Introductory Organic Chemistry-II
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Indian Institute of Science Education and Research, Pune
Lecture 8
Tutorial – 1

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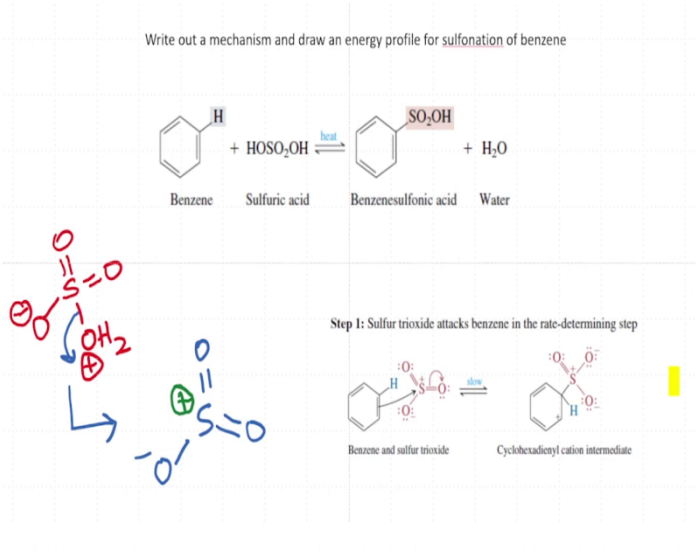

Write out a mechanism and draw an energy profile for sulfonation of Benzene. So, the overall reaction of sulfonation of Benzene is the conversion of Benzene to Benzenesulfonic acid. So, as shown here, you need some heat and you need to add Sulfuric acid. So, in Sulfuric acid, this is a protonated form of sulfuric acid and just a proton has been moved from here to there and you can imagine that this Oxygen, once it gets protonated, the loss of water can occur and it produces this SO_3 species, which now is well set up to do a reaction with the Benzene ring.

So, once Benzene ring electrophilic aromatic substitution can occur and this is an equilibrium process and it can be or it can give you this kind of an intermediate which is a cationic intermediate.

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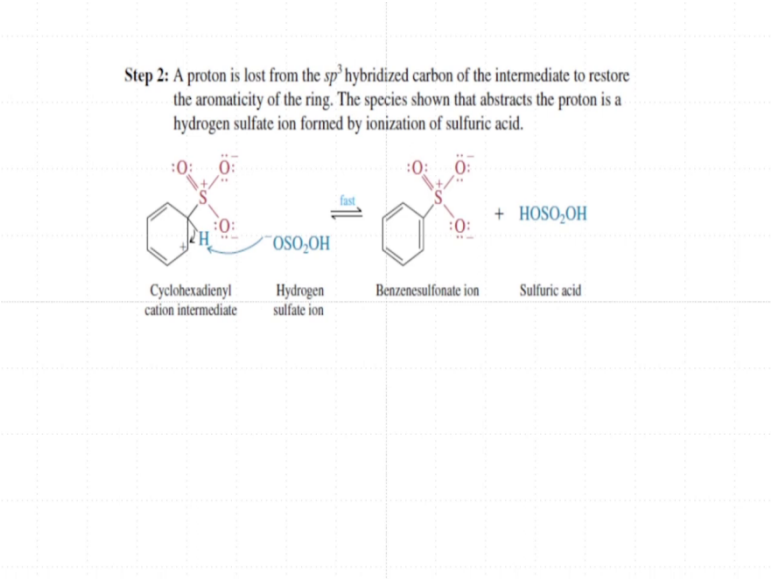

And in the next step, there is a loss of H^+ that can occur which is mediated by this Hydrogen Sulfate ion, which is basically the conjugate base of Sulfuric acid and it is going to give you this benzene sulfonate ions and Sulfuric acid and now once this is formed, the benzene aromaticity is restored. So, we would expect that this process is quite fast. So, one thing, one aspect about this reaction that is different from regular electrophilic aromatic substitution is that this reaction requires a reasonable amount of heat and the second thing is that it produces an anion, which is benzene sulfonate ion.

