

**Introductory Organic Chemistry II**  
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**Module 08**  
**Lecture 54**  
**Rearrangements - Part 1**

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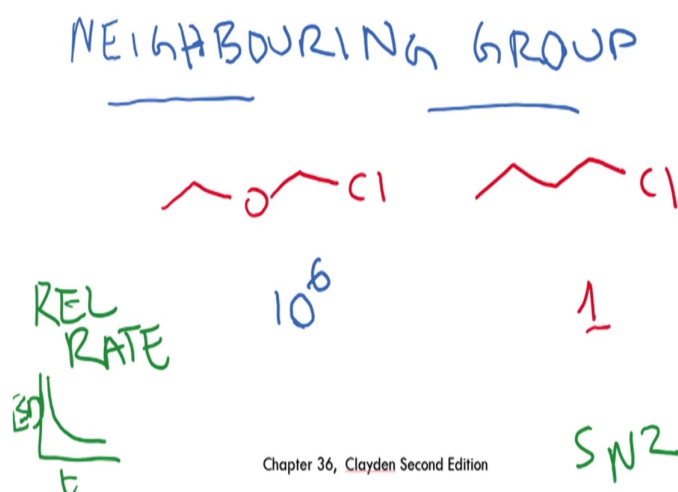
**PRINCIPLES OF ORGANIC CHEMISTRY**  
**II : REARRANGEMENTS**

Harinath Chakrapani

So, in the next lecture, we are going to look at the principles of Molecular Rearrangements. And as the name suggests, rearrangement means that when you start with a molecule with a connectivity, you end up with similar molecule, but with different connectivity. And so, the functional groups play an important role here.

And there is a movement of, there is usually a breaking of a carbon-carbon, or carbon-nitrogen, and sometimes breaking of a carbon-oxygen bond. And this results in movement of either atoms or functional groups. We have already looked at some aspects of this in carbocation-based rearrangements. But now, we look at this whole thing in a lot more detail.

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So, before we start the discussion on rearrangements, let us first understand what neighbouring group participation is. So, neighbouring group participation, as the name suggests, is a situation where something unexpected happens when you have a particular functional group near your reactive group, so this is called neighbouring group effect or participation. And this is important.

Now, so the way we understand it is that if a particular reaction happens, in a way, and if there is a new functional group that is placed in the proximity of the original reactive functional groups, then the effect of that new functional group is substantially larger than what you would expect if it is just a spectator. So, an example that we can look at is the following reaction.

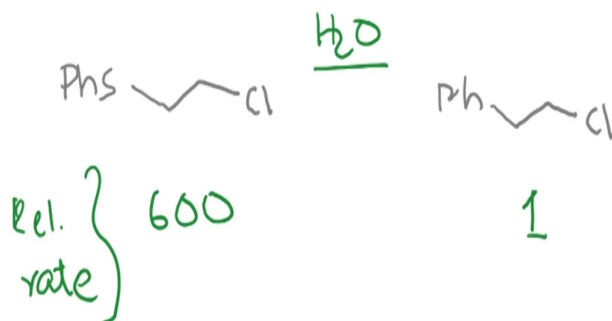
So, if you see here, if I do an  $S_N2$  type reaction; react this with an alcohol. So, the product that is formed is the ether. So, this is an  $S_N2$  like substitution reaction. And what we do here is we measure the rate of the reaction. And we measure so for example, we follow the disappearance of the starting material, let us say, over time, and we find that it goes down like this. And then what you do is, you fit this to an equation, which gives you the rate constant.

And that rate constant now becomes the basis for us to compare the relative rate. So, the relative rate is very useful, because the way we sort of understand it is that for example, the rate constant might be  $10^{-3}$ ,  $10^{-6}$ ,  $10^4$ , and so on. Whereas what we do is, if you have a series of reactions, it is a little difficult for us to look at each of those numbers and make

determination. So, what we do is we just divide all those rate constants by the smallest rate constant.

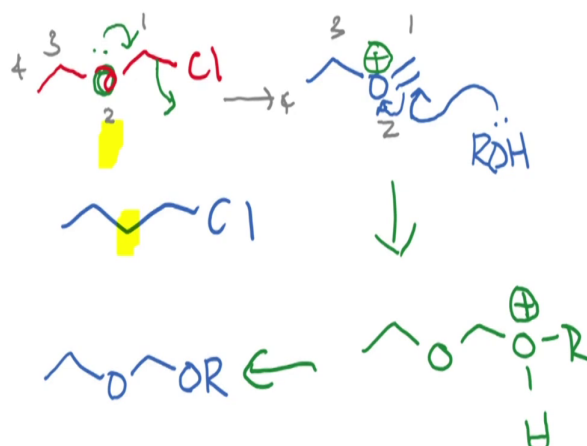
And so, if we take the smallest rate constant, and divide it by itself, the value is 1. So, if you see here, the rate constant, the relative rate for this would be 1. Because the rate of this reaction is low, and everything else that is faster will have a larger value. So, when we do the experiment, we find that the relative rate of this is  $10^6$ , so this enhancement in rate is large. So,  $10^6$  is like a million-fold increase in the rate, which cannot be due to just replacing this carbon with an oxygen, there is must be some effect of the oxygen in it.

