Introductory Organic Chemistry - II

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Lecture 48

Conjugate Additions: Hard and Soft Nucleophiles

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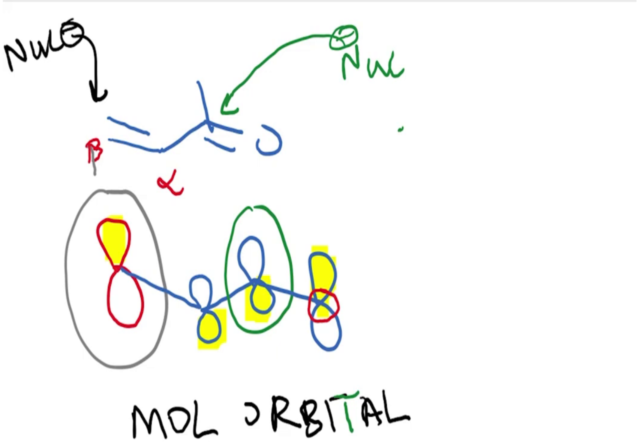

Let us understand some structural aspects of the carbonyl addition versus the conjugate addition. Now, we have already looked at the molecular orbital picture of the α, β-unsaturated ketone. So, we realize that, you know, while looking at the molecular orbital picture, that this beta-carbon has the largest lobe, and therefore, it is quite natural that we expect that the nucleophile attacks at this site.

But what we also must recognize is that this carbonyl carbon is also a site of attack, and therefore, the nucleophile although, you know this lobe here is smaller than this lobe, but it also can attack and give you the 1, 2-product. So, that is important for us to understand. Now, in order to see that, so therefore, from a molecule orbital picture, there is nothing preventing the attack happening on either of these carbons, although it is much more favored from an orbital standpoint, to attack at the beta-position. So, we will get to some of these questions later in the lecture. But now, let us try and understand the product formation in terms of energetics.

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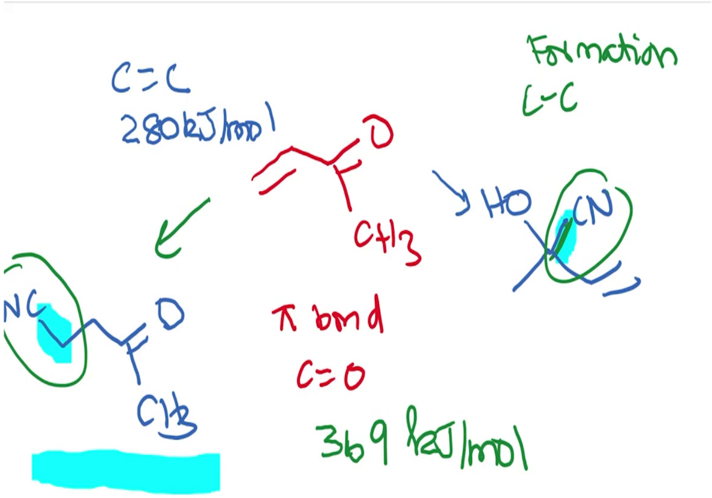

So, when we look at the molecule, you get you know, this is the starting compound and now if it does carbonyl addition, then this is the product that is formed. And what we can see here is that the pi bond is broken, between C double bond O is broken and new bond, a carbon-carbon bond is formed, formation of a new carbon-carbon bond. So typically, this pi bonds of the, you know, is around 369 kilojoules per mole.

Whereas in the second case, where there is a 1, 4-addition, the carbon-carbon double bond is broken. And this bond is about 280 kilojoules per mole, so the product that is formed is this. And again, here as well, you form a new carbon-carbon bond. So, the difference, this is a carbon-carbon bond here, and this is another carbon-carbon bond here. So, the difference between the two, you know sort of reactions is that you are breaking a carbonyl bond (C=O), which costs 369 kilojoules per mole. Whereas in the second case, you are breaking up C=C, which costs about 280 kilojoules per mole.

