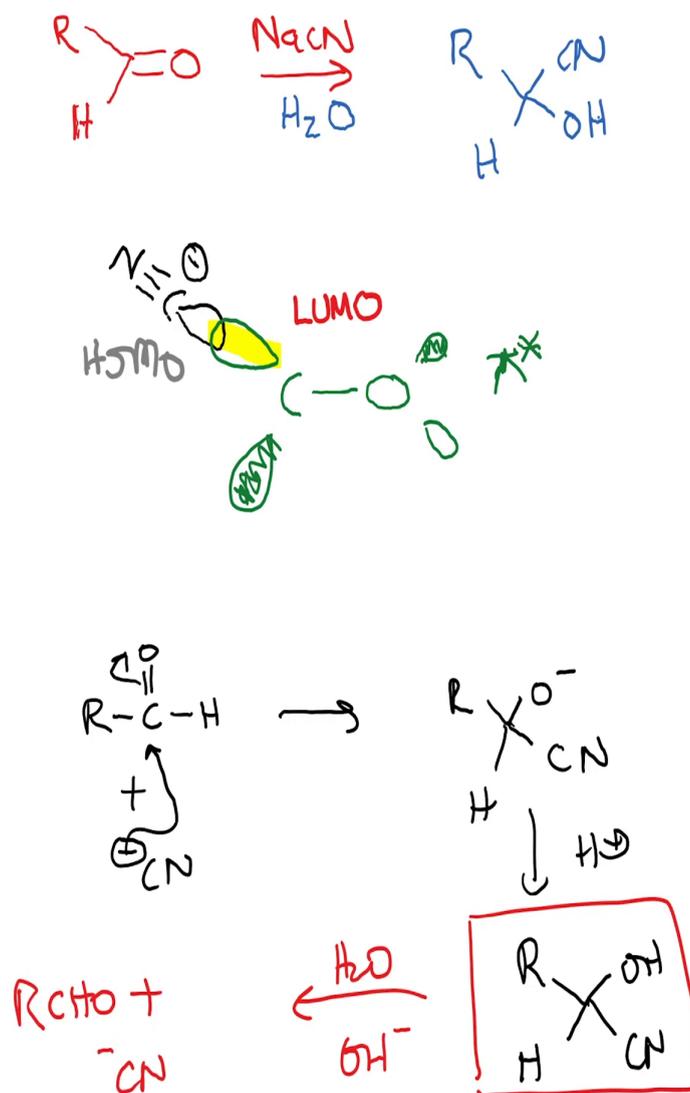


Introductory Organic Chemistry II
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Indian Institute of Science Education and Research, Pune
Module 03
Lecture 21
Addition Reactions on Carbonyl functional group

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So, in the last lecture, we were looking at various molecular orbital aspects of carbonyl functional group. And so now what we will do is we will just look at one addition reaction across a carbonyl. So, as we discussed, the addition has to happen across a C double bond O and the $C=O$ is quite polarized. And so, you will find that the addition, it is prone to attack by a nucleophile. So, the example of a nucleophile we can take is sodium cyanide.

So, Sodium Cyanide is an excellent nucleophile, and it adds to carbonyls quite nicely. And it forms what is known as a Cyanohydrin. So, we have discussed this previously in our course. And let us now try and understand the way in which cyanide attacks the carbonyl compounds. So, let us quickly recap. So, there is a carbon-oxygen bond.

And we discussed that the π^* of carbonyl is going to look like this. And so, you have π^* , which is going to be the site of attack by an electrophile. And now, when you consider the attack, what we may want to think about is that this is one of the orbitals, it is an anti-bonding orbital, but having a large lobe, it is likely that the electrophile attacks on this lobe over here.