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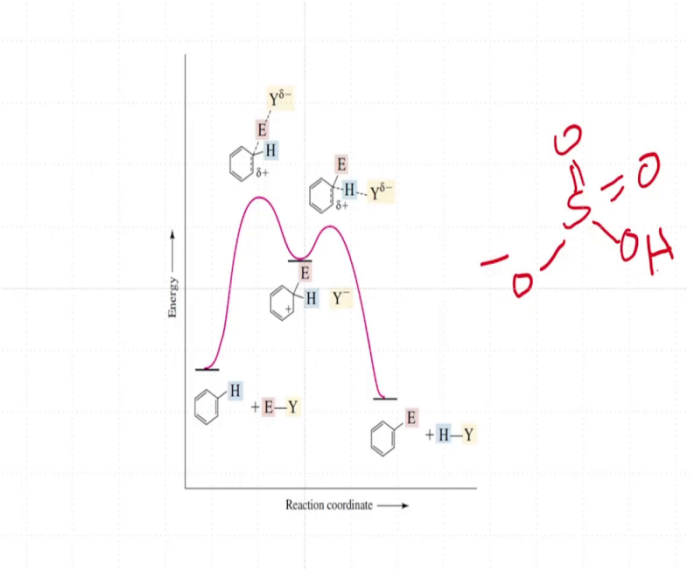

In order to look at the energy profile, the first step of the reaction is very similar to that of what we would see with an electrophilic aromatic substitution. So, you have the Benzene ring, sort of interacting with the electrophile and producing this $^{+}$ species in the transition state, which then gives you this intermediate that we are very familiar with.

The next step is the reaction of the conjugate base here which is sulfate to give you, so, it will be HSO_4^-. So, this is the species that is going to be attacking the benzene ring by picking up a proton giving you the product. One thing to consider here is that given that the first step is a slow step, so the barrier to that first step might be quite high and also being in equilibrium the reverse step is also accessible at room temperature or at the temperature at which we are doing this reaction. So together, the sulfonation of benzene is a reaction that happens which is very similar to any other electrophilic aromatic substitution reaction.

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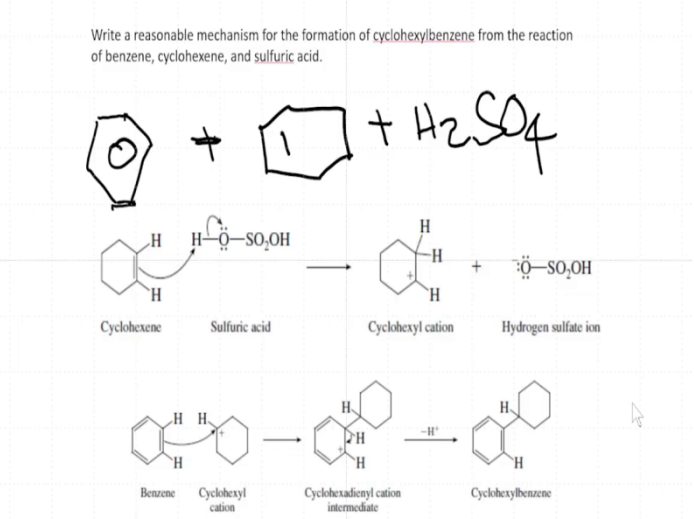

Write a reasonable mechanism for the formation of cyclohexylbenzene from the reaction of benzene, cyclohexene and sulfuric acid. So, the question here is that we start with benzene plus cyclohexene and H_2SO_4. So, the question is what is the product that is formed under these conditions?

So, when we have to look at these kinds of reactions, let us just go back to the basics and what we could expect is that cyclohexene being the more reactive of the, between benzene and cyclohexene, cyclohexene is more reactive towards electrophiles and so we would expect that this picks up a proton from sulfuric acid and it produces cyclohexyl cation and now we

know from our many examples that we have already looked at, we know that cyclohexyl cation is now going to be a system which can react with benzene and an electrophilic aromatic substitution can occur and the product that is going to be formed is cyclohexyl benzene.

When you encounter questions such as these, the right thing to do is to understand the difference and reactivity. So, an olefin is more reactive than benzene. For example, we have looked at previously that bromination of olefins is possible, epoxidation of olefins is possible, but Benzene itself does not react unless you add a Lewis acid and clear there is no epoxidation equivalent for Benzene under normal conditions.

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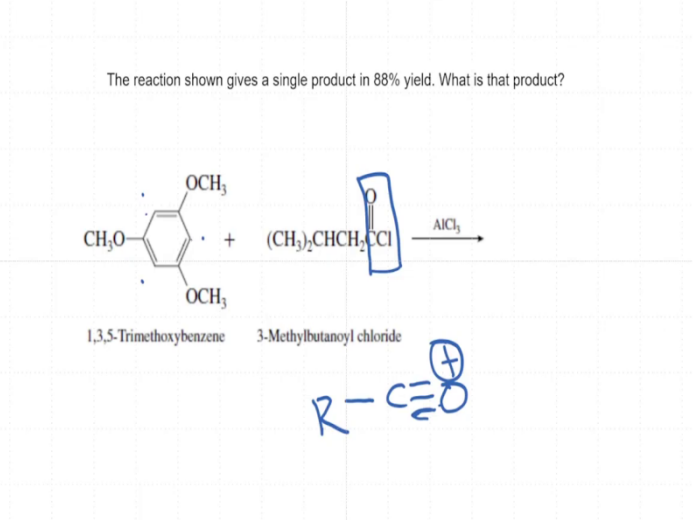