So, therefore, the stability of the 1, 4 of this product is substantially higher, because you find that the common factor here is the formation of these two new bonds, which we would expect to have similar bond style. So therefore, when you have a reaction where a stronger bond versus a weaker bond being broken, the energetics will definitely favor the breakage of the weaker part.

And yet, you get the product, the carbonyl addition product as the major product at low temperatures.

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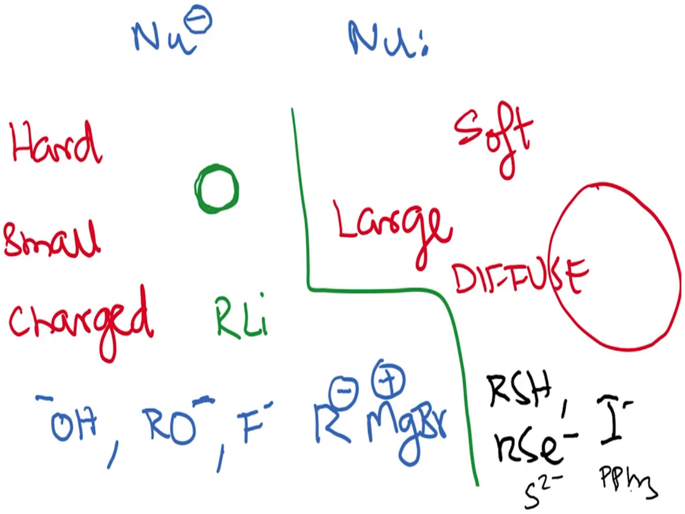

So, in order to explain this, we need to look a little bit into more detail about what factors are going to dictate these two consequences. And so, in order to understand that, I would like to explain to you the concept of nucleophilicity. So, we all know that the nucleophile is something that typically has a negative charge or a lone pair of electrons. And from the definition of nucleophile what we look at as a nucleophile is something that reacts with carbon. And so therefore, the reaction with the carbon center is what we are interested in when we are defining nucleophilicity.

So here, we would like to look at what are known as hard nucleophiles and soft nucleophiles. So, hard nucleophiles are small and have, you know a very strong charge, highly charged species and examples of hard nucleophiles are like hydroxide ion, alkoxide ion, you have fluoride, you have Grignard reagents R^-Mg^+Br, you have alkyl lithium, RLi and so on. So, these when compared they have a small and highly localized charge species and these are called as hard nucleophiles and they usually have a highly electronegative atom.

On the other hand, soft nucleophiles are large and have a diffuse charged. So, they are large atoms and they have a diffuse charge. So, you know the examples here are thiols, RSH, RSe^-, it could be RS^- also. And then you have S^{2-} which is basically a sulfide, you have iodide, I^-, and you also have PPh_3 and so on. So, these are usually fairly large atoms and the charge is quite diffuse. And so, these are the classifications of nucleophiles.

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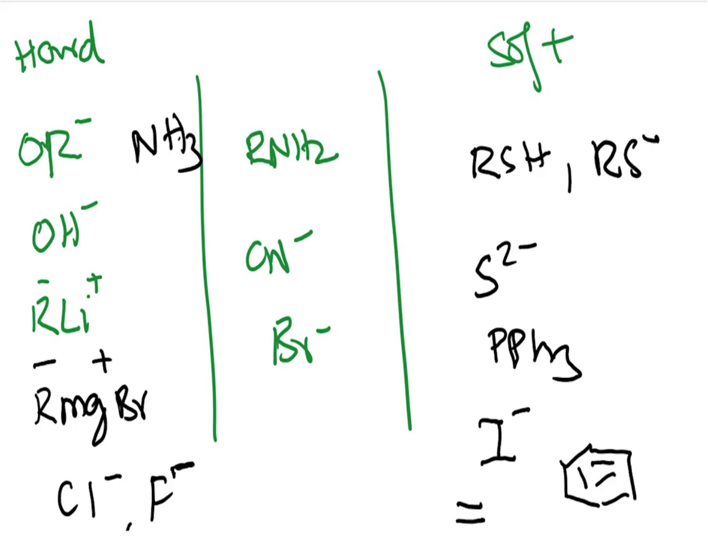

And there are also intermediate nucleophilicity, which we are going to look at. So, you have examples such as amines are RNH_2, then you have cyanide CN^-, bromide, and so on. So, these are intermediate ones. And the hard ones I am just going to redraw here, the soft ones are here. So, the hard ones are OR^-, OH^-, R^-Li^+ and then RMgBr these are the kind of nucleophiles that you are going to be sort of interacting with in this course.

