Introductory Organic Chemistry- II
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Lecture 27
Carboxylic acid and its derivatives - Part-1

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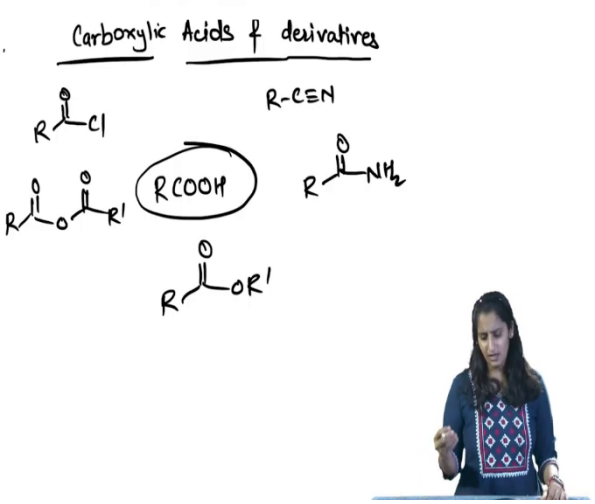

Welcome. So, now we are going to start talking about carboxylic acids and their derivatives. And as we discussed various functionalities in the start of the week, I do want to remind you quickly that we have in the center, the RCOOH, which is the carboxylic acid, we have acid chlorides, we have acid anhydrides, and then we also have esters.

We have amides, and we have nitriles. So, all of these are very important functional groups of carboxylic acids. And today let us start talking about this one first. We have discussed how to make carboxylic acids in the last course that we did. You can oxidize a primary alcohol all the way to a carboxylic acid. And with strong oxidizing agents, the reaction is very synthetically safe and also easy to do. Although, we will be covering some other reactions as well, so that I will do a little later in this talk.

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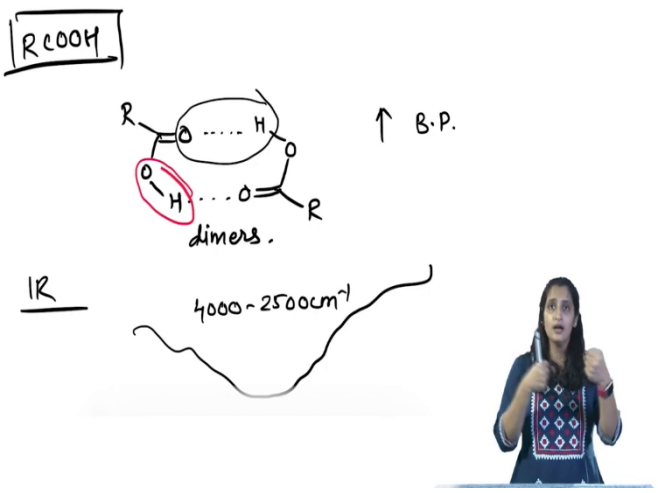

Now regarding carboxylic acids, remember, these are the molecules that were responsible for the differentiation of acids and bases, because most acidic molecules that are found in nature are carboxylic acid molecules. So, molecules like citric acid, molecules like tartaric acid, acetic acid, all of these are very sour to taste, and that is how we started differentiating acids from bases.

Other than that, there are various other physical properties that we should know. So carboxylic acids have really high boiling points. Why is that? Because remember that a carboxylic acid like this is forming hydrogen bonds with another carboxylic acid molecule. And in a solution, these hydrogen bonds are really held tight, so this is approximately 10 kilocalories of linkage and it is a powerful linkage when it comes to evaporating or boiling the molecule, and thus they have really high boiling points.

So, most carboxylic acids will have boiling points in the range of 90 to 100 ^{o}C or even higher and very difficult to boil off a carboxylic acid. Now, most of them will exist as dimers as I said. On the other hand, if you think about water, water also has the same hydrogen bonds which require or which make the boiling point go really high.

We have other derivatives like nitriles or amides, which also have higher boiling points. That is mainly due to the dipole-dipole interaction, because you have a heteroatom like nitrogen and you have partial charges developed as delta positive delta negative, and thus, you have a really high boiling point for those as well.

Now, because of this hydrogen bonding that is taking place, carboxylic acids show a very typical IR peak. Now, we have discussed a little bit about IRs, and IR, the infrared spectroscopy a little bit.

Now remember, IR is going to talk about how strong a particular bond is or how tightly it is held, and what is the vibrating frequency for that bond. Now, in the case of carboxylic acids, this OH bond here, it shows a very broad and wide peak from around 4,000 to 2,500 cm^{-1}, so it is a long range of wave number that you can see. And that is what we see here is that because that hydrogen is not held with that oxygen because it is forming that dimer, its hydrogen bonding that is the reason why you see such a broad peak for carboxylic acids.

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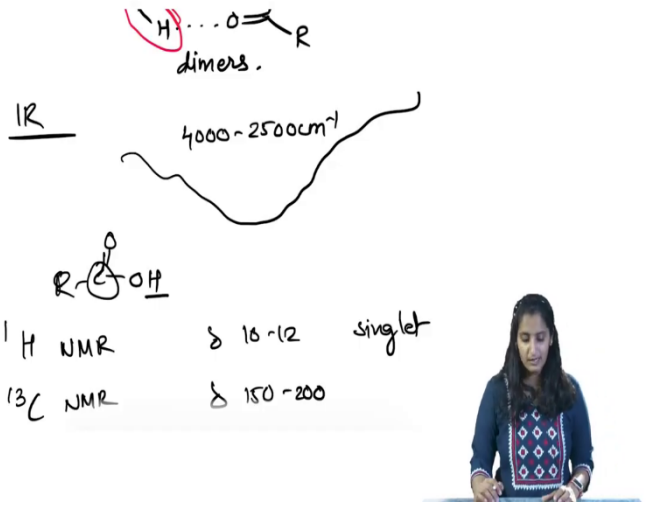

When it comes to other spectras carboxylic acids are going to show up this hydrogen, RC=OOH. This particular proton is going to show up in the proton NMR at around delta 10 to 12 and it is always a singlet. And in the ^{13}C NMR. We have not discussed it a lot, but in the ^{13}C NMR this carbonyl carbon will show up around 150 to 200 delta. So, that is about the spectroscopy or the spectral peaks of carboxylic acids.