So, the reaction shown below gives a single product in 88% yield. The question is what is the product? So, if I have to understand this reaction, what I need to do is I need to look at the compounds that are reacting. So, here is an acid chloride and acid chloride as you know, in the presence of a Lewis acid can produce the corresponding oxocarbenium ion and so this is going to be the kind of intermediate that can be produced and now, when you look at 1, 3, 5-Trimethoxy benzene, this you know if, just by looking at the symmetry of this molecule, all these three positions which are present here 1, 2 and 3, they are equivalent.

So, it is almost like a Benzene ring in the sense that it is highly symmetric and so in the presence of Aluminum Chloride, one of these positions is going to react and electrophilic

aromatic substitution would occur here and the product that would be formed is the corresponding ketone. So, this is the product that you expect from this reaction.

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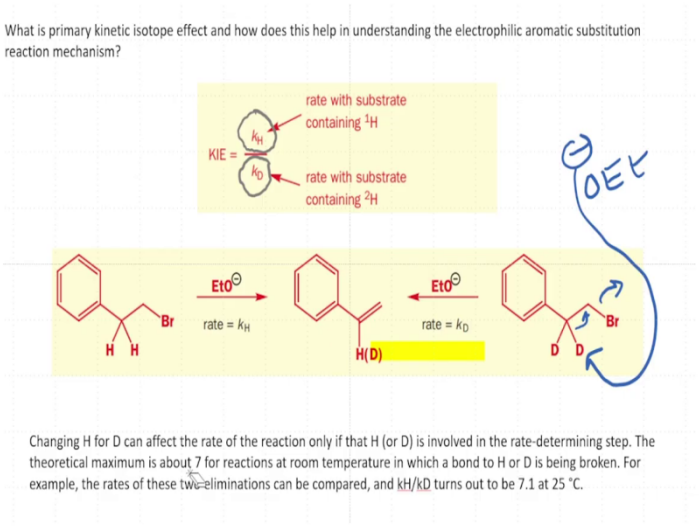

What is the Primary Kinetic Isotope effect? And how does this help in understanding the electrophilic aromatic substitution reaction mechanism? So, let us now try and understand what the Primary Kinetic Isotope Effect is and using an equation so, the Kinetic Isotope Effect is defined as the rate constant for a reaction that happens with Hydrogen and divided that by the rate constant of the reaction that happens when the Hydrogen is replaced by Deuterium,

So, this is a very powerful technique that can be used to understand reaction mechanisms. So, the example that we will take here is the elimination reaction. So, as you know the elimination reaction occurs when you have a Bromide and here, the example here, that is shown here, is the following. So, when you have this Bromide on the left, what happens is that you expect the elimination to occur.

So, one of these Hydrogens is going to be picked up and it is going to give you this olefin as the product and the base that we use is sodium ethoxide. So, what we do is we measure the rate of the reaction and determine the rate constant for this particular reaction. So, I can follow the loss of this Bromide and the formation of this olefin and when these are two Hydrogens, I can follow the reaction and determine the rate constant.

Very similarly, what I do is I replace both these Hydrogens by Deuterium. So, then what I do is I can then measure the same, under similar conditions I measure the rate of the reaction and then I determine the rate constant and the product is as shown here, where the Hydrogen is

replaced by Deuterium. So, now if these two measurements can be done so, EtO^- is expected to come attack here and kick out the Bromide.

Now, these reactions can be monitored and if the Carbon-Hydrogen bond is involved in the rate determining step. So, if the Carbon-Hydrogen bond, breaking of the Carbon-Hydrogen bond, is involved in the rate determining step, then what we expect is that the Hydrogen bearing compound reacts substantially faster than the Deuterium bearing compound.

You will probably read about this in one of your later courses, the origin of this effect, but this helps us understand whether the Carbon-Hydrogen bond is involved in the rate determining step. So, in this case, we have very good evidence that this Hydrogen is involved in the reaction and therefore, we would expect that the Carbon-Hydrogen bond would break faster than the Carbon-Deuterium bond and because it is involved in the rate determining step, and the Kinetic Isotope Effect for this reaction is about 7. So, therefore, from this we can conclude that the Carbon-Hydrogen bond is involved in the rate determining step.

