Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 03: Carbocation

Welcome back, Welcome to this online NPTEL certification course on molecular rearrangement and reactive intermediates. So, in the last class, I started talking about carbocation and I talked about carbocation stability, I talked about some of the fates of the carbocation I talked about non-classical carbocation, and I also talked about what will happen if you have a neighboring group, which could have a lone pair or be a π-bond or a σ-bond, which can participate in the neighboring group.

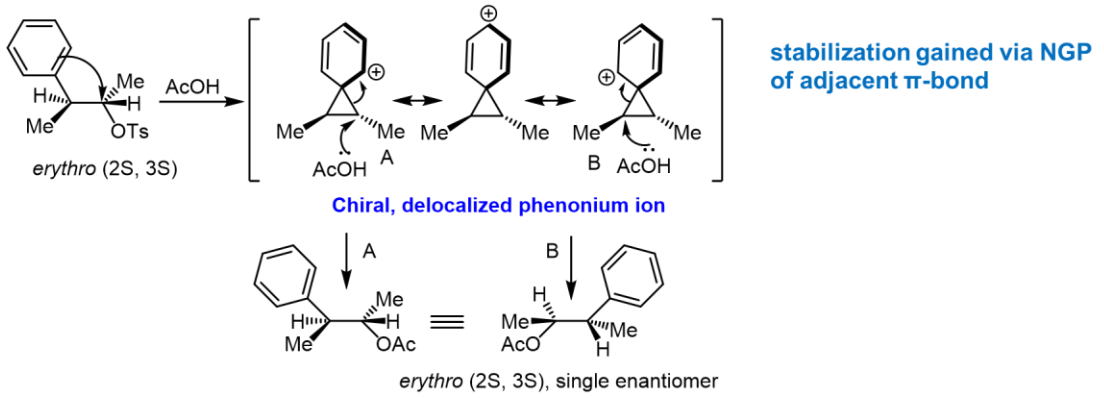
So, today I am going to mostly focus on two important rearrangement reactions: one is going to be the Wagner-Marwin rearrangement, which I am going to show you here, and the other is going to be the Pinacol rearrangement. So, today, I thought before I started about the two different rearrangements: the Pinacol and the Wagner-Meerwein rearrangements. I am going to just go back to the last class. So, there was an important problem I wanted to discuss, which sometimes came up in the exam. So, let me start talking about this example first. I am going to start talking about this example, where you can see the particular compound, I am showing here. It could be a threo or erythro.

I am sure you are all familiar with the threo and erythro nomenclature in stereochemistry, but the interesting part here is that starting from this erythro compound with 2S,3S chiral centre. What happens after going for the acetylysis using acetic acid? It ends up forming a single enantiomer. But, once the reaction is happening instead of erythro, with the threo isomer, it gives a racemic mixture. Now, the question is why? With two different isomers, we end up with two different types of results. So, in the first case of the erythro isomer, what happens once it first goes through acetylysis.

Now, you can see there is a π-electron cloud of this phenyl ring that is going to take part in the NGP. So, you know, this is the neighboring group participation. So, now what is happening is that this π- bond is going to take part here you can see this arrow here showing and leave the -OTs group out. Now, once this happens, the pi bond is attacking here, and it will generate a phenonium ion. So, we end up making a phenonium ion here.

Once you make a phenonium ion here, there will be a positive charge on the benzene ring, Now, that your nucleophile can attack this three-member ring. It will open up and

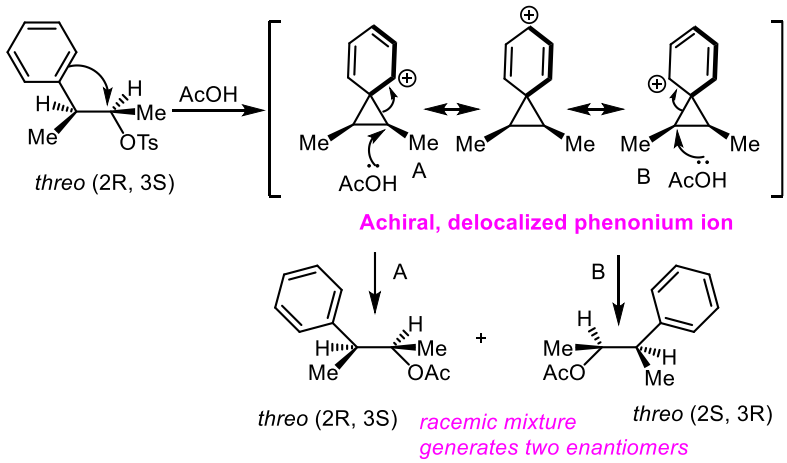
neutralize the positive charge. It can also go for another resonance structure; as you know, make intermediate **B** here. So, now the nucleophile can also attack from this side and neutralize the positive charge. So, now what is happening? It can attack from side **A** or **B**, but the interesting part is it ends up making the same chiral compound here.



But once you move to the threo compound, you can see that, starting from this (2R,3S) isomer, acetic acid again does the same thing. You know the phenyl ring π -bond is participating in this reaction. It gives this π -electron density, forming this phenonium ion. Now, if you see, one of the important things about this phenonium ion is that, if you think about the chirality of this phenonium ion, it is an achiral compound. If you see in my previous slide that I discussed about this particular phenonium ion, there is only a C-2 symmetry here, but there is no other symmetry element.