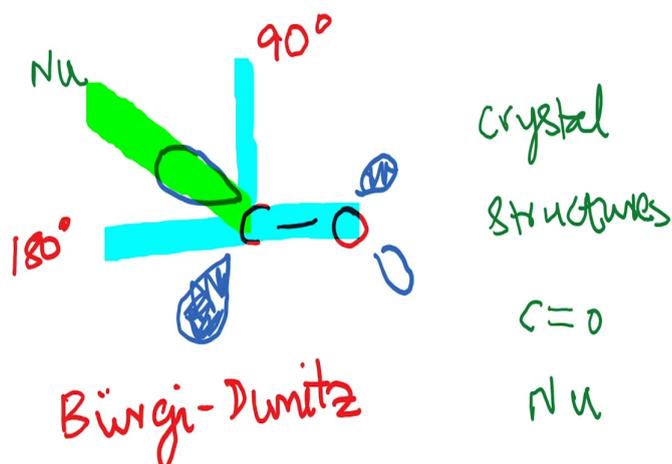
So, now, if you take a cyanide, so cyanide is $\text{C}\equiv\text{N}$, and it has a minus charge, as we know, and this has an orbital that is going to come and interact with the antibonding orbital. So, as we have looked at earlier, so this is the highest occupied molecular orbital of cyanide, which interacts with the LUMO of carbonyl. So, this is a picture that starts emerging, when we want to understand how carbonyls are going to react.

So, I am just going to push this down a little bit, so that we can get more space. So, the highest occupied molecular orbital of cyanide ends up reacting with the lowest unoccupied molecular orbital of the carbonyl compound. And so, that becomes a good starting point for us to understand about stereochemistry of addition and so on.

Now, what happens after the addition occurs, if you want to do an arrow pushing mechanism, then the way we would want to represent this is that $\text{R}-\text{C}=\text{O}-\text{H}$, plus, CN^- , so CN^- is going to attack here, this opens up and then, it picks up a proton. So, you know the rest of the mechanism, so then it picks up a proton and forms RCHOHCN . So, this is called the cyanohydrin. So, here it picks up a H^+ and gives you the final product. Now, one of the interesting things about cyanohydrin formation is that this is a reversible reaction.

So, if you isolate a cyanohydrin, and dissolve this in water, an aqueous base, so you add some mild base, for example. And what you are going to get back is the aldehyde plus CN^- , so this is going to be the product. So, therefore, it is a reversible reaction. And this is just an interesting thing for us to know. And you might have encountered this in your previous course as well.

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Now, let us get back to the attack. And let us think about how the attack is going to look like. So, I am just going to draw the C double bond O again, and here is the antibonding orbital π^* , and let us just colour this so that we are clear about the signs of the p orbitals. Now, as we looked at previously, the antibonding orbital is at an angle. So, this for example, is the CO and if I have to draw a perpendicular here, this is going to be the perpendicular and this is 180 degrees.

And so, this is somewhere in between the 90 degrees and 180 degrees. And so, it is definitely not at 90 degrees, and definitely not at 180 degrees, and it is somewhere in between. So, this becomes interesting because the lobe that is going to interact with your incoming nucleophile is going to interact at an angle. That is point number 1. Now, experimentally, people are looking for clues about how to understand this whole attack.

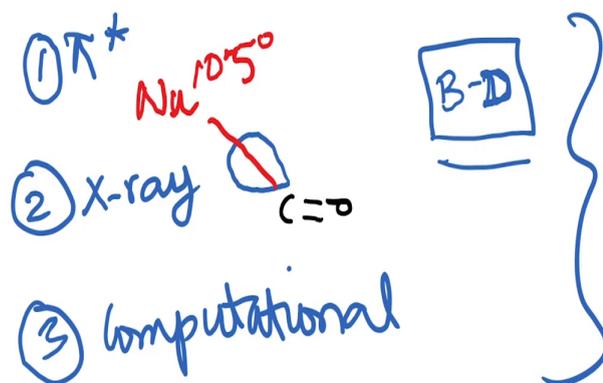
And there are these two individuals known as Bürgi and Dunitz. These two guys did a lot of work on this. So, what they did was, they went and looked at crystal structures of carbonyl compounds, they looked at crystal structures of carbonyl compounds, and not just carbonyl compounds, but carbonyl compounds, which were crystallized with nucleophiles; $C=O$, and in the presence of nucleophiles.