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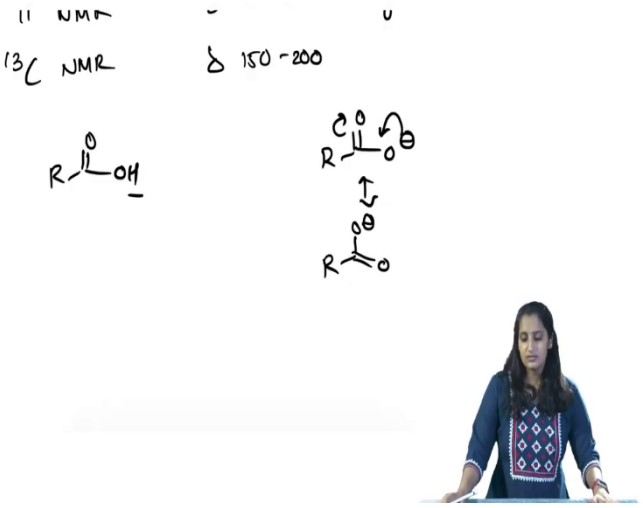

Now, we have also discussed some of the chemical properties of this molecule. And we know that they are the strongest acid molecules that are there in organic compounds. So, this particular carboxylic acid is very acidic, that proton has a pKa close to 5. And it is acidic because it forms a very stable conjugate base.

So, you have a stable conjugate base because it forms a nice contributing resonance structure, so you have a wonderfully contributing resonance structure. And the negative charge is held on oxygen making it very stable. So, that is about the acidity, and of course, it is possible to tweak the acidity a little bit.

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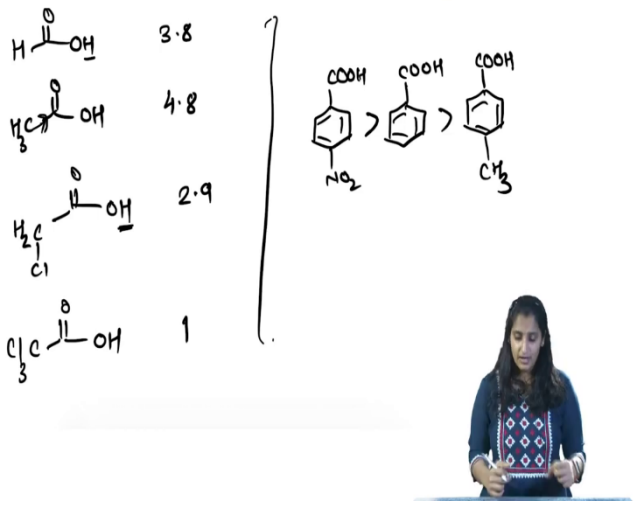

So, if we start looking at formic acid, so formic acid has a pKa close to 3.8. Whereas, if you make this R group as acetic acid, now acetic acid we use is vinegar, dilute acetic acid, it is close to 4.8. So, because this methyl is inductively electron donating, it makes the conjugate base a bit unstable. Now, if you add an ethyl group instead of methyl, it is going to increase the pKa even more. This is a good reminder to go back to acids and bases chapter in the first course and revise our pKa's is a little bit because they play a very important role later on in this chapter as well.

Now, if you add something that will instead of donating, it will withdraw electrons from that conjugate base and make it more stable the pKa will be even lower. So, for example, instead of the 3 hydrogens if I add 1 chlorine, then this chloroacetic acid will have a pKa close to 2.9. So, now we have gone lower in the pKa making it more acidic or increase the acidity.

On the other hand, if you add 3 chlorines, trichloroacetic acid, now, this one has a pKa very close to 1. So, the moment you add chlorines, which are going to inductively withdraw electrons from that conjugate base, the acid becomes more and more acidic. A very similar trend is also found for benzoic acids.

So, depending on the other functional groups on that benzene ring, whether they are electron donating or inductively electron withdrawing you will see a trend. For example, you have benzoic acid, para-nitrobenzoic acid is more acidic than regular benzoic acid and that is more acidic than p-Toluic acid (p-methyl benzoic acid). So, depending on the stability of the conjugate base the acidity is going to change. So, that is about the properties of carboxylic acids. And now we are going to start talking about the reactivity of these molecules. Now, when it comes to carboxylic acids or their derivatives they do a very characteristic reaction, and it is called as nucleophilic acyl substitution reaction.

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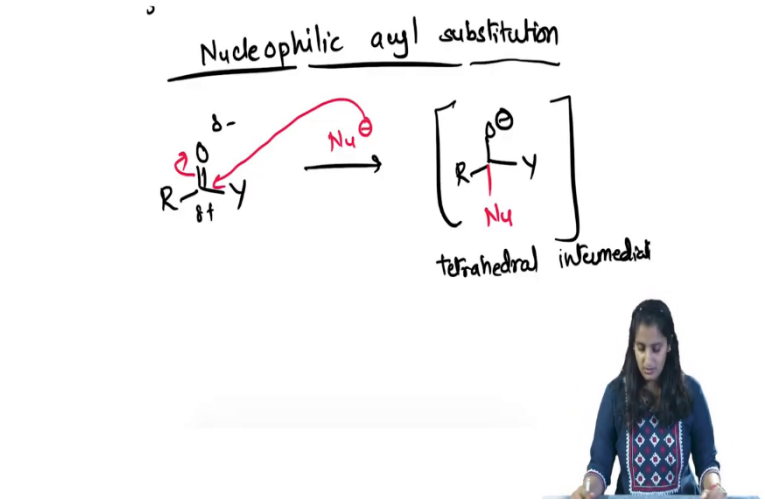

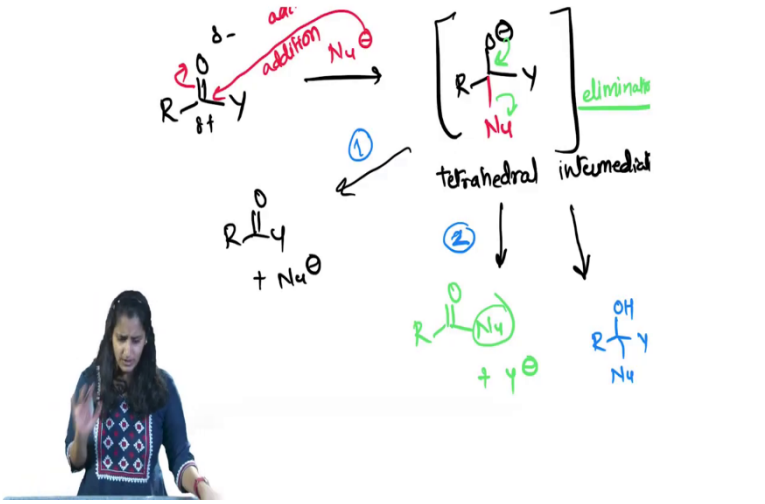

So, let me just write it down, so we are going to look at a generic mechanism of nucleophilic acyl substitution reaction. Let us look at it in detail. So, I am going to take a molecule, a very generic molecule RC=OY. And in the case of acid chlorides, that Y becomes a chlorine, in the case of esters, it becomes OR, in the case of amides it becomes NH_2 or NHR, so on and so forth. So, it is a very generic molecule.