But once you go to the next one, we find out there is a σ-plane, passing through it. So, that means this particular phenonium ion is achiral. So, now what is happening is that it can attack from side A, which I am showing here, and then neutralize this charge, or it can attack through this B side. So, attacking from the A side can generate one enantiomer, attacking from the B also can generate another enantiomer. There is a 50-50 probability of attacking both positions. So, there is a 50-50 possibility. So, what is happening? is that it ends up generating a racemic mixture as it is generating two different enantiomers in 50-50 which makes a racemic mixture ok. So, I think there are several other problems that I am going to give you from this neighboring group effect that I am going to give you during practice. So, you might find you know some more example there. So, now I am moving further.

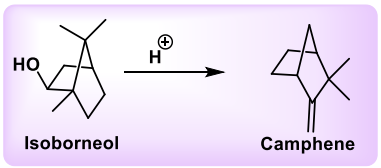
So, I am going to start talking about the molecular rearrangement for today's topic. So, we want to start with this important rearrangement called Wagner-Meerwein rearrangement. So, this is an very important rearrangement reaction. So, this is a very important reaction because this particular development of this type of cationic 1,2-shift, which I am going to discuss, is applied in many different types of rearrangement.

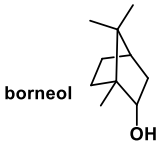


So, Wagner in 1899, published a paper where he showed that from isoborneol or borneol in the presence of acid converts to camphene. So, this was known before Wagner brought it into the picture that he found that this is going through a rearrangement. And then, 20 years after that discovery, Meerwein also proposed the very same thing. So, this is the beginning of this Warner and Meerwein rearrangement. So, there are couple of important points. So, this is, of course, a carbocationic rearrangement happening.

So, from here you can see there is a hydrogen, alkyl, and aryl groups migrating from one carbon to the neighboring carbon. So, that is the important thing here the migration happening from one carbon to another carbon, and then we are going to also learn about the stereochemical things in the next slides. So, before going further, let us try to understand how this conversion and what type of rearrangement are happening from this isobornyl to camphene.

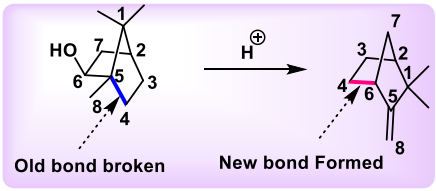
- It is a class of carbocation 1,2-rearrangement reactions.
- Here hydrogen, alkyl , or aryl group migrates from one carbon to a neighboring carbon.
- It is a cationic [1,2]-sigmatropic rearrangement.
- It proceeds suprafacially and with stereochemical retention.

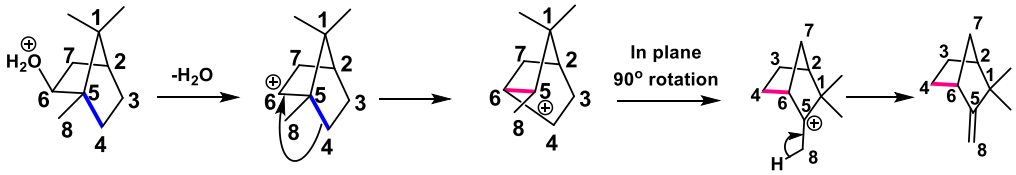




So, what is happening in the presence of acid, is protonation. So, once the protonation happen it actually eliminate the water to generate this carbocation in the carbon 6. So, now, once it is generating a carbocation if you try to draw this carbocation, there is an empty p orbital. Now, you can see this σ-bond here. This σ-bond can donate electron density to this empty orbit. So, that will allow the breakage of this C_5-C_4 bond. So, that will end up generating a carbocation at the C-5 position.

Now, if you try to just rotate that, you can write the same compound in this form. There is a proton abstraction happening here to generate this compound called camphene. So, this is the rearrangement what Wagner actually proposed.

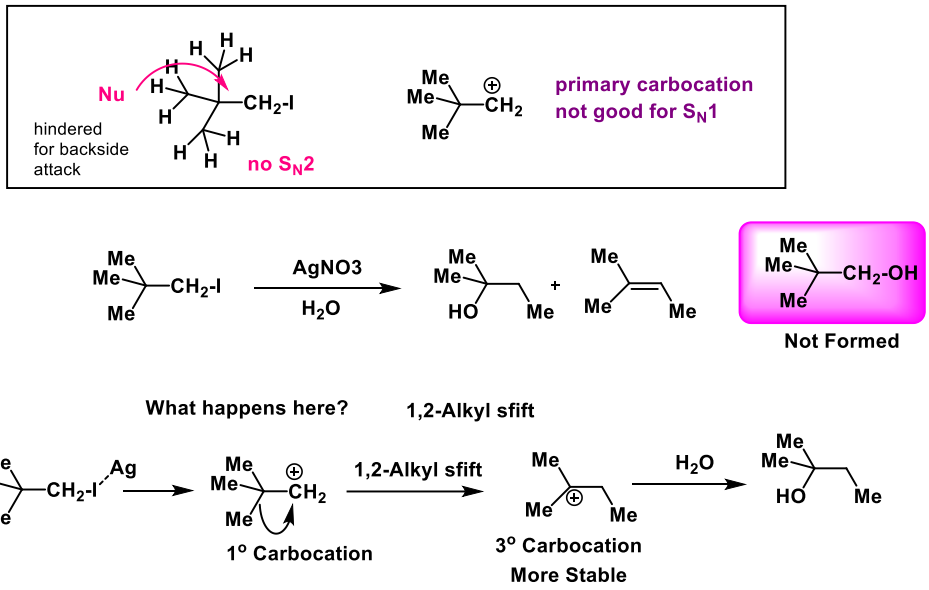




Now, we are going to find out some other examples of this type of reaction. So, we have learned about S_N2 and S_N1 reactions, but if you think about this particular example, neopentyl iodide. So, in neopentyl iodide, although there is a primary CH_2, but this is a very bad substrate for S_N2 reaction because your backside attack by nucleophiles is getting hindered because of these three methyl groups. At the same time, if you try to go for an S_N1 reaction, then it is also not a very good substrate for S_N1 because it is generating again a primary carbocation. So, what is happening if you treat with silver nitrate and water? The silver nitrate is going to activate this carbon-iodine bond to generate this primary carbocation. I am sure you understand this part and now once it is forming this primary carbocation, there is a 1,2- shift happening from this position to this position.