And what they did was they studied a large number of these compounds. And, they found something very interesting, they found that the geometric relationship between the carbonyl and the nucleophile was not random, and there was a definite pattern to this. As and when the

carbonyl compound and the nucleophile got close to each other in the crystal structure, and as you know the crystal structure gives you a snapshot of what happens in the solid phase.

So, in the solid phase, the movement of atoms is not very large. And so, once it is crystallized, it is going to pretty much stay in that position. So, and also, the interesting thing about crystal structures is they are thermodynamic minima, it is not necessarily the absolute minima, but one of the minima that can occur. So, combining these two concepts, it looks likely that it is not unreasonable to expect that from crystal structures one can deduce what are favourable forms of arrangements.

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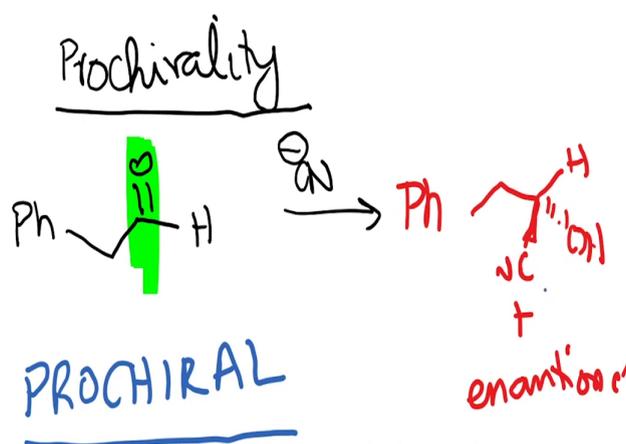
So, what they found was that the attack, I mean, the carbonyl compound was not at 90 degrees, it was in fact, when it was interacting with the nucleus, it was at an angle of 105 degrees. And so, as and when they looked at the crystal structures of nucleophiles in the presence of carbonyls, especially with the ones where the nucleophile was close enough to the carbonyl, they noticed that it was not at 90 degrees, but it was at 105 degrees.

So, there are two sort of interesting aspects here. So, one is the π^* is also not at 90 degrees and the angle at which the nucleophile interacts with the carbonyl in solid state, which is called the Burgi–Dunitz angle, is also not 90 degrees. So, therefore, the traditional picture that we understand where $C=O$ interacts with the nucleophile at 90 degrees is false. So, it is more likely that it attacks at an angle.

So, this is very important, because this is something that allows us to understand how carbon is going to react. So, in addition to these two, that is, number 1 is the π^* and number 2 is the crystal structure, X-ray structures. The third clue comes from high level computational calculations. So, very frequently, especially in mechanistic organic chemistry, we use computation to support experimental data.

So, since the angle, the Burgi–Dunitz angle suggests that it is now somewhere between 105, 106, 107 degrees, you can now develop a computational model that can help support this finding. So, all these three put together suggests that the attack of the nucleophile does not occur at 90 degrees. Now, this helps us develop a framework.

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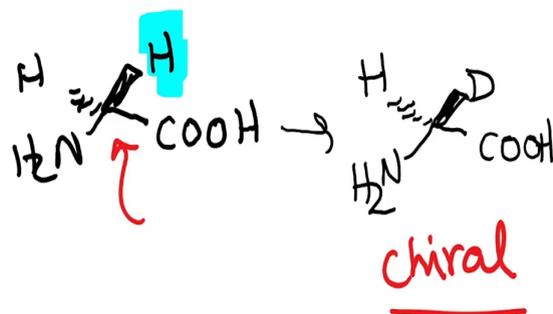


Now, before we go forward, we want to understand certain terms. So, now, let us look at some terms that are important. The first term that we want to understand is Prochirality. So we already know what chirality is. So, now let us look at what prochirality is. So, prochirality is nothing but it is a carbon center, or a center that is present in molecules that can become chiral.

