Introductory Organic Chemistry II
Professor Doctor Harinath Chakrapani
Indian Institute of Science Education and Research, Pune
Module 03
Lecture 24
Nucleophilic Addition Reactions and its Stereochemistry

So, welcome back to the next lecture. So, we will continue to discuss about carbonyl compounds. And as you may recall, in the previous several sessions we have had, we have been discussing about how to understand the reactivity of carbonyl compounds.

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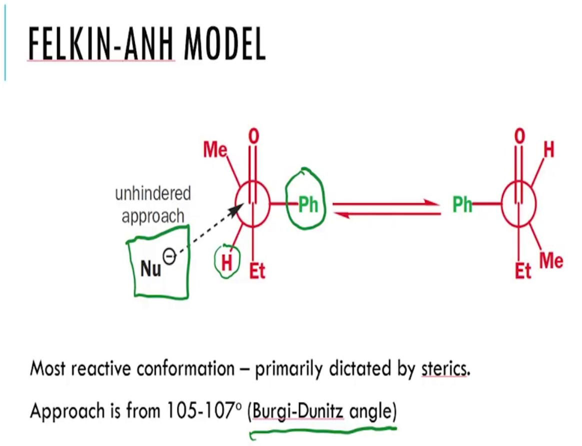

FELKIN-ANH MODEL

Most reactive conformation – primarily dictated by sterics.

Approach is from 105-107° (Burgi-Dunitz angle)

And with respect to that, we sort of quickly realized that, we are looking for the most reactive conformer. And so, as we discussed previously, there are several models that can help out in understanding the experimental outcome. One of the most successful models is with the Felkin-Ahn model. And the Felkin-Ahn model, as shown here gives us a fairly good understanding of how the reactivity of the conformer plays an important role.

So, the Felkin-Ahn model says that you draw out the carbonyl compound in the following manner where you put the largest group perpendicular to the carbonyl group. And this will occur in two conformations, two distinct conformations. And now, if these are the most reactive conformers, then there are four approaches. And the approach that we looked at, we understood from the Burgi-Dunitz angle was the nucleophile would approach between 105 to 107 degrees.

And so, of the four approaches, there is one that is more favoured. And so if you pick that one, and if you go ahead and draw the product that is formed, that will give you the major product. So, it is a very good framework that helps us sort of predict the outcome of the reaction. Now, in this Felkin-Ahn model, primarily sterics are really important because the largest group being perpendicular to the carbonyl is dictated by sterics.

And the more reactive conformer also, if you see here, we pick the most reactive conformer or the trajectory with the lowest barrier is the one where the smallest group is present, closest to the trajectory. And so, sterics play a dominant role. So, the two important points in this model are sterics and the second one is the Burgi-Dunitz angle. Now, there are other factors that can play a role in this carbonyl addition, in order to understand that I am going to change topics and go to S_N2 reaction, and we will come back to the carbonyl addition shortly.

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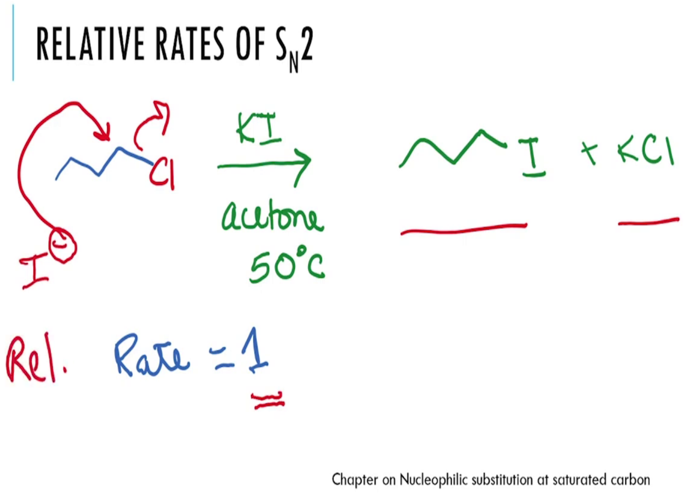

RELATIVE RATES OF S_N2

Chapter on Nucleophilic substitution at saturated carbon

So, what we do is we do a simple experiment. So, we take this chloride and react it with potassium iodide in acetone, the temperature is maintained at 50 degrees centigrade. And you all know that potassium iodide is a source of I^-, so you can expect that I^- would attack over here, and sort of kick out chloride, and the product that you would get is this iodide here and KCl.

So, this is perfectly fine. Now, what I do is I measure the rate of the reaction, and the rate of the reaction is measured, and we just call this as 1; to be technically correct, we call this as a relative rate of the reaction, we just assign it to be 1.