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Let us look at one more example. The second example that we are going to look at is this PhSCH<sub>2</sub>CH<sub>2</sub>Cl versus PhCH<sub>2</sub>CH<sub>2</sub>Cl. And here what we do is we react this with water and measure the rate of the reaction. And here, the relative rate is 1 and this relative rate is 600. So, again, the enhancement in rate is quite large. So, normally, when you have an enhancement in rate of about 1.5 or 3-fold, it still sometimes explainable just by looking at solubility or some similar factors. But when there is a rate announcement of about 100, or higher, even in excess of 10, is considered fairly large. So, looking in that context number of 600 is quite large.

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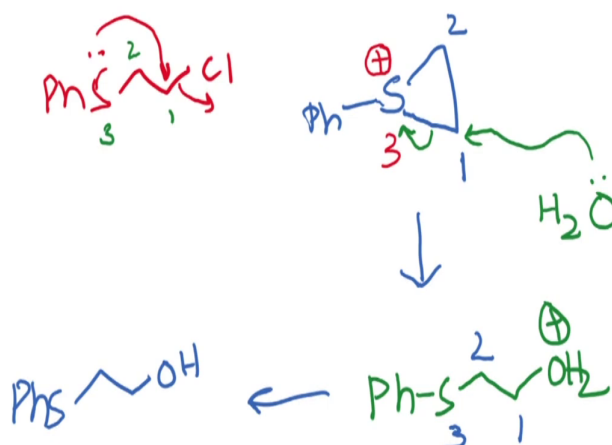


Now, let us look at how to explain this observation. Moving to the first case, the suggestion is that on oxygen has a lone pair of electrons. And so, this lone pair of electrons can participate in the following manner. And this produces an intermediate like this. So, just to be clear, let us just number these carbons and oxygens 1, 2, 3, 4, here 1, 2, 3, and 4. So now, the attack, so this is a fully positively charged oxygen, which is extremely reactive.

So, now the attack of ROH is greatly facilitated by the presence of this positive charge on the oxygen, it increases the electrophilicity of this carbon, and the product that is formed this OHR with a positive charge. And of course, this can lose a proton and give you the final product, which is this ether.

So, this is an example of enhanced reactivity due to the neighbouring group effect. So, keep in mind, if there is a, just a carbon over here, this position, there is absolutely no way that this carbon can participate in this reaction, the way we have envisioned it, the way we have laid it out. And so, this is one of the effects of the neighbouring group.

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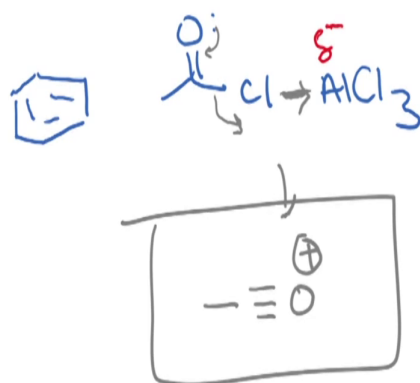


In the second case, when we look at the second case, you have a similar situation where you have  $\text{PhSCH}_2\text{CH}_2\text{Cl}$ . Now, sulphur clearly has a lone pair of electrons, so it can come here and attack here. And so, let us number this 1, 2, and 3. So, it forms 3-membered ring, where the sulphur is at one of the ends of the 3-membered ring, and so you have 1, and then you have 2, then you have 3.

So again, if it is an oxygen, this would be called oxirane or epoxide. And so, this would be a thio-epoxide kind of situation. And now, the attack of water is greatly facilitated, because of the increased electrophilicity of this carbon 1, or carbon 2 they are identical in this case. So, you will end up with  $\text{PhSCH}_2\text{CH}_2\text{OH}_2^+$ , and so just to keep the numbering the same, I will switch these two so that we do not get confused, this will be 2 and this will be 1.

And so, you end up with 1, 2, 3. This can lose a proton, give you the final product as shown here. So, clearly, the increase in rate is attributed to the presence of the neighbouring functional group that can help increase the reactivity of the reactant to give you the product.