Now, for any carbonyl, remember that it is a flattened planar molecule, it is a trigonal planar molecule right now. Add the carbon, because the carbon is sp^2 hybridized. And what is happening at that carbon, depending on the electrophilicity of the carbon, and we will go over

this as well. Remember that oxygen is pulling electrons away, it is pulling electrons towards itself, and as a result of which the carbon is now deficient of electrons.

So, you do have a little delta positive on this carbon, a little delta negative on that oxygen. So, what is going to happen, is that, any incoming nucleophile is going to sense that, electrophilic center at the carbon and it is going to attack there. So, that is the first step of the nucleophilic acyl substitution, it is the addition step.

So, a nucleophile, let me write it with a different color. An incoming nucleophile is going to target that center, and it is going to open it up. And what we are going to form here is, remember, the carbon does not want to form 5 bonds at a time, so it opens up the C=O, really creating an intermediate that looks like this. So, I am going to call it a tetrahedral intermediate.

So, chemists are kind of not so innovative with names because this tetrahedral intermediate literally gets its name from the geometry that it has, it is tetrahedral in nature. Remember, we started from a trigonal planar now, we are going to tetrahedral. Now, what is the fate of this particular intermediate? So, there are two fates that it can have or rather three fates. So, let me look at it this way.

So, now, if the nucleophile is a better leaving group than Y, Y which is a group based on the starting derivative. If the nucleophile is a better leaving group, what is that oxygen going to do? That oxygen is going to try and reform the carbon oxygen double bond, it is thermodynamically more stabilizing, so it reforms that C=O and kicks off the nucleophile. In the end, you do not get any reaction.

So, you have RCOOY + Nu. That is one possibility or what you can do is, you can put the electrons back on the carbon, the oxygen reforms the double bond. But if Y is a much better leaving group, then you have now formed a new molecule RC=ONu, so now you have a substitution. So, instead of Y you have substituted the nucleophile and you have Y^- as the leaving group.

So, that is one of the possibilities. And then there is always a third possibility, wherein, both Y and a nucleophile are really bad leaving groups, and that is what in fact, we see in the case of ketones. So, let us say this is not a carboxylic acid derivative, but let us say that if a nucleophile attacks a ketone, as a nucleophile attacks and if the nucleophile is a bad leaving

group you just form a new molecule, which is, wherein that oxygen grabs a proton and you can either form this. So, you form a hydrate.

Now, in the case of carboxylic acids and derivatives, we can either see the first or the second scenario very often. Because most of the times you have a very good leaving group and it leaves, so the second scenario is very often observed. If the leaving group is not such a good leaving group, we can do reactions to convert it into a good leaving group. And that is how this nucleophilic acyl substitution happens. The first step is the addition step, so this is the addition step. Let me just write it here, addition, and this second step depicted in green is the elimination step. So, very often, we are going to term it as addition elimination reaction.

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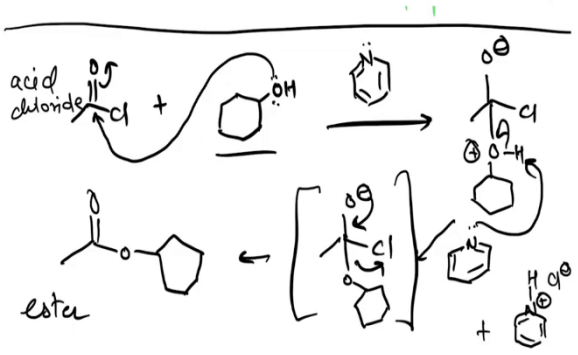

Let us look at one of the examples of this reaction, a proper example. So, I am going to start with acyl chloride, and I am going to react it with cyclohexanol. Now, what I am going to do is, I also need some kind of a solvent and a base for this reaction to happen, and that is going to take place with the help of pyridine. So, it is a good base and it is relatively nice solvent for doing this reaction.

So, what is the first step? Now, there are two nucleophiles here, really. Just to not confuse you, I am going to keep the solvent or the base a little separate right now and we will talk about what it really does later on. So, I am going to take this OH here, cyclohexanol and attack it here, and open it up; that is our addition step.

So, you have this particular intermediate formed. Now, this oxygen does not look happy because it is positively charged. Thus, what we now do is, now the pyridine comes into play, and you have it coming in as a base. And remember, now that oxygen has two choices. This is our tetrahedral intermediate that we had formed or we had talked about. Now, that oxygen has two choices, it can either kick off chlorine as chloride or it can either kickoff the alkoxide, so cyclohexanol oxide.

And just from our knowledge of acids and bases, we know that chloride is a much better stable molecule on its own, and it is a very weak conjugate base. So, what we are going to do is the elimination step, we are going to kick off the chlorine, in the end forming an ester. So, from an acid chloride we have formed an ester. And this alcohol, remember, it could be any alcohol, and you could still do this reaction, starting acid chloride could also be changed to any particular acid chloride of your choice, and thus, you have a way of really forming nice ester molecules at the end of the reaction. Here is the thing now.

Now pyridine, in this particular reaction being the base, it gets protonated. Remember, in this step, it is going to form this protonated pyridine. And in fact, with the chloride leaving you are also going to form a salt. Thus, you require equivalent amount of pyridine for this reaction to take place. Not only that, the pyridine here, instead of just acting as a base, it also acts as a catalyst. So, it does a nucleophilic catalysis. And what is that?