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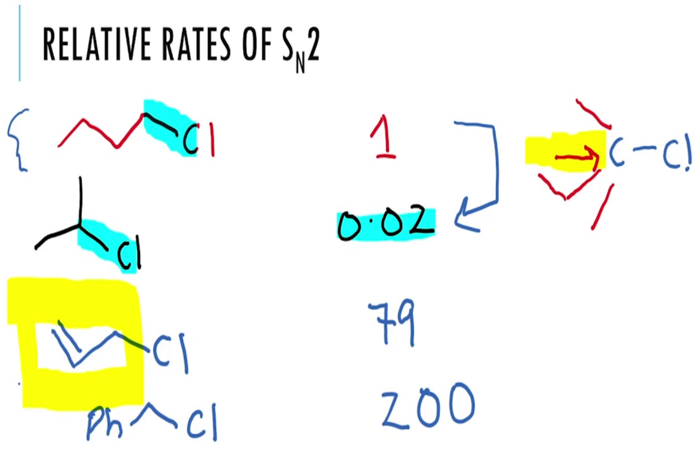

RELATIVE RATES OF S_N2

Now, with respect to this rate, now, what we do is we can do a systematic study about what happens if I change the group that is present next to the carbon-chlorine bond. So, here is the carbon-chlorine bond. And so for example, when we add a methyl group adjacent to it, so we start with isopropyl chloride, the rate of the reaction or the relative rate of reaction goes down to 0.02.

So, now, this is a fairly substantial drop in the rate of reaction. And, the way we understand it is that when the Cl, when the carbon-chlorine bond is being broken, so iodide attacks from that 180 degrees angle, and anything that sort of prevents or slows down the attack is going to slow down the reaction. So, what the way we understand this is that if you have additional groups over here, for example, then this is going to create a sort of a barrier for the attack to happen.

And so therefore, the energy or the transition state energy or the transition state is going to be achieved at a higher energy and so the reaction rate is going to be slow. So, this is fairly straightforward for us to understand. Now, when I move from this chloride to allyl chloride, so this is the allyl group, as many of you might know. And so, when I move to Allyl chloride, the rate goes up. And it goes up by about 79.

Now, if I look at the structure of this compound, this compound and allyl chloride, there is not a huge difference in the sterics. So, there is a double bond over here, and there is no double bond here, and that's it about it. But the rate increases by 79-fold. So that is very interesting. Even when I moved from Allyl chloride to benzyl chloride, the rate goes up even further up, and it goes up from 79 to 200. So, now, in order to understand this, we sort of invoke the concept of orbital interaction.

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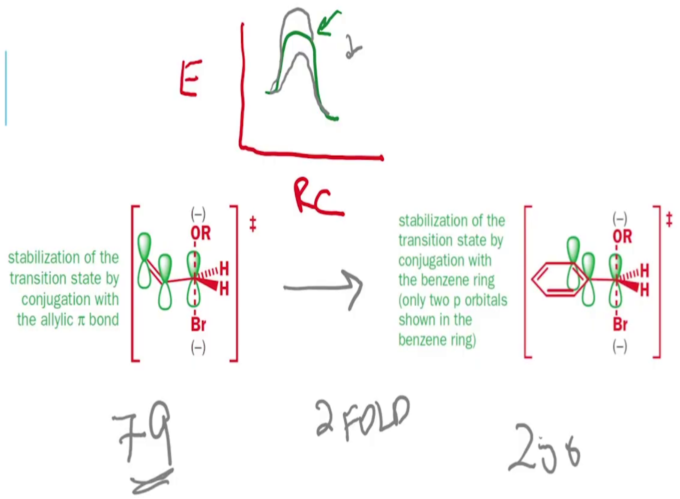

stabilization of the transition state by conjugation with the allylic π bond

stabilization of the transition state by conjugation with the benzene ring (only two p orbitals shown in the benzene ring)

So, here, as we have previously looked at, in many cases, so if I look at the energy and the reaction coordinate, and if I draw out the, let us say, the energy profile. So, anything that stabilizes the transition state, which is going to lead to an acceleration rate is going to be favoured. And anything that destabilizes the transition state is going to result in a decreased rate.

So, what we understand from the experiment is that the rate of the reaction goes up by 79-fold. So, therefore, there must be some effect on the transition state of the reaction. So, the way we understand it is that there is a pi bond next to this carbon, I mean, in this case, it is Br that is shown here, but it is the carbon chlorine bond. So, there is a this p-orbital, which can interact with the bond that is being formed over here and the bond that is being broken over here.

And that results in some stabilization in the transition state energy, and therefore the rate goes up. So, the example in Clayden that describes this figure is with OR and Br. But you can very easily substitute Br with Cl and OR with I, and the same picture emerges. So, therefore, one can understand the acceleration in rate by invoking stabilization of the transition state by delocalisation with the allylic π bond.

Now, going into the benzyl group, the benzyl group here, also, we find that the rate goes up further. And this rate, for example, in the benzene ring, you have a complete aromatic ring that can interact with this. And so, some level of extra stabilization is achieved by moving from allyl to benzyl. And therefore, the rate goes up somewhat. So, keep in mind, the rate increase from here to here is only about 2-fold.

So, this is approximately around 80 to 100 and this is 200. So, it is only about 2-fold. So, it is not like a huge increase in rate. So, it is not something that we would want to spend too much time on. But there is some level of stabilization of the transition state by the extended conjugation. But the most important experiment here is the following.