Again the σ- bond of this carbon and methyl is giving electron density to this empty P-orbital of this carbocation. So, that is generating a more stable 3^0 carbocation. As you guys know, the tertiary carbocation is more stable, now what is happening is that that it

can capture water to comes to the corresponding alcohol, or there could be a proton abstraction that can go through the corresponding olefin. So, it ends up giving ends two products in this reaction.



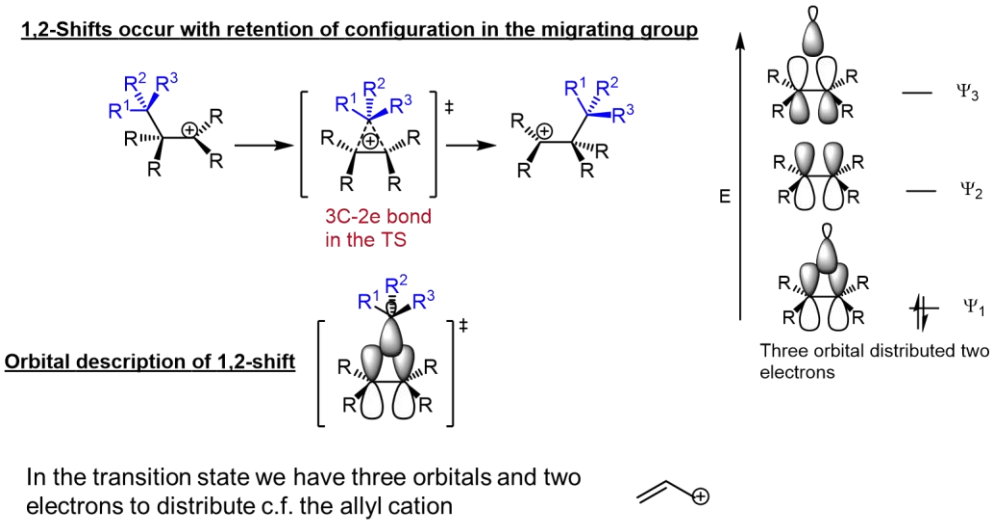
So, now we try to understand about this 1,2- shift because this 1,2- shift you are going to not only see in this Wagner-Marwin arrangement there are many other examples or many other reactions also you are going to observe this.

So, what is happening in this let us try to understand. So, one thing I think we should keep in mind that this 1-2 shift occurs with the retention of configuration in the migrating group. So, what is happening here that suppose this is the σ-bond which is actually migrating here. So suppose this sigma bond has a chiral center attached here with a particular configuration. Now that configuration will remain intact in the product as well because if you see the corresponding transition state what is happening here, the σ-bond is giving electron density to form some sort of a 3C-2e bond.

You have a positive charge here, and now this is going to shift to this particular carbon. So, now you can see that this stereo information or this particular configuration actually remains intact in the product. And if we try to understand this reaction through this orbital description, what is happening here is that we have 3 orbitals and 2 electrons. So, it forming this type of bonding here. We can compare these two I think we have previously learned about the bonding of this allyl carbocation.

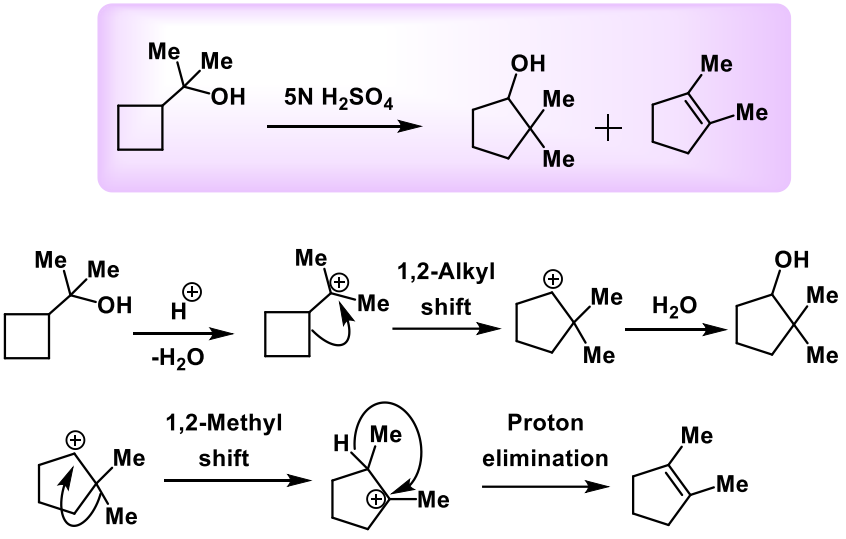
You can compare this with this allyl carbocation. So, here you can see there, but we have only two electrons here. We can also show them that there will be three different orbitals. So, there will be Ψ_1, Ψ_2 and Ψ_3. And then you can see that this it is a bonding orbital here.