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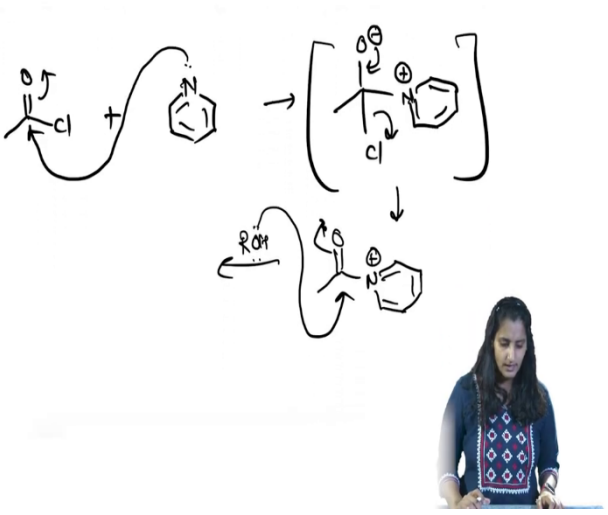

So, in the first step, instead of the alcohol attacking, remember, you have solvent molecule as the pyridine molecule, and it is lot of pyridine. So, what happens is in the first step, instead of the alcohol reacting you have pyridine reacting to form this tetrahedral intermediate. And actually, this kicks off the chlorine to form this. Now, your alcohol attacks. So, now ROH can attack and any alcohol for that matter and do the rest of the reaction. So, this is called as a nucleophilic catalysis, and pyridine will do that. So, there are two reasons why we are using pyridine here.

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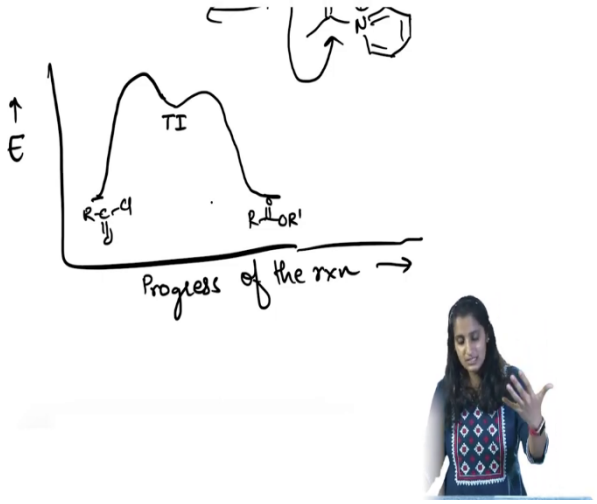

Let us go ahead. And let us look at the energy profile diagram for this reaction, and it is going to change depending on what kind of substituent we start with. So, just to give you a very simple energy profile diagram for this particular reaction, the addition step is, always remember, the rate determining step of the reaction.

So, the addition step wherein the alcohol came and attacked the carbonyl carbon and formed a tetrahedral intermediate, so you have a tetrahedral intermediate forming here. This is your acid chloride. And then later on you have the elimination step, and this is your ester and this is the progress of the reaction. So, that is our energy profile diagram.

It is very unlikely to have the elimination step as the rate determining step, but it does happen in some cases, and we will discuss those also. But very often, you will see that the addition step is the rate determining step. Rate determining step is the step that takes the longest or the highest amount of energy to go over that hill.

So, we discussed the energy profile diagram of this particular reaction, and we have accepted the mechanism that, it is addition followed by elimination, in between you have a tetrahedral intermediate. But how do we know that? How did people figure that out that you have a tetrahedral intermediate forming? Because remember, isolating the tetrahedral intermediate and really figuring out the structure of it using spectroscopic methods is a very difficult task.

And in those days, definitely, we did not have fancy spectroscopic techniques to really figure that out. It is a short lived, very short lived intermediate. So, how do we then decide that this is the mechanism, and not some other way. So, you can for example, have S_N2 type reaction, wherein the nucleophile comes from one side and then later on the leaving group gets kicked out. That is one possibility or it can have an S_N1 type reaction wherein the leaving group has already left and then the nucleophile comes and attacks.

Now, on a sp^2 center, the carbonyl carbon, both of these are less likely. But how do we know? So, in order to figure that out, scientists did various experiments and one of the scientists Bender, he came up with this particular experiment to figure out the mechanism of this reaction. So, I am going to describe that mechanism with which he figured out this particular experiment.

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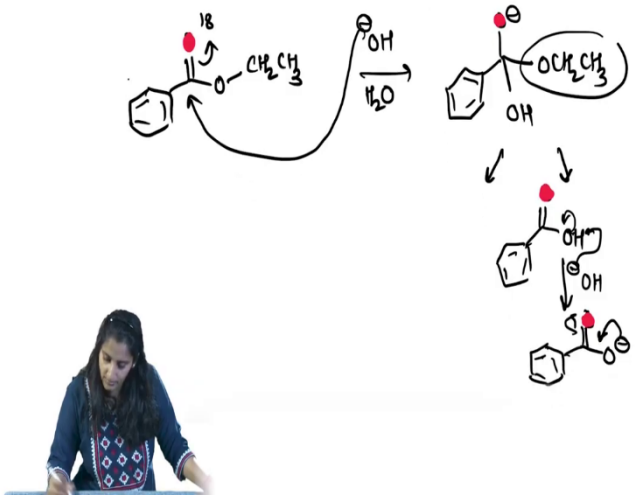