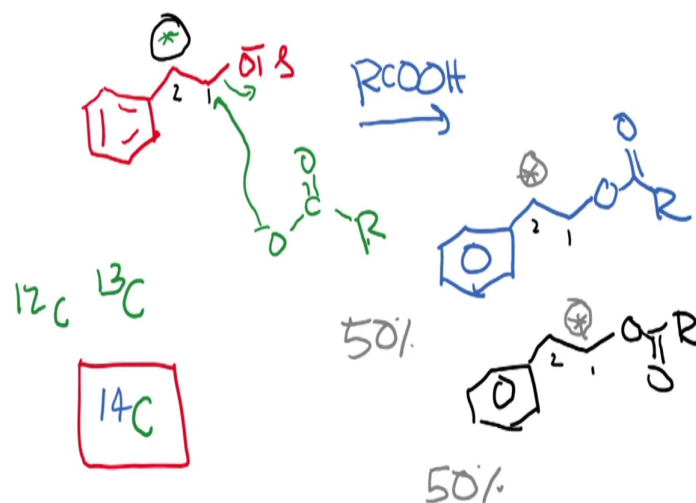
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Now, the one way to understand the increase in reactivity, as we have looked at in the past electrophilic aromatic substitution with acyl chlorides and what ends up happening in the presence of Lewis acids is that you have a bond that is being formed here. And so, you have AlCl<sub>3</sub>, developing a charge. And this is pulling electrons here, and this lone pair moves in here, and kicks out the chloride.

So, in this process, you have already seen that this can produce C≡O<sup>+</sup>, which is an oxocarbenium ion and this is going to greatly increase the reaction rate. So, I want to explain that this is not a neighbouring group participation. But this is some sort of reaction which allows us to understand how an increased reactivity can occur when you have a group that can be kicked out, and you can form this kind of an intermediate. Now moving on...

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What we are going to look at is another reaction, where you have this kind of another type of group which is neighbour. So, the reaction that is done is in the following manner. So, you take this tosylate and react it with a carboxylic acid, which is not a very strong nucleophile. But the only thing that you do here, I mean, what you would expect, is you would expect the formation of this product, which is  $\text{PhCH}_2\text{CH}_2\text{OC}=\text{OR}$ .

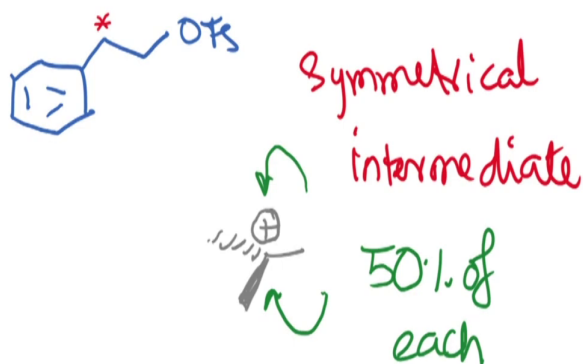
So, this is a product that you would expect, and indeed, you get this product. The only catch here is that when I insert a label here, so when this is normally Carbon-12, you know, there is a small amount of Carbon-13 but we can make Carbon-14 and insert it at this position. So, when I start with  $^{14}\text{C}$ ,  $^{14}\text{C}$  being a radioactive label can actually be traced. So, this position here is a  $^{14}\text{C}$ . And that is what I am denoting by this.

So, now, what can happen is that once you put this label here, if the direct substitution reaction that is  $\text{RCOO}^-$ , if this attack is the only one that is happening, then all the label will continue to remain at this position. So, that means that all the label will continue to remain at position 2. So, you can see that positions 1 and 2 are quite distinct.

However, when you do the reaction, you end up with two products which are nearly identical. So, this is again, carbon number 1, carbon number 2, the only difference is that the carbon label also ends up at position number 1. And these both are formed at 50 percent yield each. So, I will repeat this experiment. So, what we do is we take this tosylate and react it  $\text{RCOOH}$ , and the expected product is the ester and reaction works fairly well.

And the only difference here is that when we put in a label, the label ends up on both the carbons. So, this type of an observation helps us reason out that or gives a clue that there is an effect of the neighbouring group.