So, you can see this 2e will be in the bonding orbitals. Also, you can see in this 3C-2e transition state which I mentioned, this is actually an aromatic system. If you think about a cyclopropyl with a 2e and a carbocation we have learnt previously in the previous slide I talk about. So this will generate an aromatic transition state. So, this slide is another important thing we can bring here that explains why this reaction, this migration, is happening when there is a carbocation. You know, what will happen if there is a carbanion? Does the migration happen? No. If you have a carbanion here, then this 1,2 shift is not happening because once you have a carbanion, you have a, instead of two electrons it has four electrons. So there will be another two electron here. So that will make the corresponding transition state anti aromatic ok. So, that is the reason why you can see this want to shift happens only when there is a carbocation.



So, now, let us you know if move you further and go through some examples here. So, you can see here in this particular example we have a cyclobutane ring and then there is a tertiary alcohol here which gets protonated after the elimination of water to generate this particular carbocation. You can see that this is already a tertiary carbocation but what is happening here is it is actually migrating from tertiary carbocation to a secondary carbocation by looking into it you might think why that is going through a less stable carbocation that is not the case there is a ring strain here which is getting released here and now trapping of the water can give to the corresponding alcohol you can think about

that after it comes to this as i was telling you it can also go for another important thing, is 1,2-methyl shift, because in this particular cases this is a secondary carbocation. Once the methyl group migrates here it will generate a more stable tertiary carbocation where elimination of proton can happen, which can lead to the corresponding product.



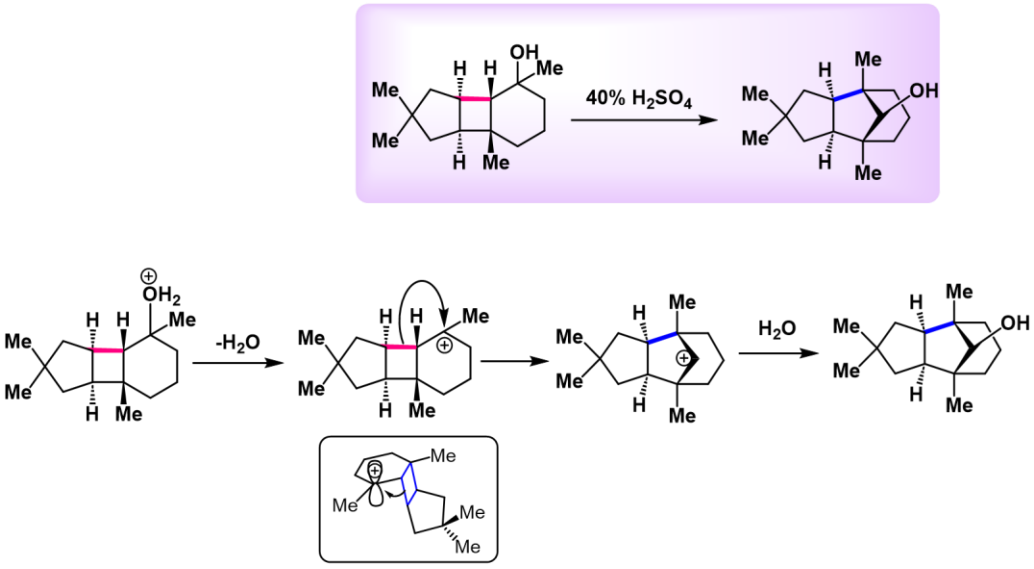
We'll go for some more example. So, this is another example of a synthesis of natural product where the Wagner-Meerwein arrangement was utilized. You can see here from conversion of this compound to that compound. You know, just looking into the bigger structure, you don't have to be scared. You just try to look for what changes happen.

From going from here to here. You can see at the beginning I have a 5, 4 and 6 member rings. Now, I have so, so there was 5, 4 and 6. Now, it was 5, 5 and 6 here ok. So, what happen we can see a clear ring expansion happens ok. So, let us try to understand what is happening here.

First thing is the protonation. Then after the elimination of water, it will generate this more stable tertiary carbocation. And after forming this tertiary carbocation, what is happening? Now there is a four-member ring attached here. So this four-member ring will try to get expanded to release the strain. It will go to this five-member ring, forming this particular carbocation here. Once it forms this carbocation, it can trap water in this corresponding product.

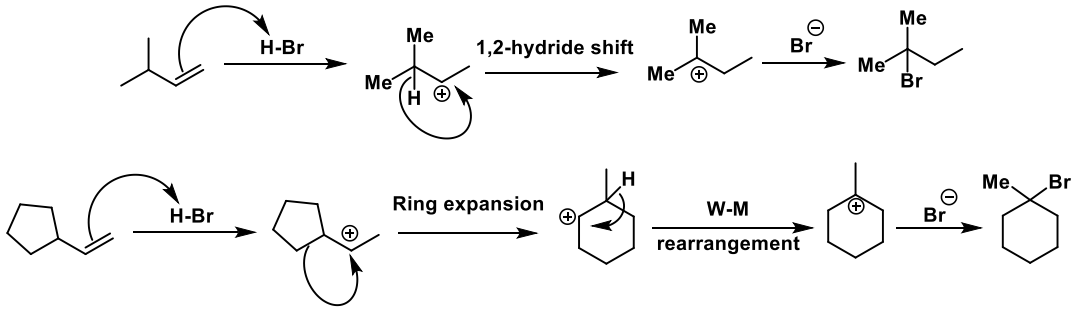
I try to draw this in the in this fashion also to give you an idea what is happening here. If you look into this particular carbocation, you can see there is an empty p-orbital here and

now this is a particular 4-member ring. You can see this σ-bond is now ready to give the electron density.