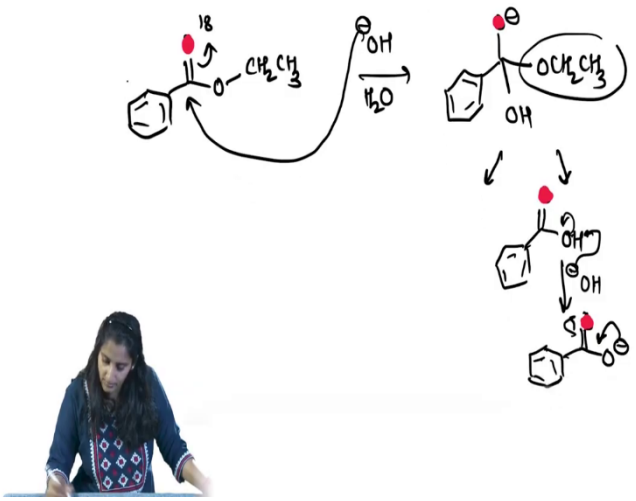

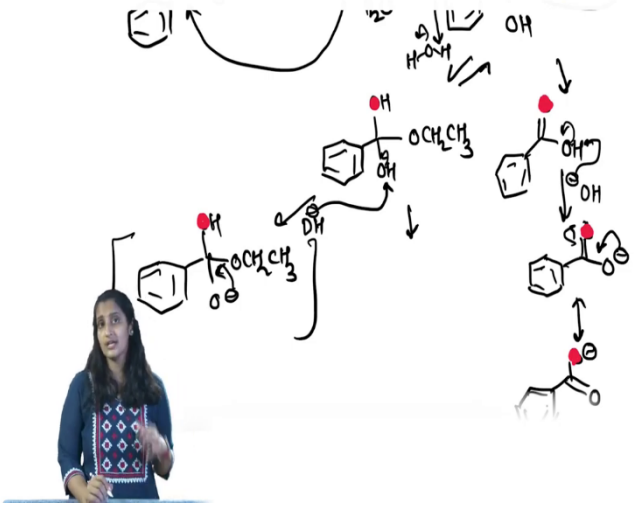

So, to begin with, we are going to start with an ester. But it is a special ester wherein the carbonyl oxygen is labeled with ^{18}O oxygen. So, it is not the regular oxygen or isotope of the oxygen that we see typically, it is the ^{18}O oxygen. And now, if we put this particular ester into base, so OH^- and water. Remember, hydrolysis of ester in the basic conditions is a very important reaction because the base catalyzed hydrolysis is also called as saponification with which we form the soap that we use.

So, the esters of long chain fatty acids when we form the corresponding saponification reaction, we obtain the soap. So, this is the mechanism of saponification. So, let us look at it in detail. So, what is going to be our first step? We have a nucleophile, we have a carbonyl carbon, it is going to come and attack. And it is going to attack here, it is going to open it up.

Now, there are possibilities such that. Now, this is one of the intermediates that is formed. Again, this intermediate has multiple possibilities that it can do.

So, remember in the case of we have always talked about OH^- as bad leaving groups. Although, when we are in really basic condition OH^- does not remain as bad a leaving group. So, OH^- is or hydroxides are bad leaving groups in acidic conditions. They are bad leaving groups in neutral conditions as well, but when the compound is in a really strong basic solvent or a really strong base itself then kicking out an OH is not very difficult.

So, now this can be kicked out in multiple ways. So, the first possibility is that, it kicks out this, the ethoxide. Between OH^- and ethoxide both of them have very similar leaving group abilities. So, either it can form this or this. And I am going to first draw the possible product. This wherein the carbonyl oxygen is still the ^{18}O oxygen. Now, we are in strong basic conditions again. So, the particular acid that you have formed is quickly going to react to form the corresponding conjugate base and this conjugate base is going to have a resonance structure that looks like this.

Now remember, you have moved the position of the ^{18}O label from the carbonyl and to the non-carbonyl oxygen. So, that is one possibility. What is the other possibility? The other possibility, is that, both OH^- (hydroxide) and ethoxide are terrible bases, so they are not like great bases. Although, they can be expelled in strong basic conditions, it is quite likely that the O^- that is present here can get protonated.

So, it gets protonated with water, and we form this. What else can happen? Now, there are again, this particular molecule can undergo different fates. One of them is that, a hydroxide comes in and grabs proton from here, really creating this tetrahedral intermediate. So, this is my tetrahedral intermediate. And when this tetrahedral intermediate collapses it is going to kick out either the ethoxide or it is going to kick out the hydroxide wherein the O is O-18 (^{18}O) labeled.

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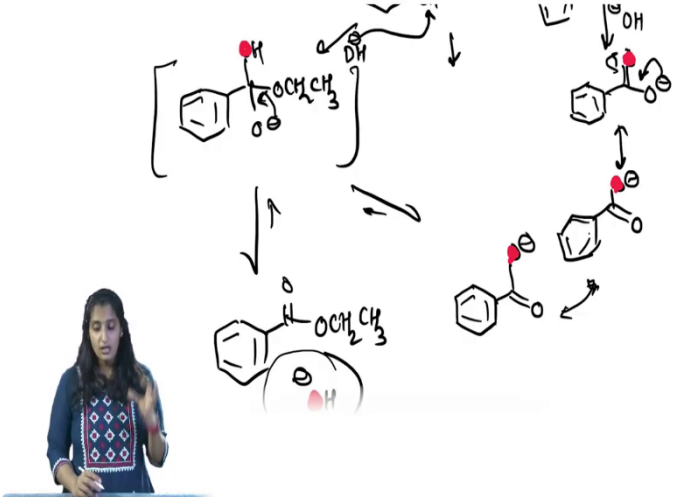

So, now there are two possibilities, let me draw those two possibilities. And remember, we are only drawing one, one molecule, but there are so many molecules in the solution and different molecules are undergoing different pathways of this reaction, so you are going to form multiple products. So, you are not only going to get one product, you are going to get a mixture of product at the end of this particular reaction. So, that is one possibility, wherein the leaving group is this particular OH^-.

So, now you have kicked out a ^{18}O hydroxide away. And the other possibility, as we were discussing, is that ethoxide gets kicked out, so you have this, which is very similar to or which is the same molecule as this one, the earlier one. And because this particular reaction happens, so that we form all of these products, wherein the ^{18}O labeled is seen to shift to a non-carbonyl oxygen or it is even seen to move away from the ester to really form OH^- or hydroxide in the solution. That is the reason why we know that a tetrahedral intermediate was forming.

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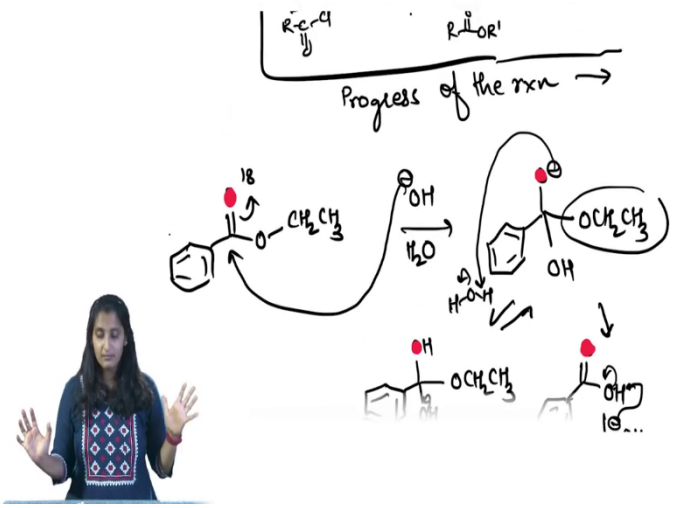