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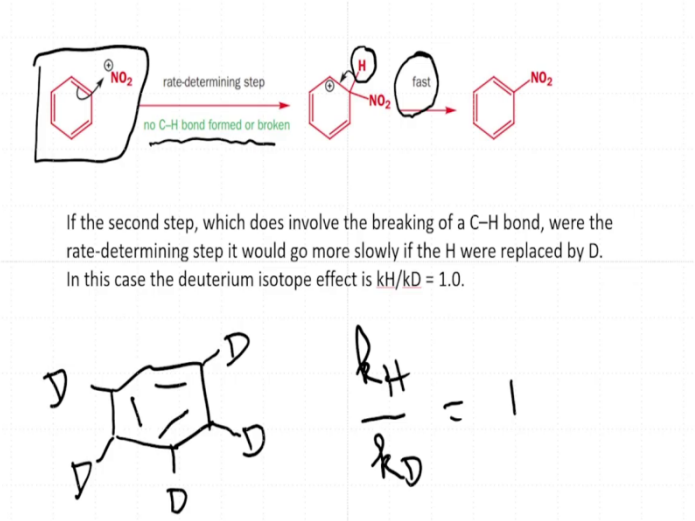

Now, when we come to Electrophilic Aromatic Substitution, as you know the mechanism of the reaction, the first step of the reaction is the reaction with the electrophile and producing this cation which then subsequently loses a proton to form the product. So, in the first step, there is no Carbon-Hydrogen bond that is being formed or broken and therefore one cannot expect a primary hydrogen isotope effect.

But in the second step, which we have designated as the fast step, there is a Carbon-Hydrogen bond that is being broken. Now, when we do the reaction, we do the experiment where we replace all Hydrogens by Deuterium and measure the rate of the reaction, what we find is that $k_H / k_D = 1$.

So, what this tells us is that the breakage of the Carbon-Hydrogen bond, although it occurs during the reaction, it is not involved in the rate-determining step. So, because the rate determining step is the loss of aromaticity, which is the first step. So, the primary hydrogen isotope effect can be used to understand Electrophilic Aromatic substitution reaction because it supports the mechanism that we have proposed where the rate-determining step is the first step and the primary hydrogen isotope effect being one tells us that the Carbon-Hydrogen bond is not being broken in the rate determining step, but it is being broken after the rate determining step is happening.

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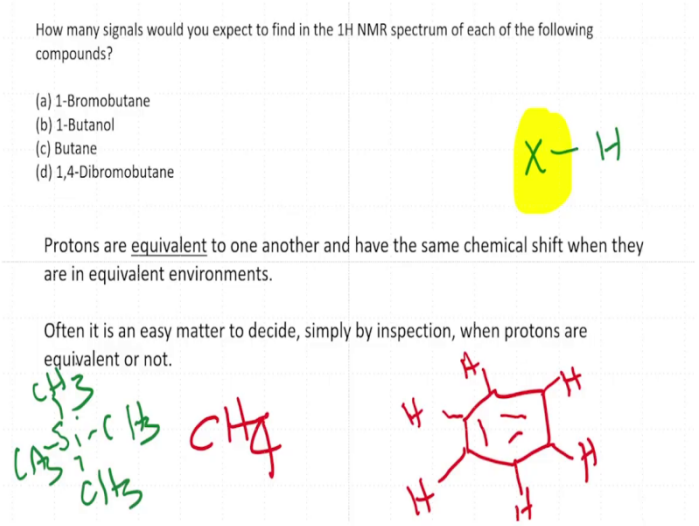

How many signals would you expect to find in the Proton NMR spectrum of each of the following compounds. So, there are 4 components that are given 1-Bromobutane, 1-Butanol, Butane and 1, 4-Dibromobutane. So, from our previous discussions on NMR we know that protons are equivalent to one another and have the same chemical shift when they are in equivalent environments.

So, the key word here is the environment. So, whatever a particular proton is, the kind of environment that is around it has to be similar. Usually, in many cases it is very easy to

decide. So, for example, if I take the example of Benzene, all these Hydrogens that are shown here have the same chemical shift and they are equivalent because they are in the same equivalent environment.

So, methane for example, is another example, where you can clearly say that all of them are equivalent. The last example is Tetramethylsilane, which we have seen many times $Si(CH_3)_4$, all the 12 Hydrogens are equivalent, because they are in exactly the same environment.