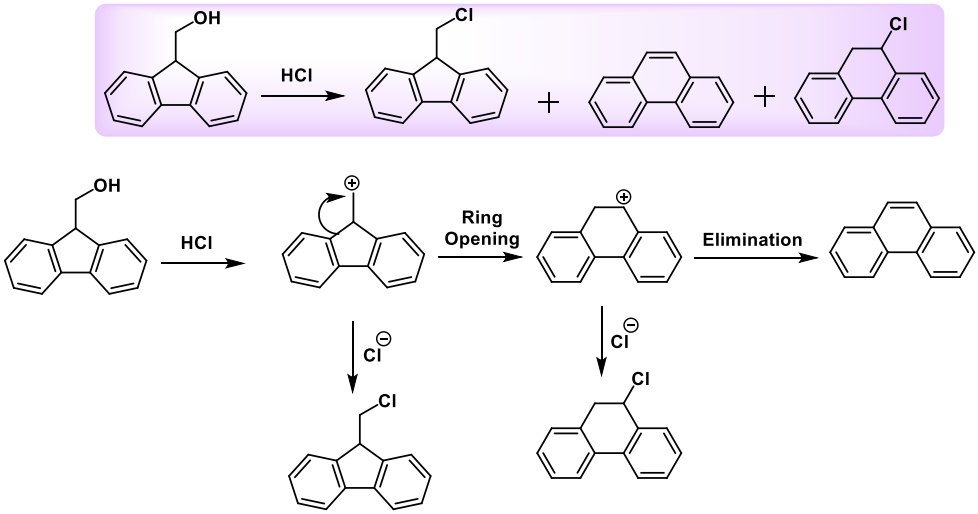


Let us move on so you know some other examples here. So, this is another example where we can see the first thing is happening: once you treat this compound with HBr. The first thing is going to form this corresponding secondary carbocation. So, you can think about the Markonikov rule I think we have learned about that is going to form the more stable carbocation here, but it is not the more stable because now once you have a 1,2- hydride shift, it can generate the more stable tertiary carbocation. So, once it forms a carbocation, you can see if there is a possibility that by doing a shift it can form a more stable carbocation, then the reaction follows that pathway, and now you can trap with this Br minus to form the corresponding bromo product. Again, a similar thing can happen here if you have a cyclo pentane ring with this vinyl group that can get protonated to correspond to this carbocation. Again here is the driving force is the ring expansion.

So, in the previous case, what we have seen a 1,2- hydride shift. Here what we are seeing. Instead of 1,2- hydride shift, this is a ring expansion to make this secondary carbocation. Now it is not going to stop here in the secondary, now there will be another 1,2-hydrate shift is going to happen. So, this is after 1,2- hydrate shift, it will form the more stable tertiary carbocation which is going to form the corresponding product.

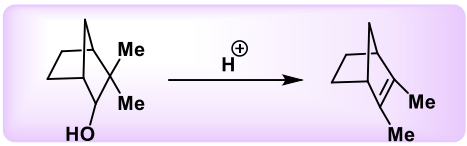


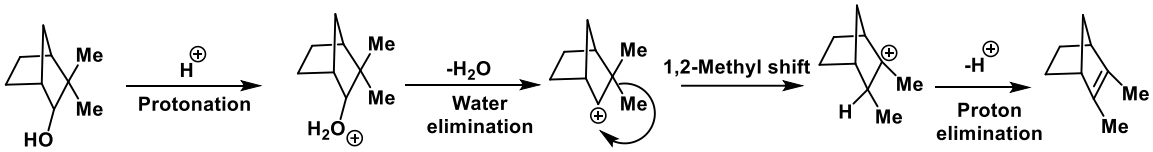
So, these are what I am going to teach you throughout this journey that we are learning different different examples. Not every cases there is a general rule cannot be followed that always there will be hydride, always there will be alkene. You will try to understand what are the different stereoelelectronic effects, and why the migration is happening. So, next example also about the ring expansion. So, starting from this alcohol once we treat with HCl is going to protonate first, then there will be ring expansion happening to form this particular carbocation as I said ring expansion is a very important reaction to release the strain, and then there will be a hydride abstraction happening from here, which will generate the corresponding phenanthrene which is a stable compound. It can also take a Cl^- here to form some of this by-product.



So, let us try to go to is this particular example here what is happening here first thing again the protonation of this OH to generate this compound. Now water elimination is happening to generate this carbocation. So, now it is very interesting once it is coming to this particular carbocation. Now things are interesting because there is couple of different possibilities: one it can go for this methyl shift or one it can go for this particular shift because it can also have this σ-bond. you know give electron density, but the problem is if you do that you end up generating a secondary carbocation, but here once you go for

1,2-methyl shift you generate a more stable tertiary carbocation. Now, after that proton abstraction we will able to give it to the more substituted olefin.