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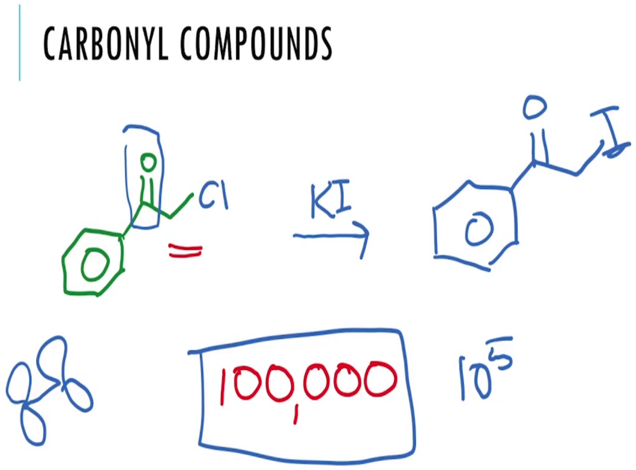

CARBONYL COMPOUNDS

When I do this experiment in the presence of benzoyl chloride, that is this chloride over here, I find that the rate of reaction goes up by 100,000. So, this is a 10^5 increase in rate of the reaction. So, as you can imagine, this is a very, very large increase in rate. And, we know that there is going to be some stabilization that can be afforded by the C=O, because that the C=O is going to have two p-orbitals over here, and so on.

But yet, it is not something that will completely explain the experimental outcome, because the rate of the reaction is going up substantially. So, in order to understand this, what we propose is a model such as this.

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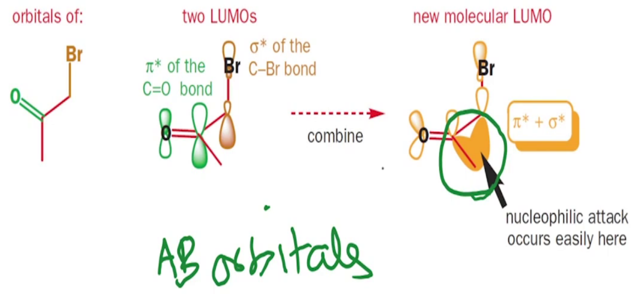

So, when we look at this molecule orbital picture, we know that, the C=O, and if you look at the π^* of C=O, the π^* is going to, there is going to be a smaller component from oxygen, and there is going to be a larger component from carbon. This is something that we have done previously in the course. And now, if you imagine that this π^* is going to interact with this carbon-bromine bond or the orbital there.

And here, keep in mind, we are looking at the antibonding orbital, which will be the σ*. And so, the σ* orbital of the C-Br bond is going to look like this. And whereas the σ* of the C-Br bond on the other side is going to look like this.

But if we propose that there is a combination of this anti bonding orbitals, so combination of the anti-bonding orbitals can result in a new orbital that is being formed over here. And this orbital is going to further more delocalized. And one can suggest that the nucleophilic attack happens much easier here, when compared with the aliphatic bromide.

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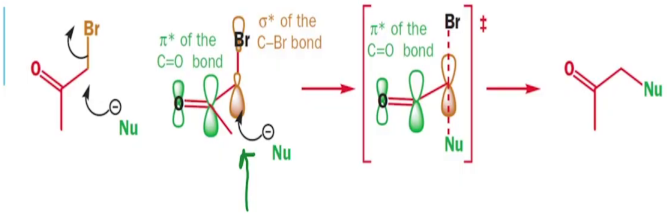

So, the idea here is that when the nucleophile attacks, the nucleophile attacks from 180 degrees from this carbon bromine bond, but since we are looking at this combined sort of more stabilized anti-bonding orbital over here, it is more facile.

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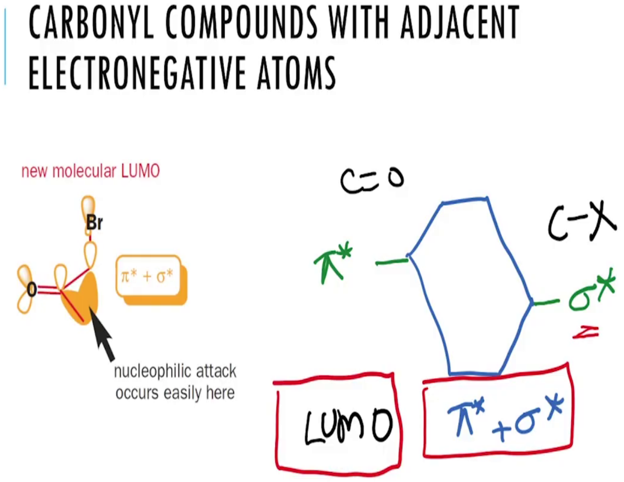
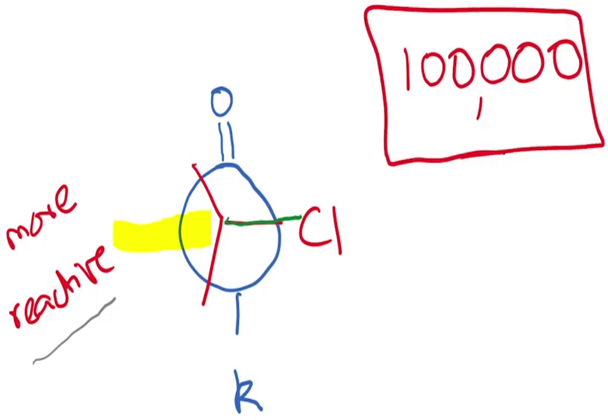