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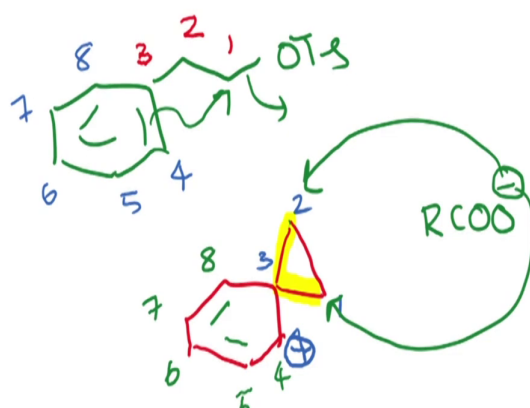
So, the way we explain this result or rationalize this result is in the following manner. So, let me just draw this out once again. And here is the Carbon-14 label. So, one way we can understand this is that both these positions seem to be equivalent in some way. And so, the attack on this carbon versus this carbon has to be the same that is why you are getting a 50 percent yield. And so, it is possible that you have a symmetrical intermediate that is produced.

So, when you get an equal amount of two products being formed, you know you can suggest that they would be a symmetrical intermediate. So, the example that we are all familiar with is the formation of the carbocation. So, when you have a carbocation that is formed, the attack from the top face versus the bottom face is nearly identical, so you end up with 50 percent of each.

So, and from this result we can argue that symmetrical intermediate which is a carbocation is formed, this side has a plane of symmetry and it reacts in this particular way to give you a 50-50 product formation. Now, what is the symmetrical intermediate that can be formed over here.



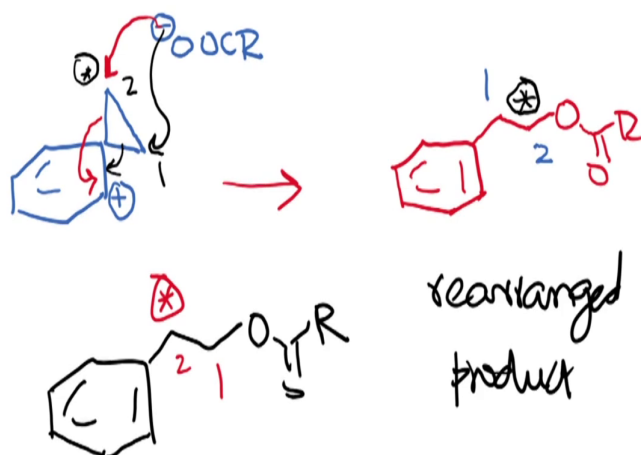
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So, the clue here is again, the reaction that we are all quite familiar with, which is the electrophilic aromatic substitution. So, you can have the attack of the benzene ring over here. And, again, let me just number these carbons this is 1, 2, and this will be 3 and so an attack from this benzene ring over here give us a 3-membered intermediate of the following manner and you will have a positive charge over here. So, just to be clear, this is 1, this is 2, this is 3, and this is 4, 5, 6, 7, 8.

So, this is 4, 5, 6, 7, and 8. So, these two double bonds remain intact and this could be the symmetrical intermediate that we are interested in. So, you see here these three carbons are quite symmetrical. And now, the attack of the nucleophile which is  $\text{RCOO}^-$  can attack, the attack can occur on carbon 2 or it can attack on carbon 1. And as you can see this is equally likely, and so you end up with 50 percent of the one product being formed and 50 percent of the other product being formed.

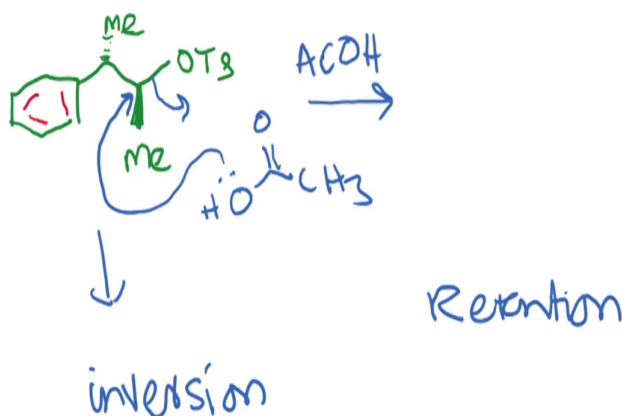
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So, just to complete the arrow pushing let me just redraw this intermediate, so you have a triangle, cyclopropane ring, and then there is a positive charge here which can be delocalized in the aromatic ring. And so,  $\text{RCOO}^-$ , so this attacks over here and this bond is going to move here and you get this benzene ring back. And so, if the label to be on carbon 2, so just to be clear, this is 1, this is 2, the label is on carbon 2, the attack happens on carbon 2. So, this ends up carbon 2 and this ends up carbon 1 and so the label ends up here.