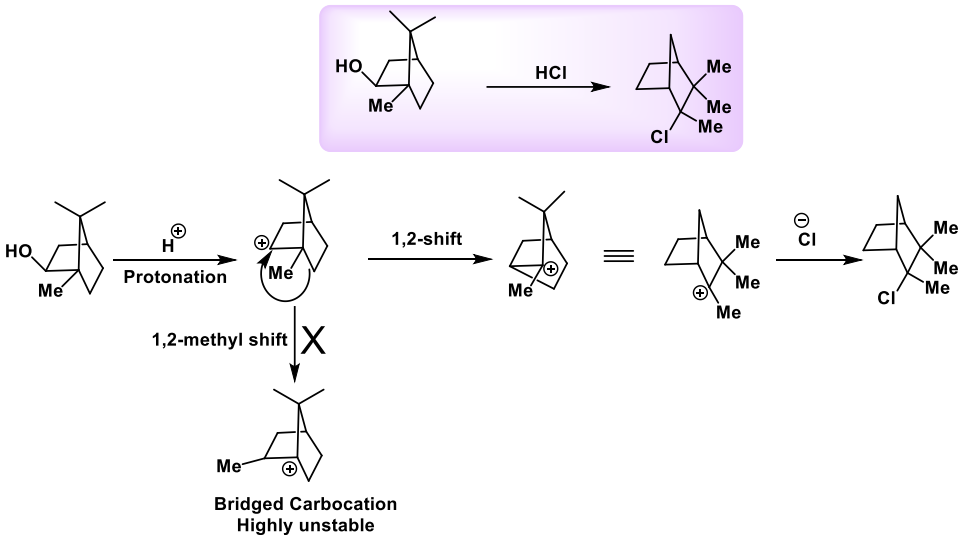




So, moving further, there is another example here. So these are the cases of these norboronyl examples here. If you are able to treat this corresponding alcohol with HCl, it's end up making a different product here.

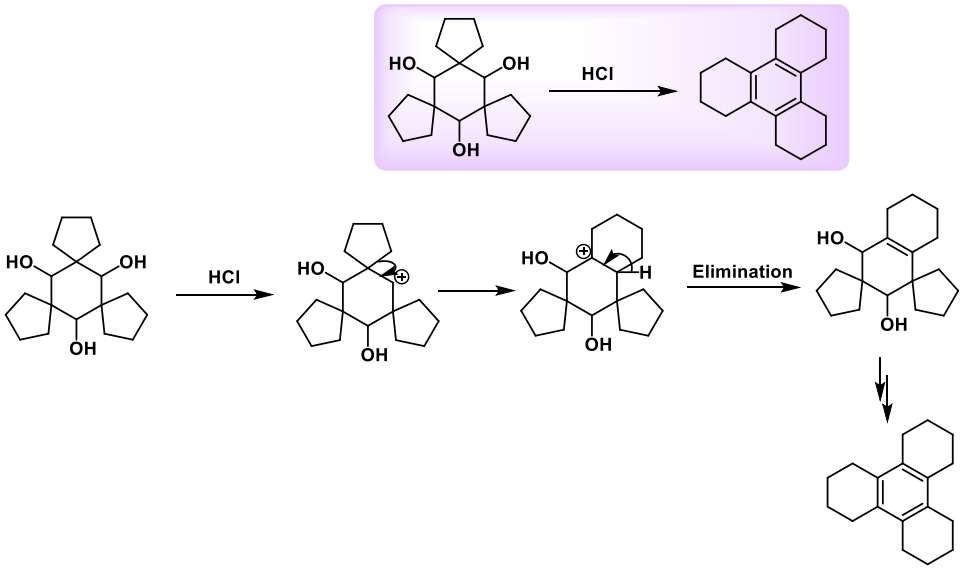
So it's not just, getting out of here and putting a Cl back there. It is not happening like that. So first, thing is the protonation, then the elimination of water to get it to this particular carbocation. Now there is a 1,2-shift happening. Again there are two possibilities first thing it can be1,2- methyl shift or it could be this bond going to get migrated, which we have shown here so what is the problem? if you have a 1,2- methyl shift you end up making this bridgehead carbocation guys.

This is very difficult because making this are bridgehead position planar will be very difficult so that's why the bridgehead carbocation is not going to form. What is going to end up seeing? You going to end up seeing this sigma bond is going to give electron density to form this carbocation here ok. So, you end up seeing this particular carbocation here. Now, we can write this in this form and which is a tertiary carbocation which can take this Cl^- to form this particular, product.



So, moving further we have another example here you have three cyclopentane rings using three different three alcohols here. What is happening once you treat with the HCl first you know it is getting protonated, and then water gets eliminated to form this. As soon as form this carbocation there is a ring expansion is happening which is the driving force here. So, ring expansion is happening to form this. Now, if you have this tertiary carbocation formation happening, there will be a proton abstraction to form this double bond. Now, the next is protonation to the corresponding, and it can eliminate the water.

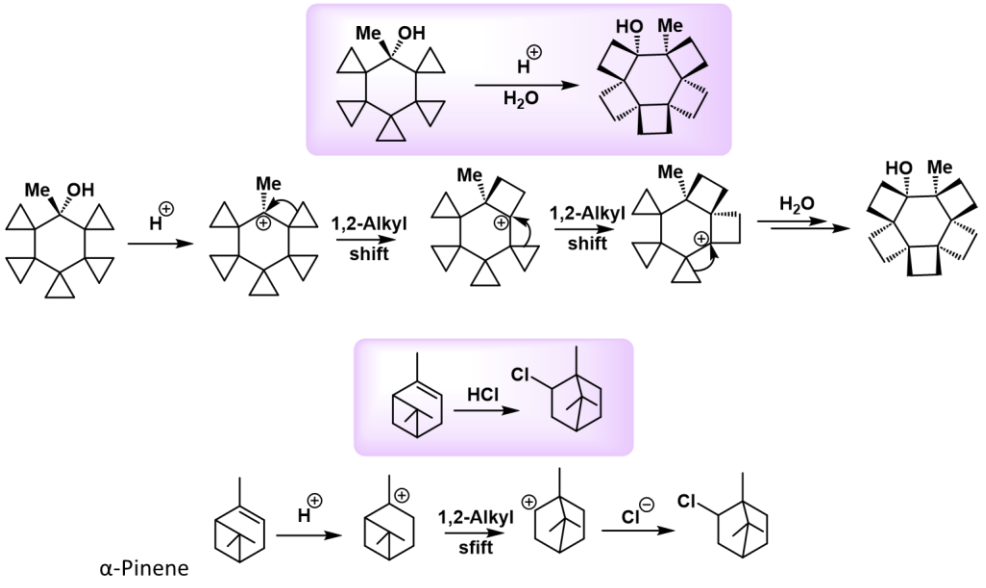
Go for, the next shot of carbocation, then it will form this bond, and then it will continue and form a phenyl ring with 3 cyclohexyl ring fused into it.