CARBONYL COMPOUNDS WITH ADJACENT ELECTRONEGATIVE ATOMS



So, therefore, the carbonyl compound with an adjacent electronegative atom is a very special situation and we can draw out an orbital picture such as this. So, here is the π^* of the carbonyl compound, and here is the σ^* of the Carbon-X bond. Now, when they combine, they produce a new orbital which is of substantially lower energy compared to the π^* and the σ^*.

And therefore, the reactivity of the center goes up, that is the reactivity of the center as we know, is dictated by the energy level of the LUMO. And the energy level of the LUMO goes down because of the combination of the σ^* and π^* leading to a new further stabilized antibonding orbital. So, if I have to draw this picture a little differently when the carbon chlorine bond is perpendicular to the C=O.

So, keep in mind that the stabilization that we are suggesting happens when the carbon-bromine bond is perpendicular to the carbonyl. So, as to maximize the orbital interaction. So, when the carbon-chlorine bond is perpendicular to the C=O, then the attack which happens on this carbon here is going to happen at a much easier or in a much faster way, because this kind of arrangement is more reactive.

So, of the various conformations of this compound, this conformation is the more reactive conformation and the rate of reaction is substantially higher than the other conformations. So, this is how we understand the 10,000 or the 100,000-fold increase in rate of the nucleophilic substitution reaction.

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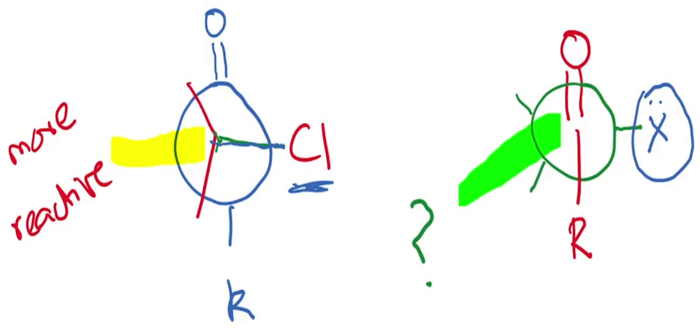

If X is not a leaving group, attack on this orbital will result not in nucleophilic substitution but in addition to the carbonyl group.

Again, this effect will operate only when the C–X and C=O bonds are perpendicular so that the orbitals align correctly.

Now, when I go to the same picture, if I have a compound X, which is an electronegative atom, which does not leave, so this X is not a leaving group, how does this influence the reactivity of the carbonyl? So, let us pause here for a minute and try to understand this because this has a consequence on how reactive a particular conformer is when there is an electronegative atom adjacent to the carbonyl.

So, whatever we are proposing, that increases the rate of the substitution at this carbon, also will have an impact on the reactivity of the carbonyl. So, of course, when X is not a leaving group. So, let us assume that X is not a leaving group, then there is going to be still combination of the orbitals, there is still going to be a combination of σ* and π^*. But instead of activating the carbon-chlorine bond or carbon-bromine bond as here, what it is going to do is it is going to activate the carbonyl carbon also towards nucleophilic substitution.

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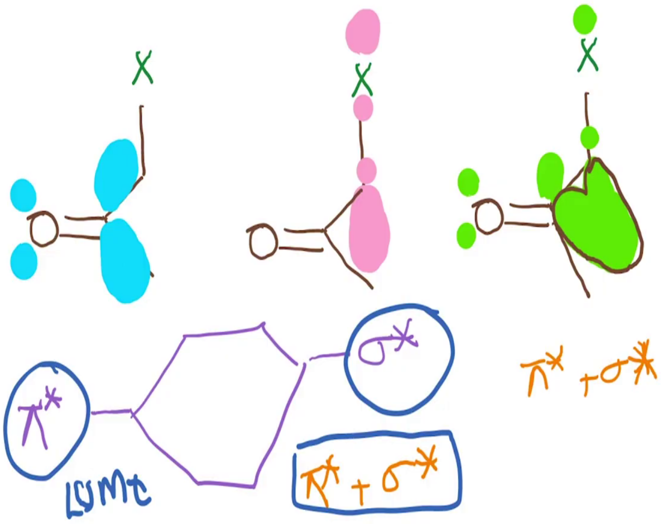

Now, if we want to look at it in terms of pictures, I have drawn it in the following way. So, this is the π^* of the CO, which we are very familiar with by now. This is the σ* of the C-X bond where, there is a level of orbital here and there is going to be a level of orbitals, some amount of orbital here. And now, when these two combine, they are going to produce a new set of orbitals, this combination of orbitals, which is going to be the new LUMO.