So, this is one way to explain the observation that you get a scrambling of the  $^{14}\text{C}$  label and this is the rearranged product. And to complete the discussions if the attack happens here, you have this bond being broken and you end up with  $\text{O=C=O-R}$ . And so, the label is here, this is 1, this is 2. And so, this is the unrearranged or the non-rearranged product. So, there is additional evidence that we can get.

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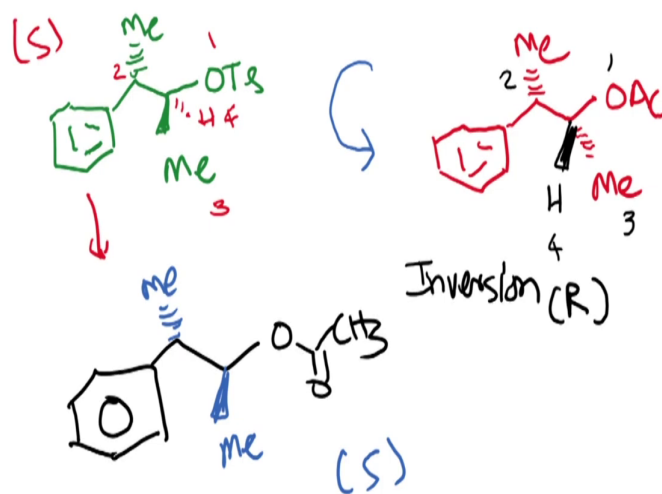


In addition to labelling, we can explain this result in a slightly different way, which is to invoke stereochemistry. So, what we do is, we start with this compound, it is going to take me a little bit of time to draw it out. But all these explanations are available in Chapter 26 of Clayden, I would urge all of you to go and look at it and get yourself familiar with this neighbouring group participation.

So, as we have just explained or just realized, if you have a compound like this where you have the stereo-chemically well-defined compound, then a mechanism becomes easier for us to follow. So, when you react this with acetic acid the product that you would expect if it is a traditional product, you would expect that there would be attack of the nucleophile  $\text{CH}_3\text{COOH}$ .

The attack of the nucleophile will happen from here and this would result in an inversion in stereochemistry. Whereas when you actually do the reaction, you get a retention in stereochemistry, that means the product that is formed is going to have the same absolute stereochemistry or arrangement of atoms as the starting material.

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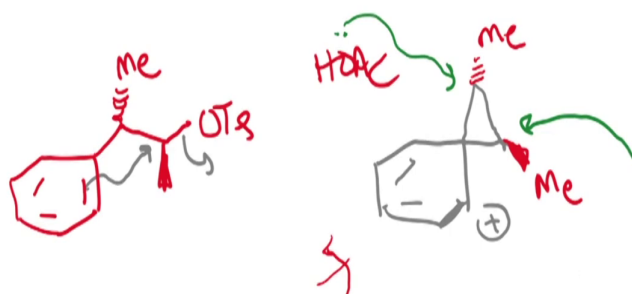


Now, let me just draw this out so that it becomes easy for us to understand. So, let us say I start with this benzene ring. Now, I am just going to assign the stereochemistry. So, that we understand this, so this is methyl and the second methyl is going into the plane of the board. And so, let me just do the priority. So, this is priority number 1 for this carbon, this is priority number 2, this is priority number 3, hydrogen is going in, is priority number 4 and so this is going in this direction.

So, this would be S. So, if there is inversion in stereochemistry then the product that is expected would be OAc, and so the methyl here would be going in, methyl here would be like this and the hydrogen is coming towards the plane of the board. So, again the numbering is in the following way 1, 2, and 3, and 4. So, if I look at this, this is anti-clockwise but the hydrogen is towards me.

So, therefore, it would be R. So, this would be the inverted product, inversion in stereochemistry, but the actual product that is formed is this. So, if I assign the stereochemistry here, I would end up getting S. So, this has a retention in stereochemistry. So, this is an important observation because this helps us sort of understand the mechanism better.

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So, now, the way we explain this is that we already looked at the formation of a symmetrical intermediate. So, it is fairly straightforward for us to propose this, going forward. So, you have Me here, the attack happens at this carbon center and it gives you a symmetrical intermediate like this and it has a positive charge over here.

And now, the way we would draw these groups is in the following manner, the methyl is here, and the other methyl is here. So, the beauty about this compound is that if you rotate it along this plane, you will end up with the same compound. And so, this is highly symmetrical. And now, the attack of the nucleophile HOAc can occur from the top face or from the bottom face.

And in both these cases, you will get the same product and that product is the product with the retention in stereochemistry. So, I will let you go back and work out the details of this reaction and more details are available in Clayden. So, please go take a look at it and then we can continue the discussion.