So, here is the example that we looked at from the previous lectures. So, when you add a cyanide to this molecule, you end up having a racemic mixture. And so let us look at that structure over here, Ph, you have the possibility of CN being front and OH being behind and hydrogen here plus enantiomer. So, this is something that we looked at previously.

And so, I am not going to repeat this, but this center, which is the carbonyl over here, is called a PROCHIRAL centre, so this molecule is a PROCHIRAL molecule because it can form a mixture of enantiomers depending on which phase the attack happens. Now, a PROCHIRAL center can also be defined in a different way.

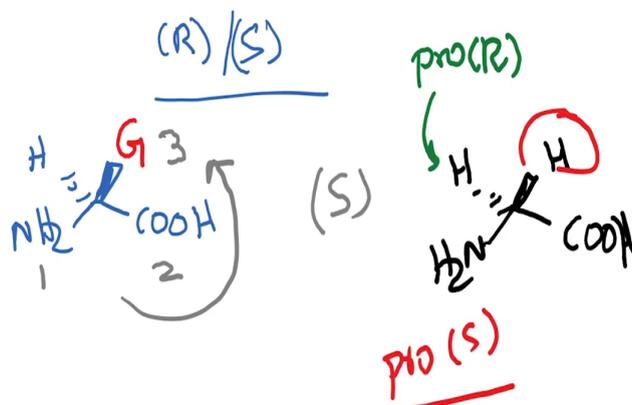
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So, for example, if I start with glycine, so glycine is nothing but COOHCH₂NH₂. Now, if I replace one of these hydrogens, with a deuterium, what happens is I get the exactly the same molecule, except that this is deuterium, and this is hydrogen. So, this molecule, this center is actually a PROCHIRAL center, because replacement of one of the hydrogens results in a chiral molecule. So, this as you know is chiral.

So, just to recap, PROCHIRAL center is nothing but a molecule, or a center, which is symmetrical other ways. But once you do certain modifications to it, either addition of a cyanide, or addition of nucleophile, or replacement of one of the hydrogens with deuterium, you end up with a chiral compound. So, this helps us understand what are the centers that can potentially form new chiral centers.

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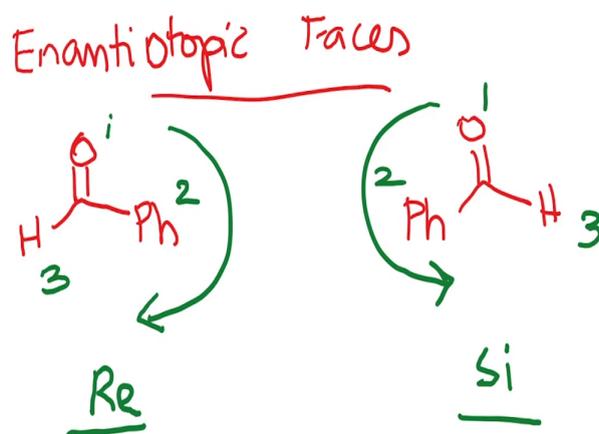


Now, we just want to understand how to define these molecules. And so, the way we do this is we use similar R / S nomenclature that we are very familiar with by now. So, for example, NH_2 , the same glycine example that we take, so we have one hydrogen here, and one hydrogen here. And what we are going to do is we are just going to replace this one hydrogen, as we discussed with the new group, so when I replace this with a new group, which I am going to call as G.

And what I need to do is I need to figure out whether this is R or S. So, let me start doing the nomenclature. So, nitrogen center gets 1, carboxylic acid gets 2. And let us assume that this G has a lower priority than NH_2 or COOH . And, for example, if G is deuterium, then it is going to be priority number 3. And now if I look at the rotation, this is going to be anti-clockwise.