So, this is going to be the new LUMO. And as we saw with the previous case, the new LUMO is substantially lower in energy compared to the original LUMO that we had considered. So, the way we would draw this picture is that if I consider the π^* of this carbon-oxygen bond, and if I consider the σ* of the carbon-X bond where X is an electronegative atom, they both combine and they produce another orbital which is a (π^* + σ*), which is going to be substantially lower in energy and this is going to be my new LUMO or the more reactive LUMO.

So, what we are trying to tell you is that when you have an electronegative atom next to a carbonyl, so the first situation that we looked at is when there is a carbonyl next to the electronegative atom, which happens to be a leaving group, then a particular conformation where in the carbonyl is perpendicular to the Carbon-X bond substantially increases the rate of the reaction or makes that conformation much more reactive due to the appropriate combination of molecular orbitals, or the way we understand it is that the appropriate combination of these orbitals produces a conformer that is going to be substantially more reactive.

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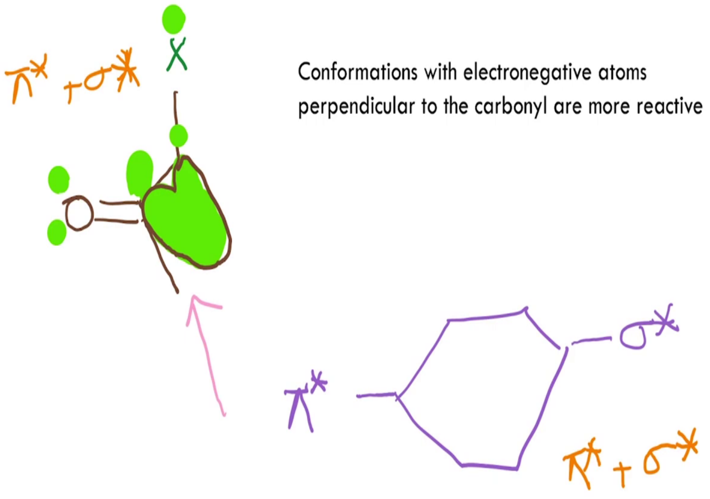

Conformations with electronegative atoms perpendicular to the carbonyl are more reactive

But now, when X is not a leaving group, the same combination of orbitals can occur for that particular conformation. And what we might expect is that particular conformation is more reactive towards the nucleophilic addition reaction, which is what we are looking at when it comes to carbonyl compounds.

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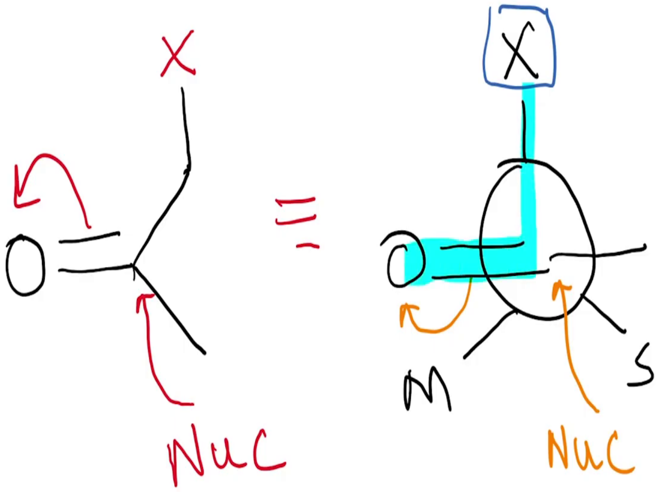

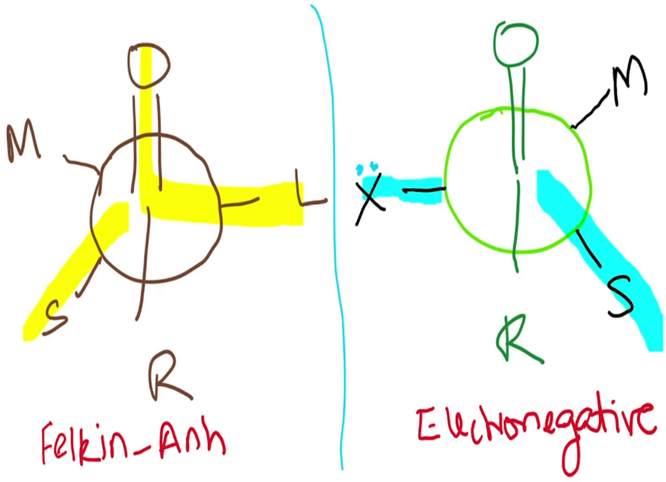

So, therefore, when X is an electronegative atom, which is not a leaving group. Now, what we can expect is that the nucleophile attacks the carbonyl, which is likely to occur, and the conformation where in X is perpendicular to the carbonyl is going to be the most reactive conformation. So, just to put this in perspective, the Felkin-Ahn model is dictated by sterics, wherein the largest group is perpendicular to the carbonyl functional group.

And that is what will tell us whether this is the conformation that is going to be the most reactive conformation. And essentially, the conformation wherein the attack happens at 105 to 107 degrees. And this helps us predict the major product. But when there is an electronegative atom adjacent to the carbonyl, then the electronegative atom ends up at the position which is perpendicular. And the most reactive conformation is this wherein the smallest group is now situated over here. And the attack happens from here.