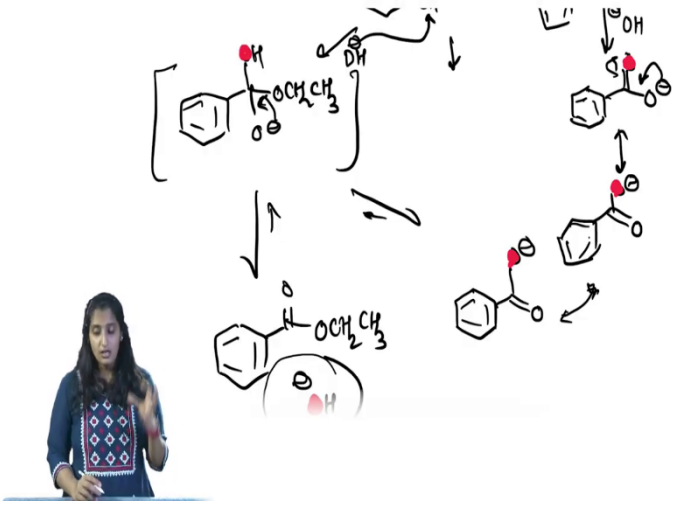

Remember, if there was no tetrahedral intermediate forming, then what would be happening, then you will have that carbonyl oxygen stay put throughout the reaction at the carbonyl position only, it will not change its place. So, the reason why we are seeing it move through the molecule and sometimes even leaving the molecule is because you have a tetrahedral intermediate happening. And that is how the mechanism of this particular reaction was figured out.

And it is really a genius way of figuring it out. And this is very often one of the ways that people figure out mechanisms is by adding a label that you can track throughout the reaction. And depending on various starting material and possible intermediates you can figure out which one pathway is being taken by the reaction.

So, we are discussing this nucleophilic acyl substitution, and we are still a long way to go. We have various of these acid derivatives to start with, which one amongst them really does the reaction more efficiently than the other? And if we have to put them in the reactivity trend, we will have to think about the two steps. First is the addition step and second is the elimination step.

The molecule that does the addition step the fastest is typically going to be the one that reacts in a better reaction. So, how do we know the tendency of these different derivatives to do this reaction, to do this addition step? It is going to depend on the electrophilicity of that carbon. If the carbon is a much better electrophile, the nucleophile is going to find it easier to attack, very simple logic. So, how do we decide the electrophilicity?

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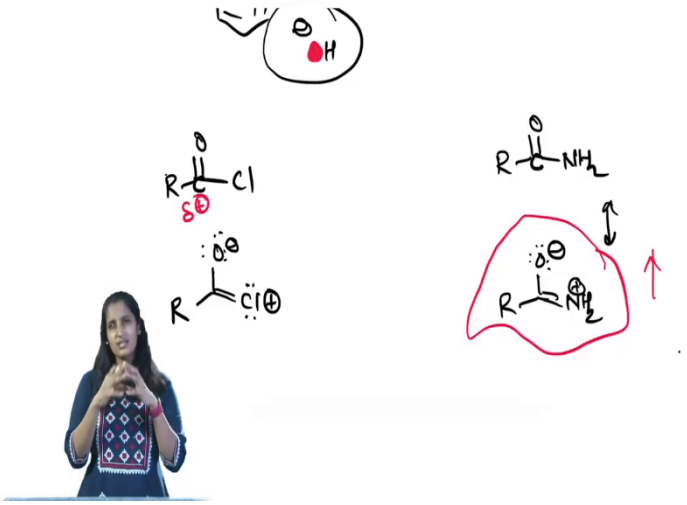

So, you have acid chlorides and I am going to take the example of amides. We are going to take two different examples. One is acid chloride and one is amide. Now the carbon here, if we ask the question, which of these carbons has a distinct positive charge, which one will we say? Both chlorine and nitrogen are actually equivalent in electronegativity, so both of them are inductively pulling electrons in the same manner, so then it becomes the resonance contribution.

Now, in the case of chlorine, you can have this resonance wherein this is a possible resonance structure. You can also have the other resonance structure as our $RCO^{-}=NH_2^{+}$, so that is a

possible resonance structure as well for amides. Let us look at this. Now, these are the possible resonance structures.

Now, if we ask the question which one amongst these is more contributing resonance structure? Depending on our knowledge of organic chemistry, so far, we know that chlorine been a third-row element, carbon mean being a second-row element, that orbital overlap is not as efficient as between carbon and nitrogen, which are both second row element. They have very similar sizes, the orbital interaction is much better, so the contribution of this particular resonance structure is way higher, as a result of which the carbon there not as electrophilic.

And this particular $^{+}$ on the acid chloride is way stronger, as compared to the amide and thus acid chlorides will undergo this reaction in a much better manner. They are more reactive in this particular reaction. Now, we can also discuss this based on the molecular orbital theory and the molecular orbital overlap. So, remember, what is happening. The lone pair on the nitrogen is being donated towards the carbon. Now, which orbital will it go in?

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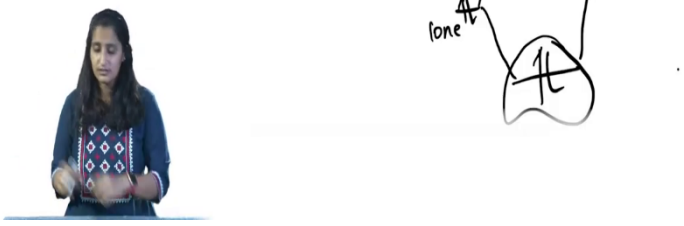

So, if we draw the diagram, the pi bonding molecular orbitals are here and the pi star (π^*), so these are the bonding and then you have the π^*, that are the anti-bonding molecular orbitals, which is here. To this, if the nitrogen then puts in the lone pair, you have them here. So, you have the electrons going from lone pair of nitrogen, that is the non-bonding electrons, they are going to the π^* of the carbon-oxygen bond, so it makes it more stable.

So, this addition into the π^* is one of the more stabilizing factors, and we can even show it with the help of the molecular orbital diagram. In this case, you have the lone pair of nitrogen, which is at a lower energy than the π^* because π^* is an antibonding orbital. Now, when the lone pair gets added to the π^*, you form a new more stabilizing orbital here, and that is why you have this kind of interaction being favored. So, that is one way to look at it.