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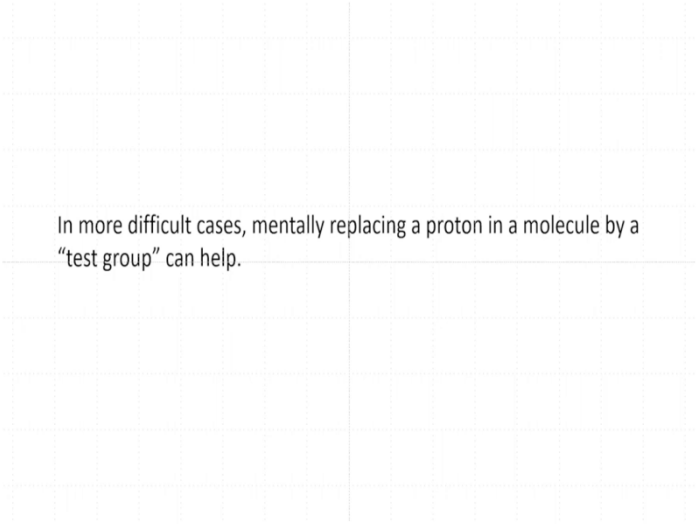

But in some cases, it may not be as straightforward to understand this and so what we can do is to mentally replace a proton in a molecule by a test group.

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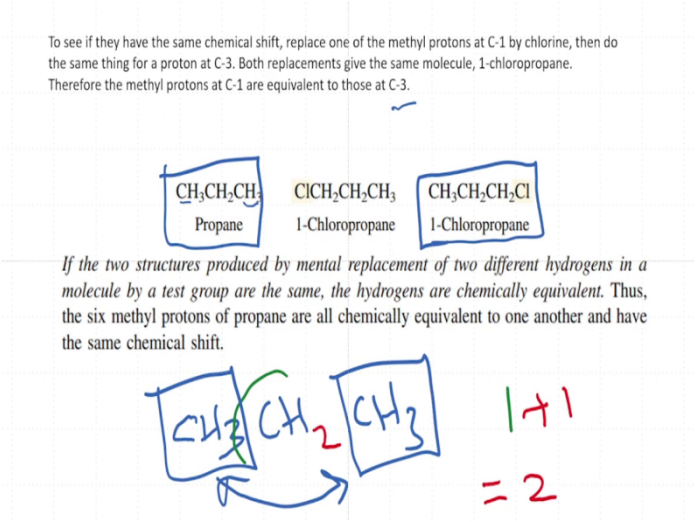

So, what I mean by that is that, in order to see if two Hydrogens that you are interested in have the same chemical shift, what we need to do is we need to replace one of them by another atom. So, for example, let us take Propane. So, Propane structure is shown here and if I want to understand whether this methyl group and this methyl group are the same, one way to do this is I take this carbon-1 and one of the Hydrogens I replace it with Chlorine.

So, then the resulting molecule that I get is 1-Chloropropane. Now, I do the same exercise on the other methyl group, which is at carbon-3, where I replace one of the Hydrogens by chlorine and I get exactly the same molecule which is basically 1-chloropropane. So therefore, if the two structures provided by, produced by a mental replacement of two different Hydrogens in a molecule give you the same molecule, then the Hydrogens are chemically equivalent.

So, from this exercise, what we can figure out is that the methyl groups of Propane are identical. So, in case of Propane, these 6 Hydrogens are the same and therefore this will contribute to one signal and this methylene group would be the second signal and so therefore, the total number of signals that you would see here is 2. So, this is a very, very standard way to identify how many distinct signals are there, or expected in a molecule.

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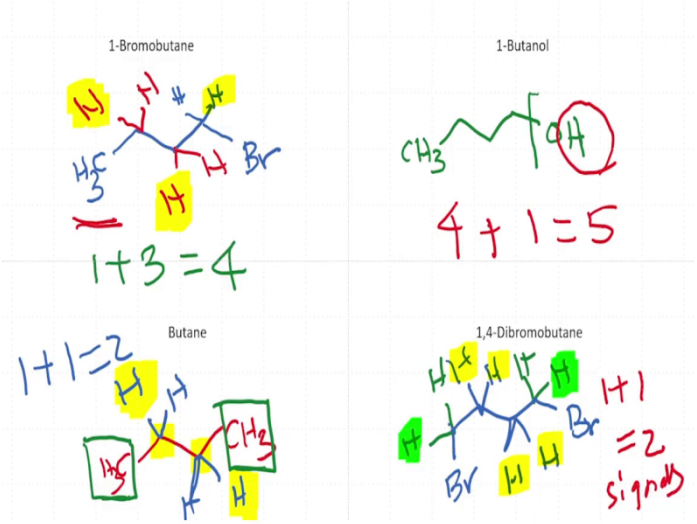

So now, let us go to the question. The question that we have is 1-Bromobutane. So now in this 1-Bromobutane, there are three methylene groups. So, CH_2, CH_2, and CH_2, and then there is one methyl group. So, the methyl group is clearly one signal and there is no sort of dispute about it. Now, what we need to understand is whether these two CH_2's or these three CH_2's are similar.