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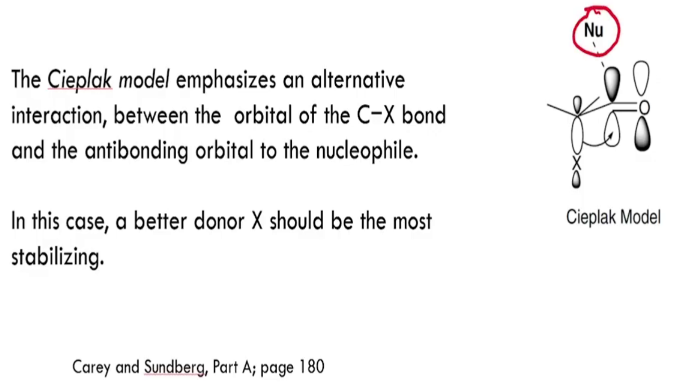

The *Cieplak model* emphasizes an alternative interaction, between the orbital of the C−X bond and the antibonding orbital to the nucleophile.

In this case, a better donor X should be the most stabilizing.

Cieplak Model

Carey and Sundberg, Part A; page 180

So, this effect of the electronegative atom has been given a name and that is called the Cieplak model. So, the Cieplak model emphasizes an alternative interaction between the orbital of the C-X bond and the anti-bonding orbital to the nucleophile. So, in this case, what happens is that the interaction between the C-X bond and carbonyl group here produces the most reactive conformation, and the better the donor, the more electronegative X is the better this interaction is and the more reactive that particular conformation is.

So, the Cieplak model suggests that an alternative interaction between the Carbon-X bond and the antibonding orbital is important. And that dictates the most reactive conformation wherein the nucleophile can approach. Now, in order to understand this, let us look at an example.

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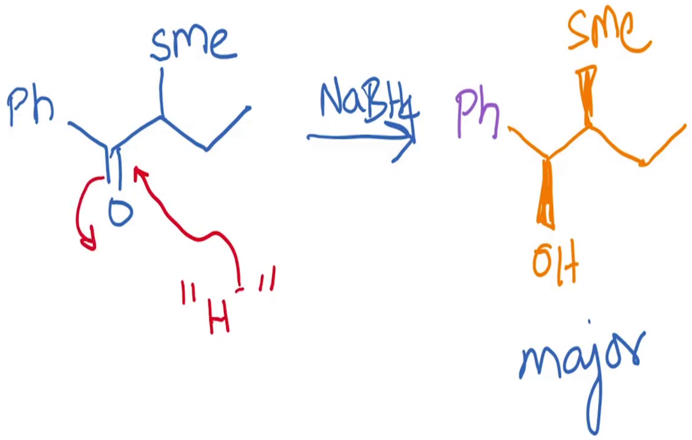

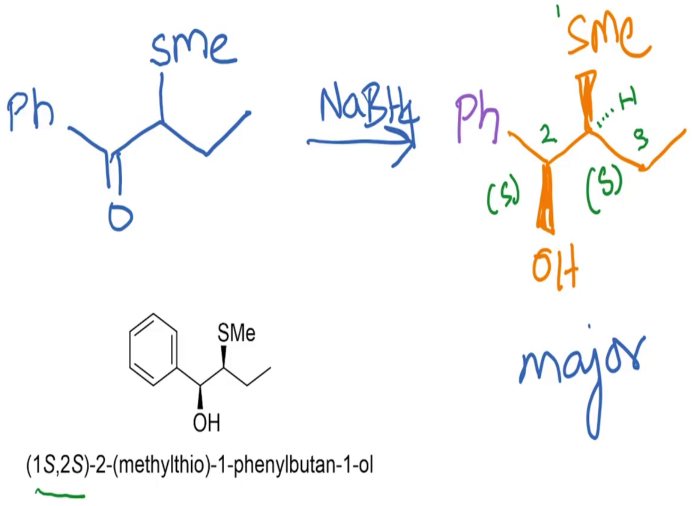

So, the first example that we are looking at is if I take this compound, which is shown here, and I react this with sodium borohydride, the major product that I get here is the following compound. Now, Sodium Borohydride is a source of H$^-$ as all of you know, and so H$^-$ is going to attack and then form an alcohol.

So, now in order to make things sort of clear, let us first assign the stereochemistry for this compound, and so that we can find out whether the model predicts the outcome correctly or not. And so, the way I would assign this stereochemistry, I would label this as 1, and this carbon as 2, and this carbon is 3, and the hydrogen is over here. And so, this would be (S).

And similarly, if I assign the stereochemistry for the other chiral center, I get (S). And so therefore, it is (1S, 2S) -2- (methylthio)-1-phenylbutanol. And now, let us move to the model.