We can go for another example where there will be 5 cyclopropyl groups here. So, there is 1, 2, 3, 4, 5 with this corresponding alcohol here. So, this is a very interesting reaction because this is kind of a chain reaction once something trigger it will continue. So, what is happening first step is the formation of this carbocation after water elimination.

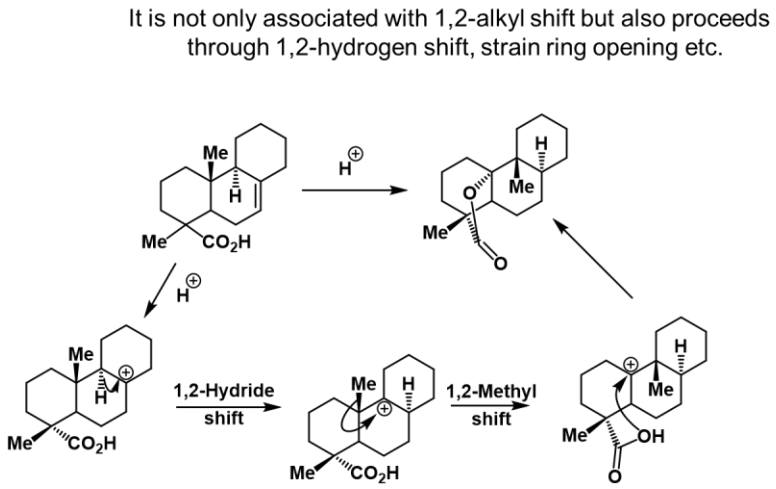
Once this carbocation is formed the cyclopropyl group is going to get migrate to release the strain to cyclobutane and after this migration is happening you can clearly see there will be a positive charge going to form here in this carbon and that is happen in form a positive charge. Now, as soon as there is a positive charge and there is another cyclopropyl group it will keep on doing ring expansion using the cyclopropyl. Then the next cyclopropyl is going to go for expansion. So, it will keep on expansion still it form this particular compounds. So, it is a very important things that starting from this thing you can convert all these different cyclopropyl group to the cyclobutyl group.

Then there is another important example here where if you treat alpha pinene with HCl. In general if you look into this alpha pinene you might say sir if I treat with this it will go to the double bond from this more stable carbocation. and then it will treat with Cl minus to form this corresponding chloride in this position. In this carbon the chlorine will attached, but actually it is not happening. After this carbocation although this is a tertiary carbocation, but there is a 1,2- shift happening from this. Why 1,2- shift is happening? Because you can see there is a 4 member ring here. This 4 member ring is going to get expanded to 5 member ring. So, then it is although it is a making a secondary carbocation, but the driving force is the ring expansion and then it will take the Cl minus to form this particular product. So, you are not getting the chlorine here which you thought at the beginning that it will form the chlorine here, but it is not it is going to get further expanded to form this particular form.

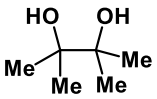


So, moving further, we are going to learn about the last example here, where we have an olefin that can get protonated with H+ to form this, carbocation, which is tertiary.

Then it is going to get migrate to form another tertiary carbocation here. Then, but this is happening very stereospecific manner. The methyl is also getting migrated to form this carbocation, which is finally getting trapped with this lone pair of this oxygen to form this compound. So, you might see that I am talking about different example because again I told you at the beginning that this particular topic there are lot of question comes in the exam.

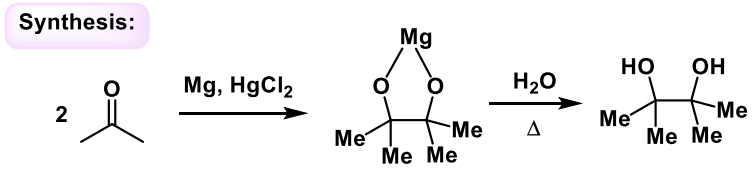


So, you can able to prepare for the exam as well. So, now I am going to talk about another important example called pinacolone rearrangement. So, before I go to the pinacolone rearrangement, I want to see what is called pinacol. So, these are vicinal 1, 2 diols. Again, if I talk about vicinal 1,2 -diol you might think about the synthesis of using osmium tetroxide dihydroxylation of olefin. But there are, other method you can able to make you can, from ketones using magnesium $AgCl_2$ you can able to cleave this single bond to make a di radical. I am going to discuss those reactions in the radical part, then it can have a formation of a dimer that can be able to make these corresponding pinacols. But again, in this method, you can only make symmetric diols. So, both sides will have the same group.