The other way to look at it is based on, if we look at various derivatives of carboxylic acid and derivatives. The other way to look at what is the more contributing resonance structure is to look at the carbon oxygen bond strength. Now, if the carbon-oxygen bond is really held tight, the double bond, carbonyl bond, then it is much more likely that the substituent on this end is not donating electrons to form that particular resonance structure or does not have a very contributing resonance structure.

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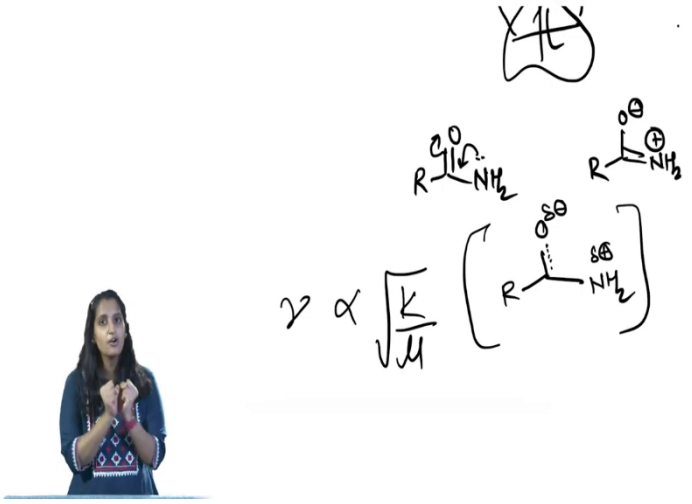

Why is that? So, remember, the moment you have this RC=ONH$_2$ verses this resonance structure; in the resonance hybrid, you are going to have a partial double bond character for that particular bond. So, that is the resonance hybrid of this particular molecular or amide. And the carbon-oxygen bond is no longer an intact double bond. It is a partial double bond, kind of a mixture between single and double bond, and thus, it is not as strong.

And one of the ways to look at it is based on the IR spectrum. Because remember, we talked about IR and we talked how the frequency or wave number at which we really see the IR is

proportional to √K/μ. So, we imagine different bonds to be of like of spring and K being the spring constant, that is how strong or weak the bonds are and mu (μ) is the reduced mass.

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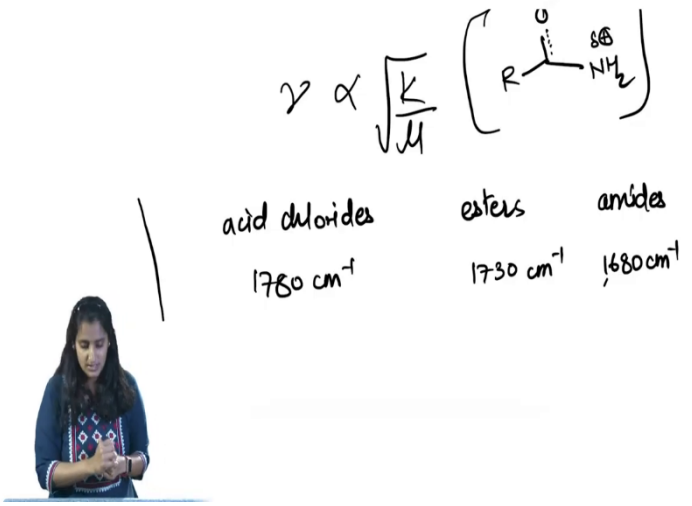

Now, if we see this or if we compare this, the bond that are really strong and intact, the ones having more double bond character are going to have a higher K, and they are going to vibrate at a higher wave number. And that is what in fact we find acid chlorides are going to have a wave number close to 1780 cm^{-1}, whereas, esters are going to be somewhere in between. So, 1700 or 1730 to 1750 cm^{-1}. And amides which have the maximum contribution by the resonance structure they are very low at 1680 cm^{-1}.

So, that is what we see that depending on the strength of the C=O the IR peak is also indicating where, in what frequency does it vibrate. That is one way to look at it, you can also look at the bond length, and the COO bond in acid chlorides is really short, as compared to in amides the C=O is increased in length.

So, for the addition reaction, acid chlorides are going to have it favored. So, acid chlorides are going to do, they are going to be more reactive than anhydrides, anhydrides are going to be more reactive than esters, and esters are going to be more reactive than amides because of the electrophilicity of the carbon, but they also have a preference for the leaving group which is the elimination step.

Now, in the case of acid chlorides remember the leaving group is chloride, whereas, in the case of amides, the leaving group is NH_2^-. So, you can really see, which one is a much better

leaving group because chlorides being stable on their own are kicked out just like that, so elimination step is also much, much faster.

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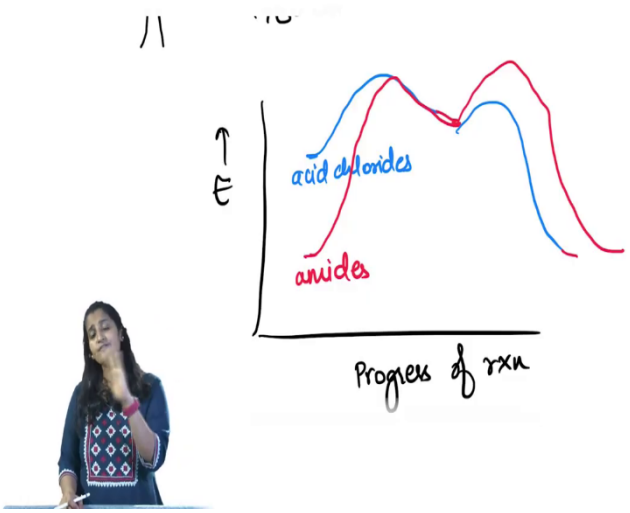

So, if I have to think of it from acid chlorides versus amides, and if we want to plot the energy profile diagram of both of these reactions reacting with the same nucleophile. If we put acid chlorides here because they are already more reactive, the electrophilicity of the carbon is high, amides have to start somewhere here, and this is energy, this is the progress of the reaction.

Acid chlorides are already starting at a very high point, and both of these have to climb the same peak to get to the tetrahedral intermediate. But for both of them the route is quite different, because acid chlorides have an easier way out. Not only that, not only in the addition step, in the post intermediate formation step, which is the elimination step, in that step also acid chlorides have a much easier leaving group and you form the product.

