is there but that has been overlooked. So, if you overlook that otherwise the calculations are more or less and always think that this is an approximate value, the anomeric effect of 1.40 kilo calorie is an approximate value but it is a good approximation because there are many cases where utilizing this value, the equilibrium constant and the ratio of 2 conformers have been properly matched, they properly match if you take this 1.40 value, so this is pretty accurate in that sense 1.40 so that is how the value came.

Now, let us do some problems on anomeric effect, very simple problems I will. Now, so far we have considered the acetal system in order to explain the existence of anomeric effect, now a very similar system also exists in the ester. Let us draw the acetal system, what is an acetal? A carbon bearing ah oxygens in case of acetal it could be aminal also, a

nitrogen oxygen, all sorts of possibilities are there but the acetal type system is a carbon with 2 hetero atoms.

And then if you talk about ester, see a very similar, the carbon which is attached to 2 oxygens that is an ester. So, we can expect anomeric type activity or anomeric type effect in this system also which can dictate it attaining a preferred geometry, so let us talk about this.

(Refer Slide Time: 12:44)



Now, the ester molecule can exist conformationally into this, this is what is called the transoid conformation because this around this bond this R2 and the R1 are trans to each other, so this is the transoid, you can have also the cisoid conformation which is R1 double bond o, o and R2 this is what is called the cisoid. Now, the question is which one is more stable? Now, you can say that one group of thought may be that this because R1 and R2 are close to each other, so this cisoid will be less stable than the other.

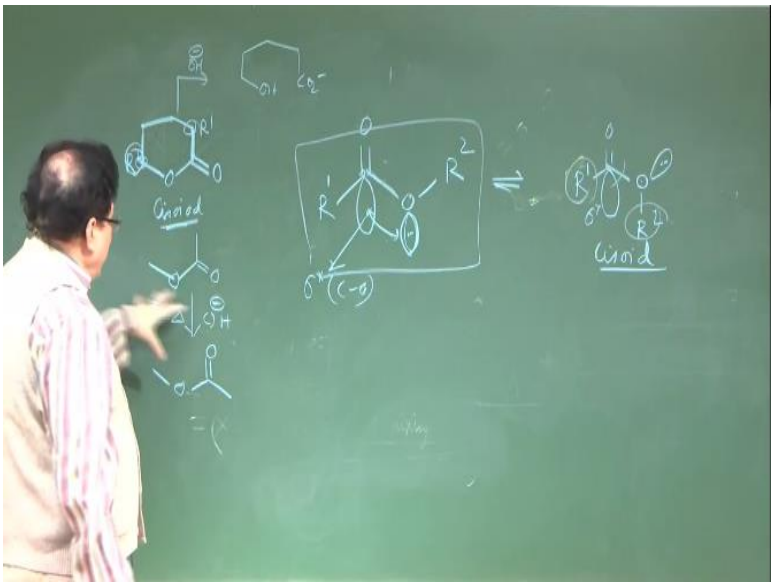
However, nobody knows that if R1 and R2 are only methyl groups, what is the extent of its interaction we are not sure, so the question is whether there is any other reason apart from the steric reason because if you say that R1 and R2 are close together and there is a steric factor which is operating between the R1, R2, that means you are bringing a steric effect to explain the preference for this transfer conformation, always that is there I said

that there are 2 ways of explaining things, one is you apply the destabilizing effect of the less preferred conformation or you try to adapt or you try to propose a stabilizing effect of the preferred conformation.

So, the preferred conformation is the transoid, so where could be the stabilizing effect? Now, in this oxygen, the oxygen, the alcoholic oxide, the alkoxy oxygen, the alkoxy oxygen the lone pair is almost having a p type character because of its conjugation with the carbonyl, so what is the other lone pair? The other lone pair is mostly in the plane of this board.

So, it looks like this, so this is the lone pair which is not participating in formation of the pi bond of the carbonyl system. However, it is perfectly situated if you draw the antibonding orbital of the carbon oxygen sigma bond, remember carbon oxygen sigma bond we are not talking about the pi bond, this is the sigma star of the carbon oxygen sigma bond, then you see that these 2 are perfectly aligned, they are parallel to each other, so they can now interact in a positive fashion, they can overlap and that overlap like the anomeric effect gives an extra stabilization. So, what is the conclusion? The conclusion is that esters will try to adapt this transformed conformation if it is possible provided other type of factors are not there.