Now, what I am going to do is I am just going to highlight this Hydrogen over here and now if I replace this Hydrogen by Chlorine, then what I am going to get is 2-Chloro-4-bromobutane (correction:1-Bromo-3-chlorobutane). Now, when I replace this Hydrogen by Chlorine group then it becomes 1-Bromo-2-chlorobutane.

So clearly, these two are very different compounds. Needless to say, if I replace one of these two Hydrogens with a Chlorine, I am going to get an entirely different component. So therefore, what we can conclude from this discussion is that these three CH_2's are different. So therefore, you will get 1 plus 3 i.e. 4 distinct signals in the NMR spectrum.

Now, 1-Butanol is exactly the same. Until here, you get the same pattern. That is, you are going to get four signals, as we discussed and 1-Bromobutane. The only additional hydrogen here is the OH and so you would expect 5 distinct signals in 1-Butanol. Now, the next compound that we are going to look at is butane. So, in the case of butane, what we have is that we have these two methyl groups.

Let us start with this. Now, if I replace this methyl group with a Chloro, I get 1-chlorobutane, and if I replace this with Chloro, then I also get 1-chlorobutane, so therefore, these two methyl groups are indeed identical. Now, coming to the next set of CH2's, if I have to find out whether they are equivalent or not, let me replace one of these Hydrogens by a chloro. So, then I would get 2-chlorobutane.

Now, if I do the same thing for this Hydrogen, I end up getting 2-chlorobutane. So therefore, these two CH_2's are also identical. So, the number of signals that you would expect to see here is 1 for the methyl and 1 for the methylene. So, it will be 2. Now, the last question here is 1, 4-dibromobutane. So again, here there are four CH_2's, and we essentially need not compare the green CH_2's and the blue CH_2's, but let us take the two terminal CH_2's first.

So, if we replace this Hydrogen, one of these Hydrogens by chloro then you get 1-Chloro-1-bromo-4-bromobutane. Similarly, if I replace one of these hydrogens, I get 1-chloro-1-bromo-4-bromobutane. So, these two compounds are identical. So, therefore, the green CH_2's are the same. Now, if we do a similar exercise with this, you will find that these two CH_2's are also identical. So therefore, you get 1 plus 1 that is equal to 2 signals.

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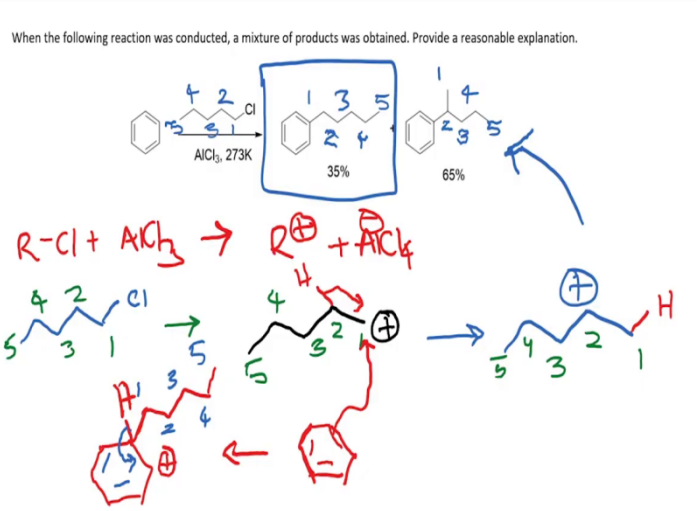

So now, this problem basically shows us that, when benzene is reacted with this aliphatic chloride, you end up with a mixture of two products and so, first we will try and tackle why there are two products formed, and then we will try to understand the sort of ratio that is formed and why there is a major product and so on.

So, as a general rule, let us say we start with any chloride. So, let us say you take R-Cl plus $AlCl_3$, so we already discussed this in class and other things. So, you will generate, basically carbocation plus $AlCl_4^-$. So now, when R^+ is actually very stable, then it is fine, but if it is not very stable and if the reaction conditions allow us, then you could actually imagine that there could be a rearrangement of the carbocation which you have already studied previously.

So, let us take this example over here. Let me just number these carbons so that it is easy for us to keep track. This is number 1, 2, 3, 4 and 5. So if we keep the same numbering 1, 2, 3, 4, 5. So, here if we keep this as 1, 2, 3, 4, 5. So now that we established this numbering, it becomes quite straightforward for us to address this question. So, R-Cl here is basically 2, 3, 4. So, we start with Cl so 1, 2, 3, 4 and carbon number 5.