So, this is going to be called as S. So, therefore, this original hydrogen that was drawn here, COOH , NH_2 , and this hydrogen which is here is Pro S. So, the reason is that if I replace that hydrogen with deuterium, or another group, it is going to form S isomer. And as a corollary, if I replace the other hydrogen with deuterium, then I am going to get R and so the other hydrogen is going to be called as Pro R. Now, what about faces, so these are already tetrahedral centers. But what about the sp^2 hybridized centers which we are going to deal with.

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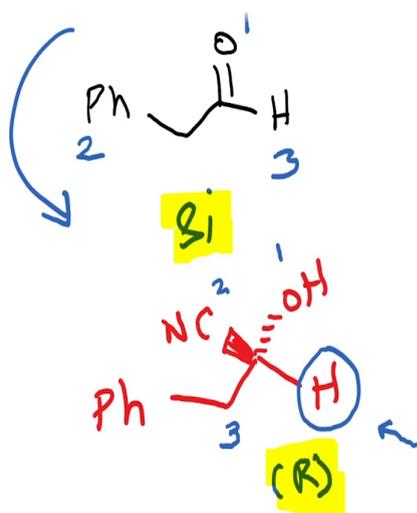


So, the way we would call this is these are called as Enantiotopic Faces. So, we have two faces for a carbonyl. And just to make things easy, I am just going to draw it in this following manner, $\text{H}-\text{C}=\text{O}-\text{Ph}$ and the other phase is $\text{Ph}-\text{C}=\text{O}-\text{H}$. So, if we have to draw it in this following manner, then this if I have to number this as 1 2 3, then this is going to be clockwise.

So, this is called the Re phase. And the same thing is 1 2 3, this is going to be anti-clockwise. So, this is called the Si face. So, whether a compound is reacting through the Re phase, or the Si phase, is something that we can very clearly define. So, in the case of tetrahedral molecules, you replace hydrogen with deuterium, and you label them as Pro R or Pro S.

In the case of carbonyl compounds, you can go ahead and put them in and then just number it in the priority. And if it is going to be clockwise, it is called Re. And if it is going to be anti-clockwise, it is called the Si phase. So, this helps us with precisely defining terms when we go forward.

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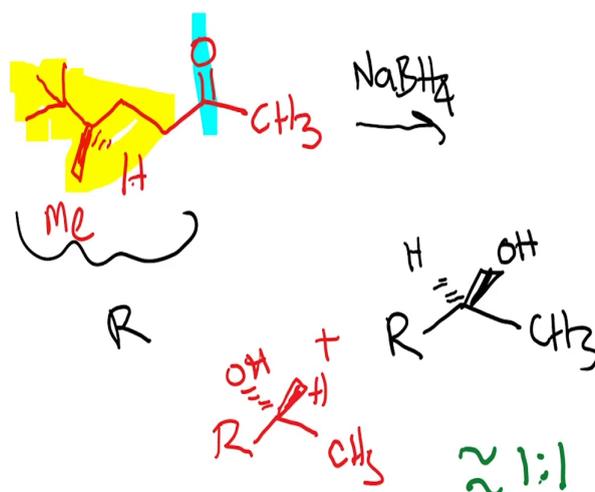


Now, let us just do a simple exercise of addition of a molecule. So, let us take $\text{Ph CH}_2 \text{C}=\text{O}$ H, the way I am drawing this is if you have to number this priority wise, will be 1 2 3. So, this is going to be the Si phase. And now if the Si phase reacts, then we are going to get CN over here, OH over here, H here, and Ph over here. So, if the Si phase reacts, then now I am going to get this compound, with cyanide So, that is the example that we looked at previously.

So, now if I have to number this, then I would get, this is priority number 1, this is priority number 2, and this is priority number 3. And so, if I am looking at it from here, then it is going to be anti-clockwise. But since the fourth priority is towards me, so this is going to be R.