(Refer Slide Time: 15:58)



What is mean by other type of factors? Other type of factors means there are cyclic esters which are possible, this is a cyclic ester, a lactone cyclic esters are called lactone and this is an acyclic ester, suppose I take 2 esters, one is a cyclic ester, this is a delta lactone, and I take another molecule which is, which is also an ester sorry, which is also an ester, a methyl acetate, methyl acetate versus a delta lactone.

Now, what has been found that if I add alkali to a lactone and also add alkali to an acyclic ester, this is an acyclic ester, to hydrolyze an acyclic ester you need lot of energy, you need heat if you, if you want to do it rapidly, if you treat it for a long time it will hydrolyze definitely but if you want to do it rapidly you have to heat in order to hydrolyze this with aqueous alkali.

On the other hand lactone if you add alkali, the moment you add alkali it opens up, it opens up and it gives Co2 minus, that means the lactones are more reactive towards nucleophilic ring opening than the acyclic esters, why is that? The explanation lies in this whatever we have said about the preferential geometry of an ester.

Now, when I talk about this molecule the lactone, see this is your the substituent attached to the carbonyl carbon, so that means this is your taking up the case of R1 and this is the substituent which is taking up the case of R2, so if you see this R1 and R2 they are in the cisoid conformation, they are in the cisoid conformation and this is flexible, the way we have written is in the cisoid conformation but it can have the flexibility to go into the transoid conformation and that will be the predominant one.

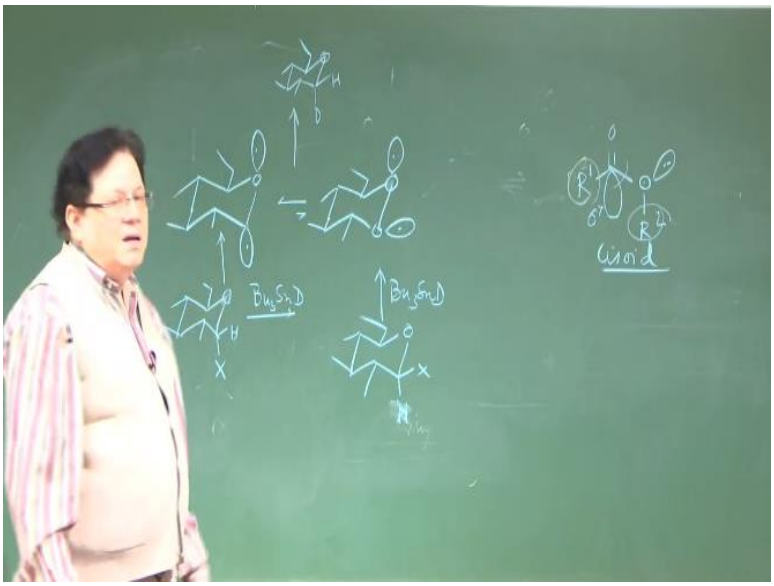
Now, the question is, this is tied up in the cisoid conformation and this has the flexibility, so that will add up the transfer conformation, now the question is that then what this n sigma star overlap has to do with the reactivity of the system? Yes, it has to do with the reactivity of the system because what you are doing by this conjugation, you are actually pushing electrons towards this carbonyl carbon or you can say that you are lowering the electrophilic character of this carbonyl carbon by this n sigma star overlap, another way of explaining it is that you are making this a stronger bond, a carbon oxygen with a partial double bond.

So, all these are basically going against the breakage because ultimately the hydrolysis means breakage of this, breakage will be difficult, so you have many arguments, one is that you are lowering the electrophilicity because of this conjugation of the oxygen lone pair with the sigma star, okay, basically you are pushing electrons towards the carbonyl carbon, thus lowering its electrophilicity.

Another is that you are strengthening this carbon oxygen, the carbon alkoxy oxygen bond which is the bonds to be broken. So, that will make anything which is in the transoid form it will be more difficult to hydrolyze than something which is in the cisoid form because in the cisoid form this is the lone pair and this is your sigma star, so there is no connection between this sigma star and the lone pair.

So, that means there is no conjugation, and it is actually whatever conjugation you have that is natural, that is the p the lone pair which is occupying the p orbital and this carbonyl that is present in both the systems but this extra conjugation that is absent in the cisoid and that makes the cisoid more vulnerable than the transoid and that exactly what happens here because this delta lactone cannot adopt a transoid conformation. So, it is has to be locked in a cisoid, so it hydrolyzes faster than any acyclic ester which is in the, which can adopt the transoid conformation, so that is a very simple example.