So now, once you go through the coordination with Aluminum chloride and the formation of the carbocation, you will end up with carbocation, which is our primary carbocation. So, let us just keep the same numbering 1, 2, 3, 4, 5 and we all know that primary carbocation is fairly unstable and it can rearrange. But nevertheless, if it reacts from this, as this carbocation, so then you can imagine that it attacks here, then it gives you a benzene ring

with a positive charge and there is a Hydrogen over here. So let me just number the carbons , 1, 2, 3, 4 and there is actually one more carbon.

So, we will just add this carbon number 5. That is carbon number 5 over here and the rest of the aromatic ring basically remains the same and then if this gives up a proton, then we will end up with this product. Now, if there was a situation where this carbon number 2, I just want to have a Hydride. So, let me just number it over here. This carbon number 2 is going to have a Hydride, as shown here you could have a Hydride migration and that will give me the most stable secondary carbocation.

If we just keep the same numbering so 5, 4, 3, 2, 1. So the positive charge, the hydride has moved from carbon 2 to carbon 1. So, that hydride I am going to draw with the same color and this going to be a positive charge over here and now when this carbocation reacts, then you are going to end up with this product as shown here. Now, this gives us a framework for explaining the formation of the two products.

But now, how can we account for the compound number 2, I mean the substituted compound on the right being higher in yield. So, what actually happens is that the benzene ring reacts with the primary carbocation, perhaps as soon as it is formed and some of the carbocation is still available for to undergo rearrangement to give you the secondary carbocation, then the secondary carbocation being more stable is going to be, you know, the reaction is going to move towards the right.

In this case, the carbocation is going to rearrange to give you a secondary carbocation and that is going to react and give you the major product. So, you can explain both the formation of the product and the ratio using the formation of the carbocation and the stability of the carbocation.

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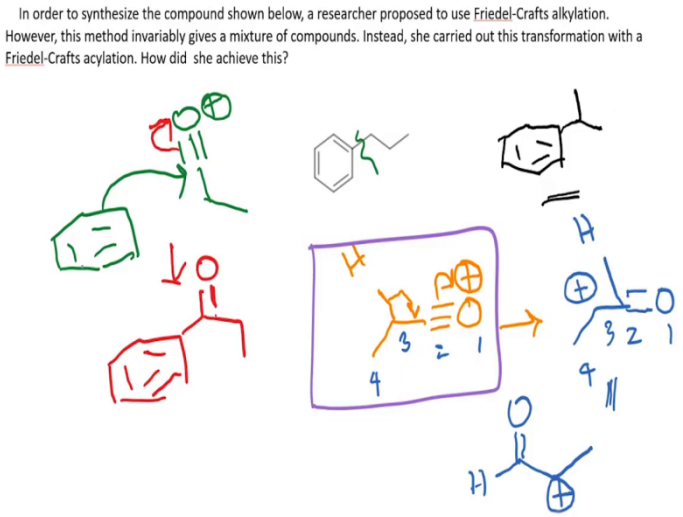

So here, the question is, how would you synthesize this compound using Friedel Crafts Acylation reaction? So, because we saw in the previous problem, that if you have a Friedel Crafts Alkylation that is going on, then you invariably end up with a mixture of products. So, if you attempt Friedel Crafts Alkylation reaction, then you are going to get a mixture of this compound as well as the rearranged product.

So, this is going to be a problem there and in fact, this might even be the major product. So, in order to avoid this, I want to use a Friedel Craft Acylation. Now, let us look at the steps that are going to be involved. So, Friedel Craft Acylation basically would mean that to break this carbon-carbon bond, and so you have two fragments here, you have the benzene ring and you would need a carbocation or a oxocarbenium ion such as this.

So, this is going to be the most important step and so if you attack, imagine that there is going to be an attack here and then this movement of this bond to the C=O, then you will end up with a product such as this. C=O and then you have the ethyl group outside. So, this is basically Ethyl phenyl ketone and this can subsequently be reduced.

So, we will come to the reduction part. But now the question is, in Friedel Crafts Acylation, you do not see a rearrangement. Now, let us look at why or how we explain that we do not see any rearrangement. Let us now look at the structure of the acylium cation. So, you have a $C \equiv O^+$ and unlike a carbocation, where there is a beta hydride which can move and give you a more stable carbocation when you go from primary or secondary, or secondary to tertiary,

here the movement of hydride ion can certainly occur but that will result in a cation that is less stable.

So, if you sort of push the arrows, then you end up getting. So, if your number this as 1, 2, 3 and 4, then this is 1, 2, 3 and 4, and so your hydrogen ends up here and it is a cation over here. So, if I redraw this, what I get is C double bond O, H with a positive charge over here.