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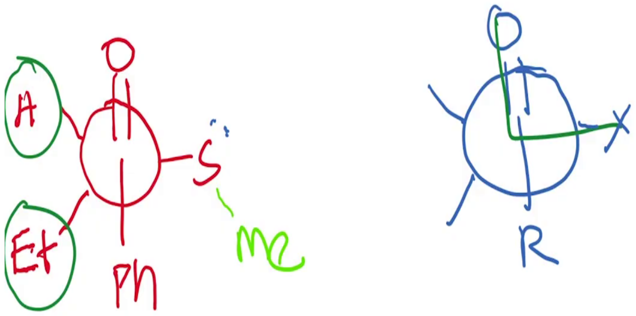

So, the model tells us that for the conformation, the C=O and let us say the electronegative atom, so the electronegative atom or the atom with the lone pair of electrons here is sulphur. And so, sulphur is going to be perpendicular. And, then you have the other groups, which could be the large group and small group and so on over here.

So, the key assumption in this is that the C=O is perpendicular to the electronegative atom. So, based on this, we can draw out a conformation like this, where this hydrogen is here, this ethyl is here, and the phenyl group is here. I would urge all of you to go back and draw this out by yourselves.

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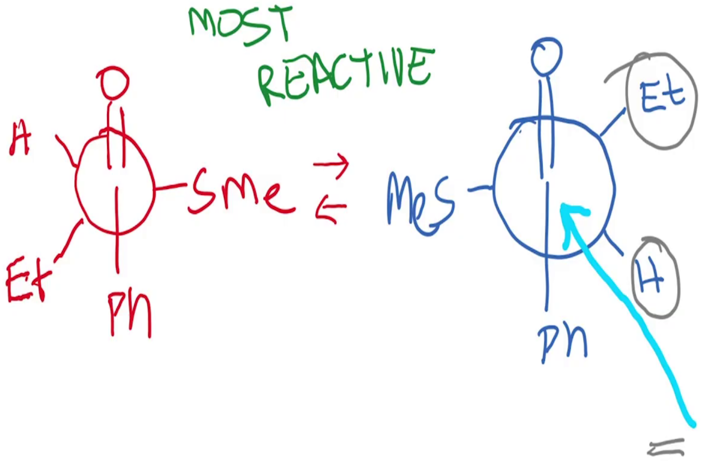

And so, when I do a rotation across this carbon-carbon bond, then essentially, I have these two conformations. And this model tells us that these are the most reactive conformations. So therefore, the barrier towards reaction of these two conformers is going to be the lowest. And now in these two situations, there are again, as we know, there are four approaches. And so, the approach wherein the smallest group here is hydrogen, and the next largest group is ethyl. And so, this approach from here is going to be the most favoured approach.

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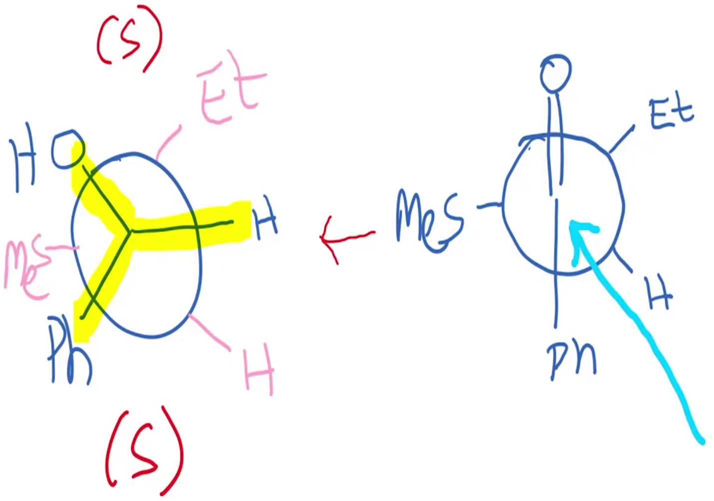

So, if I go ahead and draw out the product that is formed. Now, once this approaches, we know that the C=O is going to break the O H is going to end up here. And the phenyl ring is going to end up here. So, that is where this is written out. And the hydrogen which comes in or hydride which comes in is here. Now, if I assign the stereochemistry over here, what I will find is I get the (S), (S) configuration.

So, with this in mind, we can try and understand, or we can try and predict the product that is formed, as long as we know that the atom has a lone pair of electrons. And if it is electronegative, then the model that needs to be applied is this. If there is no such situation, then we are going to apply the regular Felkin-Ahn model and predict the product that is going to be formed.

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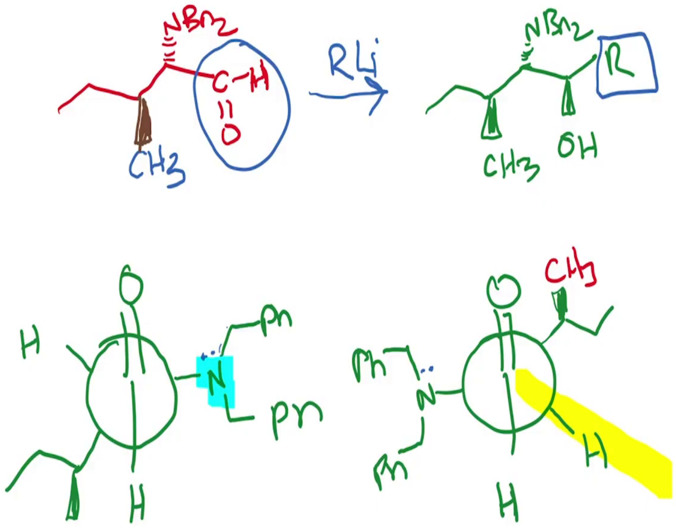