(Refer Slide Time: 21:11)



There are many reactions, these are basically stereoelectronic effects controlling the reactivity of a molecule, there is another interesting aspect of the stereoelectronic effect, one is I should mention here that this stereoelectronic effect is also or this anomeric effect in sugar that we have is also applicable in case of a radical at the anomeric carbon, in the case of a radical at the anomeric carbon.

So, that means if you are making a radical at this anomeric carbon, the radical tends to adopt a geometry where it is axially oriented and not equatorially oriented, the same anomeric effect also plays a role in the geometry of the radical, how was it proved? It was proved by taking this molecule and X, equatorial X and then it is a sugar moiety reducing it with tributyltin deuteride, you know that any halogen can be reduced and replaced by hydrogen if it is tributyltin hydride, if it is tributyltin deuteride, then deuterium will replace the X.

However, since the intermediate for this reaction is a radical and then radical can invert, invert very easily, that means an axial radical can become equatorial radical, equatorial radical can become axial radical is just like your nitrogen pyramidal inversion, that is the same story here. So, when you generate the radical, that means this will give and from this radical because you have started with the axial one, so it will first generate the axial radical and then start equilibrating between the 2.

On the other hand, you can start, your change the starting material, these substituents are there I am not putting it substituents are always there, if you take this molecule, the beta one, the beta halo compound and do the same reaction, reduce the tributyltin deuteride, okay. So, the first radical that will be formed will be equatorial radical, then there will be equilibration and the final product what they got is this, the final product what they got is this (())(24:02) deuterium.

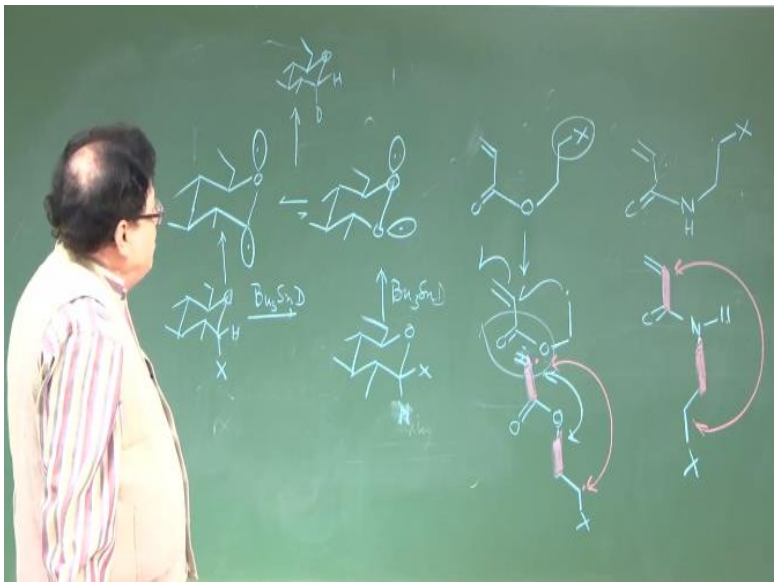
So, this actually clarifies several things, one is that it goes by an equilibrating set of radicals, even if you start with axial, it will go to the equilibriation between the axial and the equatorial, that is one point which is proved and the other point which is proved that anomeric effect is still operative in the radical also, radical at the aromatic center. So, that experiment was done in case of sugar moiety.

Now, these radicals you know, the radical chemistry we will talk about radicals in our later lectures because that is a reactive intermediate and very useful reactive intermediate. Radicals reactivity is we know that radicals are extremely reactive but extremely reactive means reactive with whom, there are basically 3 types of reactions that the radicals can participate, one is that radical if it sees any labile atom nearby like a hydrogen, then it will abstract the hydrogen and become a paramagnetic, become a die magnetic species, sorry, diamagnetic species.

So, it was earlier a single electron containing molecule, paramagnetic, so that will become a diamagnetic molecule by abstracting an atom, it could be hydrogen, could be halogen, iodine. So, any labile atom has to be present nearby that is one type of reaction. Another is if there is a, if there is nothing then the radical, if the many radicals are produced at the same location, then they can dimerize, they can join with each other and the third one which is very important is that the radical can add to unsaturation, like the double bond.