So, just to highlight that there is no connection between the Si phase, and the eventual absolute configuration of the compound. Just to be careful, so Si does has nothing to do with S and R does not have anything to do with R. Now, what you can do is you can work out the addition through R phase, and write out the product that is formed.

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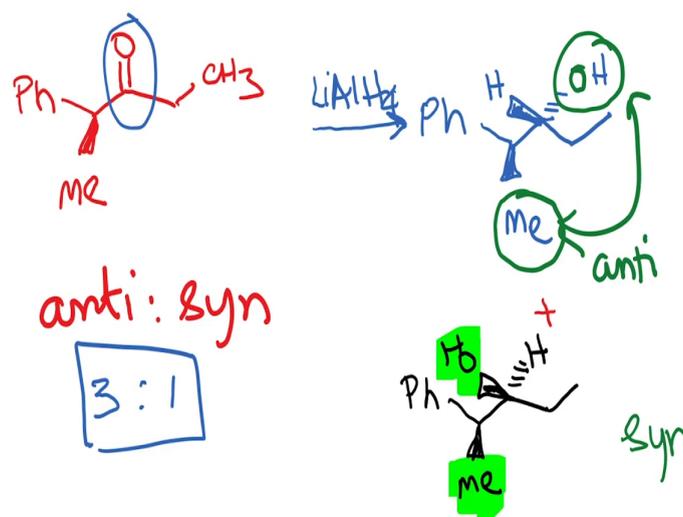


So, you are looking at an Enantiotopic faces, we have a Re face and Si face. And so, this helps us sort of understand that, if addition happens on one phase, you get a particular enantiomer. And if it adds on another phase, you get a different enantiomer. Now, we also know that, if you already have a chiral center in the molecule, then if you add to a carbonyl, then you are going to get a diastereomer.

So, the first experiment that we are going to do now is we are going to take this molecule here, this Me, H, and we get our C double bond O, CH_3 , so notice that this is the chiral center and it is quite far away from the carbonyl. Now, if you add a sodium borohydride, to this molecule, you are going to end up with a 1:1 mixture of the product and so as you know that there is a Re phase and then is an Si phase, and the addition can happen on both sides.

So, I am going to draw this whole group out as R, so you will get R CH_3 . Sodium borohydride is a source of hydrogen, H^- . So, you are going to end up with this product and you are going to get R C, if hydride comes from the other side, you get OH and CH_3 . So, these are the two products that you can expect to get and this is now approximately 1:1. So, that means that you get pretty much equal amounts of the two enantiomers. So, what it suggests is that the chiral center which is over here, which is quite far has no impact on the outcome of the reaction that means that you want to get 1:1 in product formation.

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However, the interesting thing here is that if I start with a slightly different compound, so I have a following molecule, C=O, CH₃, and I start with this compound. If we add sodium borohydride or lithium aluminium hydride to this compound, again, if our previous observation was correct, when we add source of hydride, we should get a 1:1 mixture of the two compounds.

So, let me draw out the two compounds over here. So, we have Ph Me, carbonyl over here and let us say hydride comes from the top phase and so you end up with H. And now, just to be sort of clear over here, we would call this compound as anti because these two have the two functional groups that have anti-relationship to one another. And let me draw out the second product that could be formed which will be following compound which is Ph, methyl group is over here and now the addition happens from the other side.

So, you have OH here, and a hydride is here, H is here. So, just to stick to the similar nomenclature, so this methyl is over here, OH is over here. So, this will be called as a syn. This is again something that we are already familiar with. So, you have a mixture of syn and anti-products. The only catch here is that the ratio of these two products that are formed is not 1:1. So, what we would expect based on the previous experience is that you should be getting a 1:1, but you end up with a 3:1 ratio of anti to syn.

So, this observation is very interesting, because as the chiral center moves closer to the carbonyl, you seem to have an impact on the outcome of the reaction. So, in order to explain

this, we need to be able to first understand a certain concepts. So, we will take this up in the next lecture.