Now, let us look at one more example, wherein we have this kind of group. This is NBn_2, which is nothing but a nitrogen with two benzyl groups. a benzyl group is this as shown here. And so, the nitrogen with two benzyl groups has a lone pair on the nitrogen. And so, this is compound. And what we do is we react this carbonyl compound with, let us say, methyl lithium, or ethyl lithium or some organolithium compound, and we end up with this product.

Now, let us see whether our model is able to predict the correct stereochemistry. So, the model here is that the C=O has to be perpendicular to the most electronegative atom, which happens to be this nitrogen over here. And this nitrogen's lone pair is going to interact with the C=O and increase the reactivity. So, among the two conformations, we find that this the one with the yellow drawn here, this trajectory is the most favoured.

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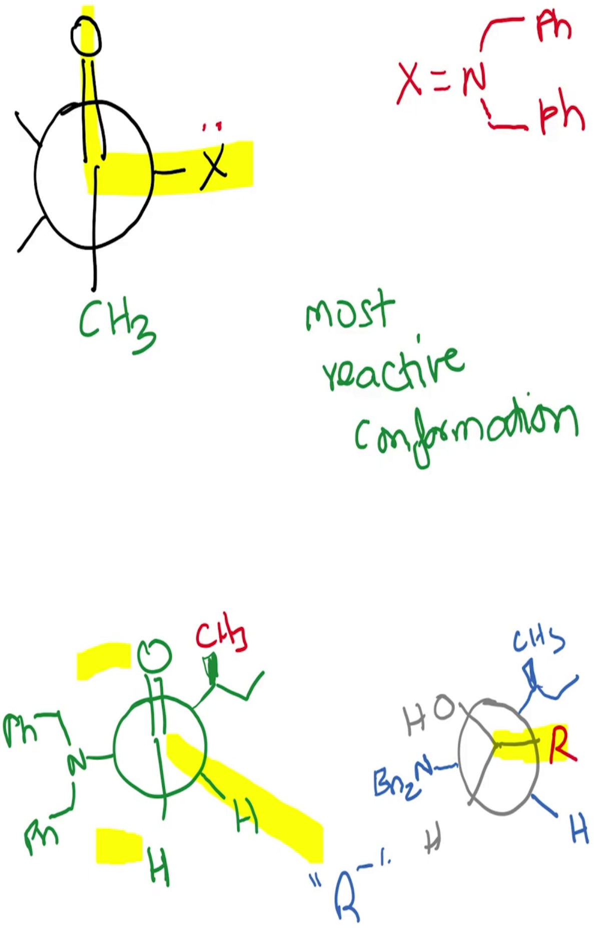

And therefore, we would predict that the attack would happen, or this is the most reactive conformation, and the attack would happen from here. And again, what we are looking at is the nucleophile, which is R^-, and when R^- attacks here, the OH ends up going here and hydrogen ends up going here. And so, the Carbon-R bond is going to be formed over here.

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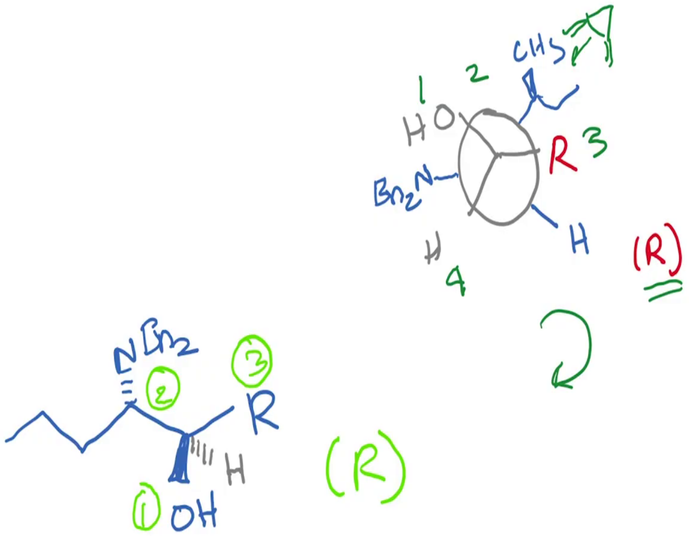

Now, the way we would check it is to assign the absolute stereochemistry, which I have done here. So, when I send the absolute stereochemistry for this compound, what I find is that, this gets priority number 1, the carbon behind gets priority number 2, R gets priority number 3, so 1, 2, and 3, hydrogen is number 4.

So, if I look from here, the hydrogen is far away from me and so it is clockwise. So, therefore, it would be (R). And now, if I redraw this, which is the structure that has been given to us, the stereochemistry that has been assigned here is also (R). And so therefore, the model that we have proposed is working.