So, radical can add to the double bond and then forming another radical that can add to another double bond and that is the basis of radical based polymerization which is very important because you are forming carbon carbon, enormous number of carbon carbon bonds and that is basically the starting point of the polymer chemistry. So, one is self-quenching, r dot r dot another is this type of radical abstracting deuterium here, that is the labile 1 and the third one which is very important is its addition to the unsaturation, like the double bond.

(Refer Slide Time: 26:41)



So, if you want to make, suppose someone has this type of system, someone, sorry, not double bond here, only an unsaturation and I put here, sorry, oxygen, nitrogen it could be oxygen also, let us put an oxygen first. Here someone wants to do a cyclization reaction, the problem is like this, that if once to do a cyclization, if one wants to do a cyclization chemistry involving this what is the cyclization chemistry?

The cyclization chemistry is basically you reduce this from a radical, from a radical and it is expected that the radical will add to this double bond in this fashion. So, in the process what you get is a cyclic compound, so this is a nice way that generating a radical and having a double bond and another location you can add the radical onto the double bond and get to a cyclic product.

You can do similar, you can try to do similar type of reaction by putting nitrogen also like N H, N H and then X, so again the same reaction that you put a radical here that adds to the double bond however, these reactions usually do not go very well and what could be the reason? The reason is the same thing the preference for a particular conformation, see when you have this, this is an ester.

So if you have an ester we know that the preferred conformation of an ester is what? If this is your R1, then this substituent will go on that side, so this is the preferred

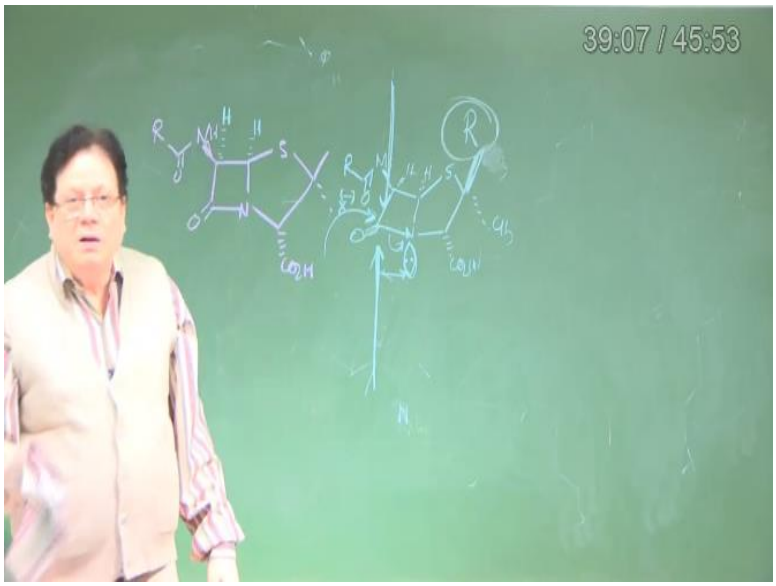
conformation because it wants to be transoid, si this is the geometry, the same is true for the amide, that also wants to adopt a transoid geometry, so these 2 are the transoid, I can use another chalk, so these are the transoid geometry and that is the preferred conformation of this molecule.

So, if it is in the transoid geometry, then you see the 2 centers which are supposed to react, these 2 centers which are away from each other, if they are away from each other then how can they react? So, because of these conformational constraints, these molecules fail to react in the expected fashion, expected fashion means you are expecting the formation of this, in the ring formation, this is more apparent this is more so in case of the amide because amides are, amides prefer this transoid conformation almost 100 percent.

So, it is almost impossible to do a radical cyclization in case of amides, in case of ester still it is possible because they are there are still some percentage of this type of conformation present and as you raise the temperature that cyclization can take place but for amides people have tried to do this reaction many times and it did not work because of this preferred conformation of the amide, the transoid conformation of the amide.

But do not forget what is the genesis of this? The genesis is a again a stereoelectronic effect, stereoelectronic effect compels the molecule to adopt this type of conformation because only in this type of conformation you get that n sigma star type of overlap, that is there.

(Refer Slide Time: 31:53)



We will discuss another one which is interesting in the sense that it has got a biological significance, it has got a biological significance, the molecule that I want to write or I will write now is nothing but a very important antibiotic which was, this is the structure of a penicillin molecule, penicillin molecule you know, the penicillin is the miracle drug that was discovered in the nineteen, early 1930, late 1920s by sir Alexander Fleming and it was then came into the market during the world war 2.