Whereas the soft ones are you know you also have Cl^-, F^-, and so on. The soft ones are RSH, RS^-, S^{2-}, you have PPh_3. So, if you compare ammonia is also considered as hard. So, if we compare ammonia and phosphorus, you know they are in the same group, but you know phosphorus has a larger atom.

Similarly, sulfur and oxygen, sulfur has a much larger atom and you also have the halides you have I^- and so on. So, you know, in terms of reactivity, the aromatic ring and olefins are also generally considered as soft. So, this sort of classification helps us understand, this division helps us understand the reactivity.

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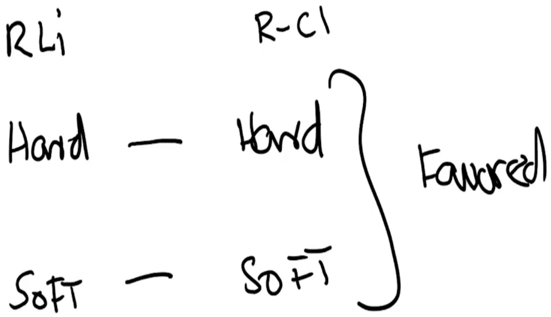

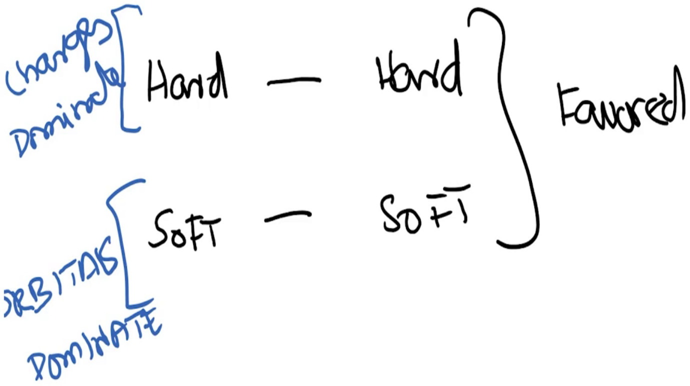

The fundamental sort of hypothesis or the premise that we use is hard atoms like to interact with other hard atoms. So, for example, RLi would like to react with RCl for example, so you have a hard-hard interaction. And you also have soft-soft interactions and these are favored. And so, from a standpoint of reactivity, when hard electrophiles or hard nucleophiles are involved, charges dominate. So, electrostatics that is anything to do with mild charges or partial positive charge or a partial negative charge they dominate.

Whereas, when it comes to soft-soft, the orbitals that is HOMO-LUMO kind of arrangement they dominate. So, this helps us put this whole reaction of organic compounds and nucleophiles and electrophiles in perspective. So, now coming back to the carbonyl example.

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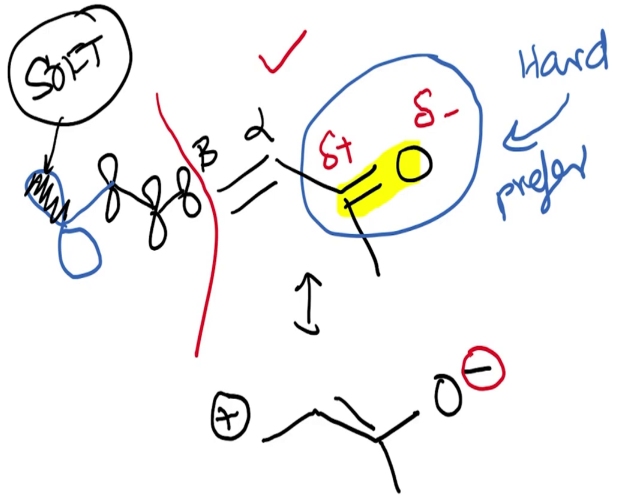

When we look at this α, β-unsaturated ketone, so if you recall we had drawn a resonance form where you had O minus and you had a full positive charge here. So, when it comes to and this is clearly the dominant form, so you have a delta minus here and you have a delta plus here. So, the amount of positive charge it is going to be produced here is extremely small. So, when it comes to a reaction of a carbonyl compound, the hard nucleophiles prefer to react here because electrostatics are actually going to dominate.