So, we know that the carbonyl group is an electron withdrawing group. So, you can certainly say that this is going to be highly unlikely. So therefore, rearrangement of the acylium cation once it is formed, is extremely unlikely, which is why the acylation reaction is more predictable.

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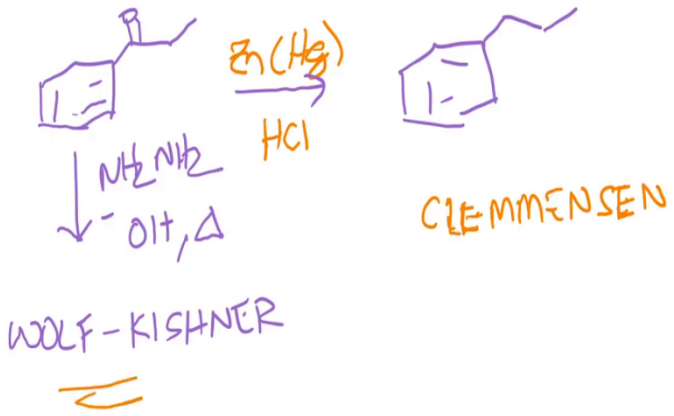

Now, let us go to the next step, which is, it is not difficult for us to now synthesize this molecule, which is this ketone and now, from the ketone, we need to get to the final product which is C, you need to get here. So, there are two strategies that have been suggested and the first one is basically the Wolff-Kishner reduction which is basically a reaction with hydrazine which is NH_2NH_2, in the presence of hydroxide ions, usually Potassium hydroxide or Sodium hydroxide and then we heat

So, this is the first condition which is used, which is known as Wolff-Kishner reduction. So, this is one way to do it. I would urge all of you to go and look at the mechanism of this reaction. The other way to do it is to use the Clemmensen reduction, which is basically Zinc

amalgam in HCl. So, you can use either of these methods and this is going to give you the product that is desired. So, I want you to go back and revise this concept that you learned previously and look at the mechanism of this Wolff-Kishner reduction.

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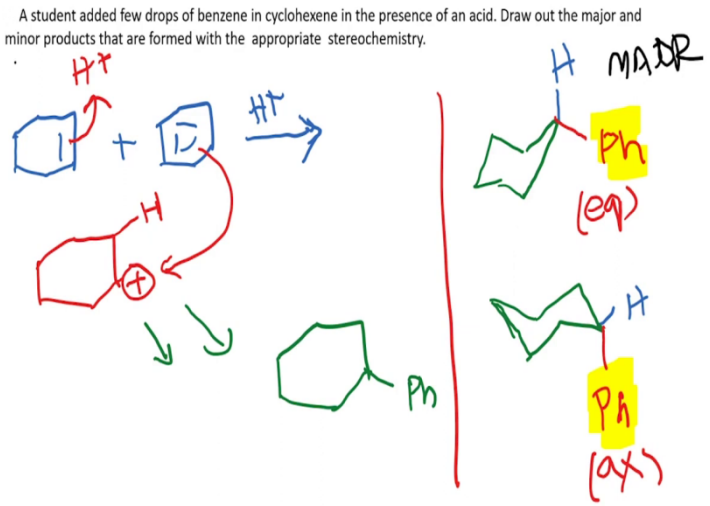

So now, let us look at this problem, which is basically the reaction of cyclohexene in the presence of an acid with benzene. So, let us draw out the structures of these two molecules and then reason about what could be the product that is formed. So, cyclohexene is basically this and then reaction with Benzene in the presence of H^+.

So, Benzene is going to be quite stable in the presence of H^+. Cyclohexene one might imagine that it can actually get protonated. So, if it gets protonated then you end up with a compound such as this where you have a cyclohexyl carbocation and now you can propose that there is an attack by the benzene ring on the carbocation and you may end up with a compound which is along the lines of this.

So, now you go through the steps of the Friedel Crafts alkylation reaction and you end up with this compound. So, the product here is actually interesting because you know that the cyclohexane primarily exists in the chair conformation. So, if we want to draw this compound out and the chair conformation, so it would look something like this and here you have two choices, that is the benzene ring could occupy the equatorial position or you can have the ring flipped isomer which is here and here the benzene could occupy the axial position.

So, just to remind you, this is the equatorial position and here it is the axial position. So, just for clarity's sake, let me just draw out this Hydrogen so that it becomes obvious. So, now, the question is, I believe that the stereochemistry is fine, but now the question is what would be the major product. So, given that there is no other driving factor over here, one would argue that the equatorial substituent or the bulky substrate, which is a phenyl ring, would prefer to occupy the equatorial region and therefore we would suggest that this component is the major product.