Now, this is the structure of penicillin, it is a 4 membered ring coupled with a 5 membered, this is beta lactam and this is called thiazolidone ring, thiazolidine ring, sorry, thiazolidine and this is beta lactam. Now, the actual geometry of this looks like this, so it is like a open book type of conformation that this molecule has, so this is the methyl, this is another methyl this is a there is a, this is the amine group, this is the amide and here is this hydrogens which are alpha to the, which are both alpha.

Now, this is the structure, so it is like a folded kind of thing, now there was a debate, first of all where is the lone pair on the nitrogen? Nitrogen lone pair is pointing downwards, now if a question comes that in this molecule, we have a carbonyl and later on when you study little bit of chemical biology you will learn, you will know later on that how the penicillin molecules shows their biological activity, we are not going any deeper into that but the biological activity is dependent on the attack by, attack by a target enzyme, a

target protein, attack by a target protein onto this molecule. So, basically at protein molecule with a nucleophile attacks this penicillin molecule.

Where does it attack? In this molecule the most vulnerable bond is this one because this is a four membered ring and there is a carbonyl, so it should be susceptible to what? Nucleophilic attack, so say X minus and this X minus is nothing but coming from the target enzyme, the target enzyme which is very important enzyme, which attacks this penicillin and the enzyme loses its activity, that is the basic principle of antibacterial action of penicillin.

So, it actually stops an enzyme from doing its function rather than it attracts the enzyme towards itself and the enzyme attacks the penicillin molecule via a nucleophile that the enzyme has and opens up this, attacks the carbonyl and opens up this bond. So, this is the simple, simplistic mechanism of the action of penicillin.

Now, the question is there was a debate, which is yet to be sorted out I believe, that there are 2 faces of the penicillin, one is from the top, another is from the bottom. So, which face, obviously the top face is because it is a con, it is a concave shape, so what will happen this will be more crowded, crowded side and this will be more exposed side, so what people might think that the more exposed side the enzyme will attack and the it will not attack from the top face.

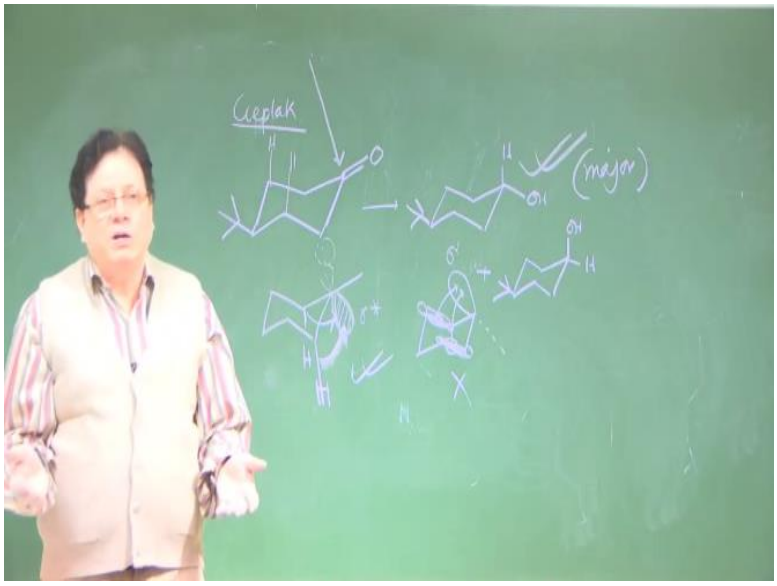
However, our stereoelectronic requirement is what? That the approach should take place in such a fashion so as to avoid any interaction and this also has to minimize the repulsion between the any electrons that may come in the way of the approach of the nucleophile.

So, each, the nucleophile should approach from a side where there is minimum repulsion, now you can I think you can answer this question because there is a lone pair here on the nitrogen, so the nucleophile if it approaches from this side then there will be a stereoelectronic violation happening because it is coming from the side where there is already negative charge present.

So, it will stereoelectronically speaking it should not approach from the bottom side and if it comes from the top side, then it is because your lone pair is perfectly anti to the approach of the nucleophile. So, that is the debate, at some point time there was an intense debate that from which direction it comes, again there are 2 schools of thought but people who believe in stereoelectronic effects they think that the nucleophile should come from the top in order to avoid the electron repulsion, electron electron repulsion between the approaching nucleophile and the lone pair.