Whereas, in the case of amides because NH_2^- is a terrible, terrible leaving group you have to kind of imagine that it is even higher. So, amides can sometimes have the elimination step also to be higher than the, I will just put it like this. So, both of them end at the same place, but both of them have a very different route of the reaction.

To think about it this way that if both of them have to climb the same mountain, acid chloride starts from a base camp of the mountain, whereas, amides are starting from like ground level or the sea level, and they both have to get to the mountain. Once they get to the mountain,

acid chlorides are probably going to take a parachute and just jump down, whereas, amides have to climb another mountain and then come down. So, that is the reason why amide hydrolysis is not an easy reaction to do. And it is actually the reason why we might find amides much more abundantly in nature.

So, amide hydrolysis does not happen very easily. Whereas, acid chloride bottles, if you just leave them uncapped or even there is a slight opening to the bottle, the moisture from the air can hydrolyze most of the acid chloride molecules. Amides, we find these bonds in nature, our amino acids are having that amide linkage. And water being the solvent of life, it is much more reasonable to have amide linkages as the building blocks of our life here on this earth because otherwise we would not have a very stable structure formed. So, that is the reason why there is a difference in reactivity.

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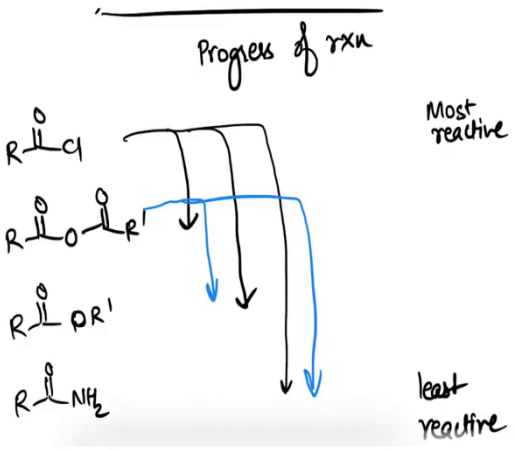

And if we plot all of these derivatives in the reactivity trend, you have acid chlorides up top, they are really, really reactive, then you have anhydrides, then you have esters, and then you have amides. The reactivity goes down, as you go from top to bottom. Let me put it this way that, if we have to write down most reactive to least reactive, then you are going to have acid chlorides as the most reactive, amides as the least reactive, and other two are somewhere in between.

And thus, as a result of which it is much easier to convert acid chlorides into anhydrides, acid chlorides into esters, and to the corresponding amines. So, it is very easy to come down this

reactivity ladder. For example, we just saw a reaction where cyclohexanol was reacted with acyl chloride and it formed an ester.

So, here is a very easy way to convert one reagent into another or one functional group into another. If you take an alcohol and react it with acyl chloride you form ester, if you take an alcohol and react it with anhydride you form an ester or if you take an amine and react it with acid chloride, you form an amide. Take an amine react it with acid anhydride you form an amide. Again, take an amine, react it with ester, you form an amide. So, it is very easy to come down this reactivity trend depending on what are the molecules.

And we see this reactivity playing a very important role in the whole synthesis flow chart that we have for most of the organic reactions is that very often you will see that carboxylic acids, which by the way do not have a much electrophilic carbon. Again, the reason is that in the case of nucleophilic reactions most nucleophiles are also good bases.

So, carboxylic acid themselves are deprotonated. And once it is deprotonated the electrophilicity of the carbon is almost gone, because you have a contributing resonance structure. So, carboxylic acids are often converted to acid chlorides and anhydrides, so that you have a much better reactive or a much more reactive analog to start with.

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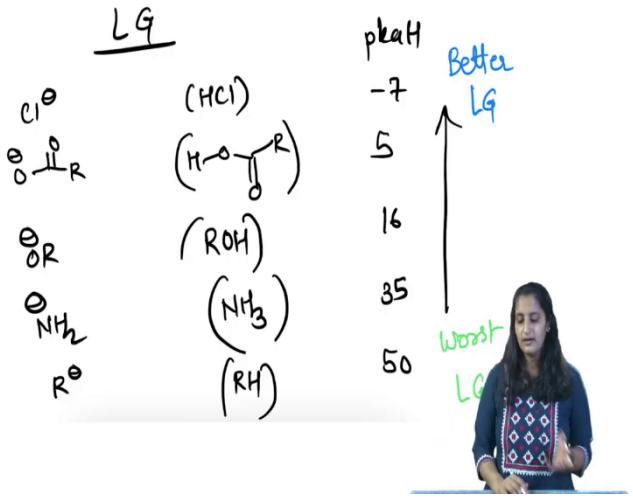

We discussed the addition step, but I also wish to discuss the elimination step in much more detail. And how do we decide if something is a much better leaving group than the other? So, let me just write down different leaving groups. In the case of acid chlorides, the leaving

group is going to be chloride and its corresponding acid is HCl. So, the conjugate base has the acid as HCl, and the pKaH of this acid is -7.

In the case of anhydrides, the leaving group is $RCOO^-$, and the corresponding acid will be a carboxylic acid, and that is going to have a pKaH of approximately 5. In the case of esters, you are going to have the leaving group, once the carbon oxygen bond is reformed and leaving group get kicked out, it is an alkoxide. Alkoxides are going to have the corresponding acid as alcohol and the pKa is approximately 16 for most alcohols. Then you have amides which are going to have a terrible, terrible leaving group of NH_2^- or NR_2^- and the corresponding acid is going to be an ammonia or some kind of amine, and that pKa is very high 35.

And the worst of all, if we have R^- as the leaving group, wherein an alkyl group leaves, which does not typically happen and does not at all happen for that matter, and that is the reason why ketone show the kind of reactivity they show, is that it is going to have an alkane as the corresponding acid and the pKa is approximately 50.

Now, the better leaving groups are the ones, who are going to have a lower pKaH. So, the leaving group ability, these are the better leaving groups, and these are the worst leaving groups. So, that is why we see that carboxylic acid chlorides are really better as leaving groups. You can also gauge it based on the stability of the leaving group as it leaves. Remember, if it is going to form something really unstable as it leaves it is not going to get kicked out, that is not favorable outcome of the reaction. And thus, that is an easy way to figure out which group will leave in a particular reaction.