When it comes to soft nucleophiles because we know that this lobe is quite large, beta-position the lobe is quite large, the orbitals actually end up dominating. So, this being large, the soft nucleophiles prefer to attack here. So, under these conditions, the cyanide being an intermediate reactivity, that is it is neither hard nor soft, it seems to prefer or it seems to behave more like a hard nucleophile when it comes to the reaction with carbonyl compounds.

Whereas, you know something like a thiol or a selenium compound prefers to react at the beta-position. So, to put this in perspective, when we consider an α, β-unsaturated ketone, the reactivity of the α, β-unsaturated ketone is dictated by how good or how hard the nucleophile is.

A hard nucleophile typically prefers to react at the carbonyl position whereas, the soft nucleophile reacts at the beta position which is the 1, 4-addition that can occur.

And the way we explain this is that, we need to invoke this concept of hard and soft nucleophiles there is a scale and this is dictated by how polarizable the atom is. So, the smaller the atom and the more localized the charge is, the harder it is. The larger the atom and the more diffused the charge is the softer it is. And the second concept here is the that hard prefers hard and soft prefers soft. And now, we come to the third concept which is looking at α, β-unsaturated ketones the reaction at the carbonyl occurs when you have a hard nucleophile and conjugate addition occurs when you have a soft nucleophile.

And the one way we understand this is that because hard nucleophiles are, or hard-hard interactions are dictated by electrostatics the carbonyl bond is actually quite polarized and the charges here are substantially larger than on this position. Whereas soft nucleophile, soft-soft interactions are dominated by orbitals and the largest lobe of the molecule orbital is actually at the beta-position. So, this helps us put these results in perspective.

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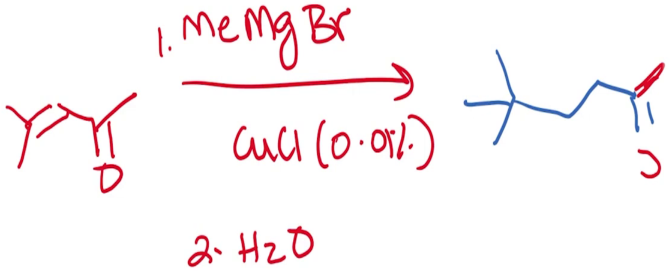

Now, coming to the last aspect of conjugate additions. If you recall the first example that I had given you, we had the addition of methyl magnesium bromide and in the presence of copper chloride at really low concentrations 0.01% and that was step number 1 and step number 2 was water and this gave you the conjugate addition product. So, this was the product that we obtained. And so, this result is needs to be explained as yet. Now, in order to understand this, the way we would like to address this problem is to understand the role of copper.

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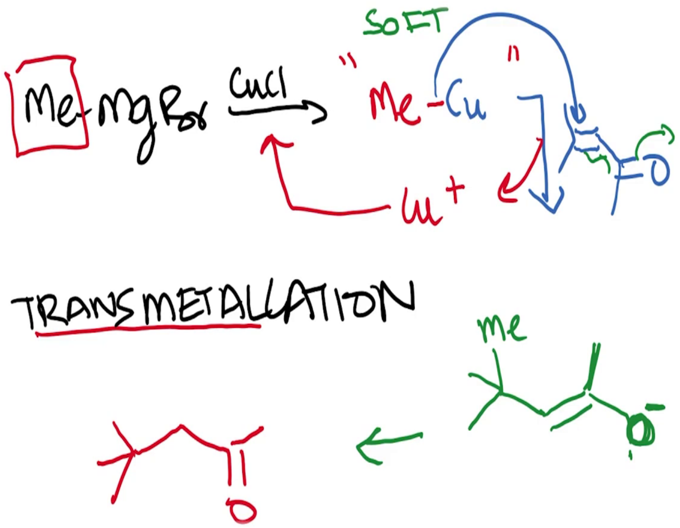