How to prove ah this type of, this type of approach this is very difficult but what has been found that if you put more bulky substituents here on the beta face, that means if you make the beta face more crowded, more and more crowded then the penicillin loses its activity, loses its activity, is much less potent than when you do not have the, do not have that much of crowding, so that kind of suggests or helps in our, that reasoning based on stereoelectronic factor that the nucleophile is approaching from the top and if you make the top more crowded, the activity goes down.

(Refer Slide Time: 39:25)



So, that is another example and the final example about stereoelectronic effect operating in a reaction and that guides the, guides the major product is what we have, this was actually discussed in our stereochemistry course that was the preliminary basic stereochemistry course. However, I do not whether stereoelectronic factor was or

requirement was introduced at that time, maybe not, so let me just quickly revisit that problem.

The problem was basically that if you have a cyclohexanone and if you reduce the cyclohexanone, say like with sodium borohydride, then there are possibilities of formation of 2 products, one is the equatorial alcohol and another is the axial alcohol. Now, what is found is that the equatorial alcohol predominates and the initial explanation was that equatorial alcohols are more stable.

So, that is being formed in a major amount but which this reason did not hold because these reactions are kinetically controlled, they are not thermodynamically controlled, it is such a fast exothermic reaction that the, it does not, is not a product development control, the product structure will not guide that what is the major product that is formed, so that was not accepted.

Ultimately, there was a theory which is called, which is based on Cieplak model which is nothing but a purely stereoelectronic effect, what is that? According to Cieplak that when a nucleophile approaches from the top, remember to get the equatorial alcohol the nucleophile should approach from the top, from the top face, from the axial phase you can say, relative to this carbonyl carbon and if you want to get the axial alcohol the nucleophile should approach from the, from the equatorial side, which is kind of more exposed because from the axial facing of this axial hydrogens which may hinder the approach of the, approach of the nucleophile.

So, there is steric effect there but in spite of steric effect the nucleophile still approaches from the top. So, there must be some other effect which is not steric in origin, that is stereo electronic in origin. So, what is that? That when this is approaching this carbonyl, there is the formation of the bond between the nucleophile and the carbonyl and that will, that bond formation will have an anti bonding scenario on the opposite side.

So, whenever 2 orbitals interact with each other an anti bonding orbital is formed which has got a bigger lobe at the back side. So, a bigger lobe anti bonding orbital, what is this anti bonding orbital? This is the sigma star of the, of the orbital, of the bonding that is

being found between the nucleophile and the carbonyl carbon. So, that anti bonding orbital has a bigger lobe at the bottom, now this is perfectly aligned to the axial hydrogens at C2 and C6, so now the axial hydrogens can interact and can interact and combine with this sigma star and donate its electrons to stabilize the sigma star.

So, that is nothing but a stereoelectronic effect, this happens only because of the proper steric disposition of this axial hydrogens and the developing sigma star orbital. What about if it approaches from the equatorial side? If it approaches from the equatorial side, yes, there is still there will be a sigma star on the opposite side, that is true and now the bonds which are in close parallelity with the, with this sigma star, direction of the sigma star are these carbon carbon bonds.

Now, the carbon carbon bonds also can interact but you know that donation from carbon carbon to an empty orbital is much less, look at hyper conjugation, hydrogens are the best atom to offer no bond resonance, it can sacrifice itself and donate the electron pair to the unfilled orbital, to the empty orbital.

In this in this case the empty orbital is the sigma star, so this stabilization is much less, this stabilization is much more, so because of this stereoelectronic stabilization by the axial hydrogens onto the sigma star, developing sigma star orbital, when the nucleophile approaches from the axial phase that gives major the alcohol, equatorial alcohol as the major product.

So, this is another classic example of stereoelectronic effect, there are many more, remember as I said stereoelectronic requirement is there for, has to be considered for every reaction, as I said elimination has a particular stereoelectronic requirement, that means how the orbitals will be arranged in space, (())(44:58) to reaction has a stereoelectronic requirement and many rearrangement reactions like Beckman rearrangement, you know that the group has to migrate from opposite to the living group.

So, all these are basically dictated by one fact that in the transition state the orbitals should be arranged in the 3D space in such a way so as to give the maximum overlap and that means the maximum possible stabilization to the transition state, then only the

reaction proceeds faster. So, that is the motto of all the reactions, to stabilize the transition state and that is by minimizing steric factor that is on one side and by maximizing the orbital which are interacting overlap in the process. Thank you very much.