So, when we carry out the reaction in the presence of copper, methyl magnesium bromide in the presence of CuCl. So, copper chloride can actually in the presence of methyl magnesium bromide can do a reaction known as transmetallation. So, what this is basically it just changes the metal. So, methyl which used to be bound to magnesium bromide, now forms a methyl copper intermediate, and I want to put this in quotes because we are not completely certain the exact nature of this molecule, but we know that there is going to be a copper species involved very shortly I will explain to you why that is.

And now, this methyl copper actually reacts with your α, β-unsaturated ketone and you know this does the conjugate addition, you generate the enolate and then subsequently the enolate picks up the proton to give you the product. Now, what happens in this reaction is that once methyl, Me^- attacks here what is displaced is actually CuCl or Cu^+ which then goes back and does the transmetallation reaction. So, you therefore, need a very small amount of copper to be present and then this does the transmetallation in situ and produces the methyl copper.

Now, the very understand this is that metal magnesium bromide is actually a hard nucleophile and copper, organocopper reagents are actually soft nucleophiles. So, what we are doing is we are converting a hard nucleophile into a soft nucleophile and we are changing the outcome of the reaction. Obviously, this requires a lot of optimization to find the right conditions under which this kind of a transformation can be completely switched and this has been done and therefore, copper is usually added into these kinds of reactions to get you the conjugate addition product.

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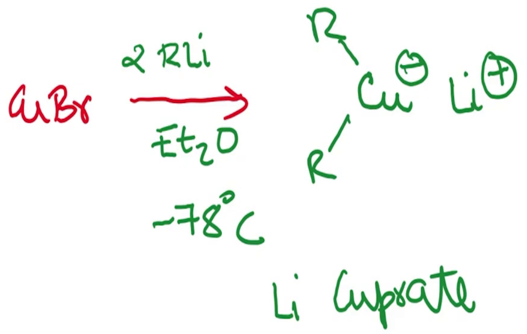

Alternatively, what one could do is to start with the organocopper reagent. So, what you do is you add, you take CuBr and then you add 2 moles of RLi and this is usually done in ether and at -78ºC conditions and this form the $R_2Cu^-Li^+$. So, these are called as cuprate reagents. So, this is called lithium cuprate and these lithium cuprates are you know they are not super stable and they must be used immediately but they can be generated and they also can be isolated under certain conditions and they invariably give you the conjugate addition product.

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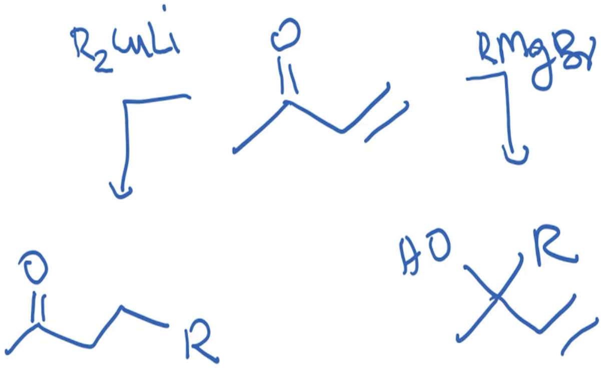

So, therefore, if you wish to do a 1, 2-addition then if you have a compound like this, and if you want to add to the carbonyl then you use RMgBr and it gives you this product after workup and if you would like to get the 1,4-addition product, then you use R_2CuLi and that would give you this product. So, this is really useful in terms of how you would like to manipulate reactivity of compounds and how you can actually get selectivity of addition. But the concepts that we are discussing here are fairly general and you can invariably predict that if you have a soft nucleophile you are going to get the conjugate addition and if you have a hard nucleophile you will end up getting the 1, 2-addition or addition to the carbonyl.