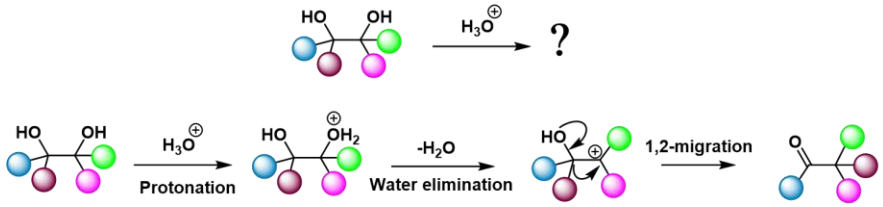
Pinacol

Pinacol is a compound which has two hydroxyl groups, each attached to a vicinal carbon atom. It is a solid organic compound which is white. The IUPAC name of Pinacolone is 3,3-dimethyl-2-butanone



So, after making this, I think the next thing is if you treat with the acid, what will happen? So, this reaction was discovered by Rudolf Wittig in 1860. So, you can see how old this reaction is. So what is happening once you treat this pinnacle with acid? It is going to protonated one of the alcohols and then after water elimination, it will generate this carbocation. Now, you can think about this 1,2- shift which you have learned the Wagner-Meerwein rearrangement. So, you will see there will be 1, 2-shifts going to happen, which will make this corresponding ketone. So, what is happening? You started with a vicinal diol, and we end up with the with the formation of a ketone. So there are a couple of important things about pinacol-pinacolon, because if you see a lot of textbooks or in the different literature, people have sometimes written them in a stepwise fashion, the reaction, that means what I'm doing here, I'm writing in a stepwise, that first there is protonation, water elimination, then 1,2- migration, then product, and somewhere you might find that people are writing this in a concerted mechanism, that means formation of the carbocation, formation of, sorry, the migration, one-two migration.

And, then you have the water elimination kind of happening in the same time, but there are a lot of theoretical studies have actually done, and some of them suggested that the reaction depends on the substrate and can be stepwise or concerted. But, one thing is they suggested that the influence of non ionizing solvents on the reaction process through a concerted mechanism. So, let us try to see some examples here. As I said, this reaction is the acid catalyst. So, if I am talking about acid, then there are two different classes of acid; we can say one is protic acid and another is Lewis acid.



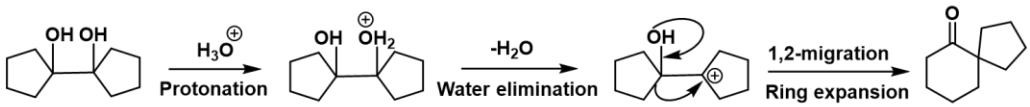
The theoretical study evaluates both concerted and stepwise pathways for the pinacol rearrangement, proposes that the pinacol rearrangement proceeds through a concerted mechanism in non-ionizing solvents

This reaction was first described by Wilhelm Rudolph Fittig in 1860.

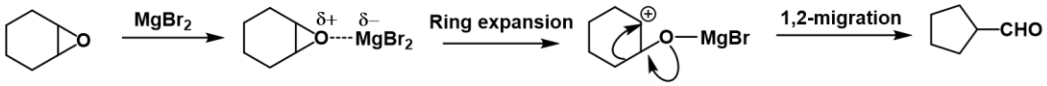
So, we can talk about the use of protic acid for this reaction. So, Lewis acid like BF_3-OEt_2, TMS-triflate, $MgBr_2$ and others. So, now we are going to look at some of these examples and try to understand them. So, let us go to the previous example really quickly, and then I will go to the next example. Suppose I have a diol that is symmetric, then there is no problem; there will be a protonation, and water elimination resulting in the formation of carbocation, and as I told you, there will be a ring expansion happening from here to here to forming the particular product. Then, if you treat this epoxide with magnesium bromide, during carbocation generation or if you treat epoxide with Lewis acid, what will happen? It will generate this particular carbocation, but now if you see about this carbocation there is a 1,2-shift happening here at the same time that oxygen is pulling this lone pair to form this corresponding aldehyde.

- This acid-catalyzed transformation of vicinal diols
- This reaction can be catalyzed both by protic acids or Lewis acids

Protic acids catalyzed: Such as H_2SO_4, $HClO_4$, H_3PO_4, TFA, TsOH

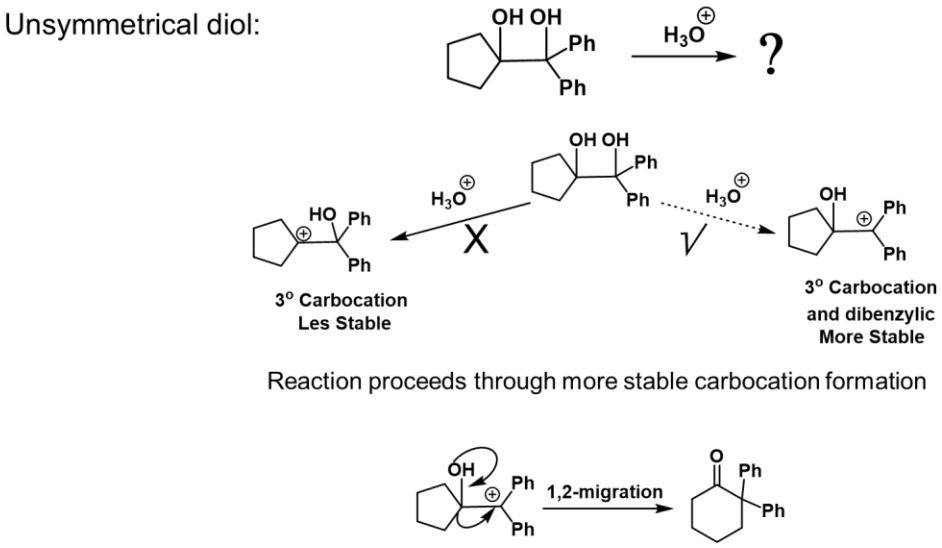


Lewis acids catalyzed: $BF_3{\cdot}OEt_2$, TMSOTf, $MgBr_2$ etc



Now, if you see the problem in the previous slide, what I have talked about is the diol, which is symmetrical. What will happen if they are unsymmetrical? What will the things be? Now, if they are unsymmetrical, in that case, the first thing is where is, the protonation going to happen. You know does it going to happen in this particular site or this particular site? That actually depends on the stability of the carbocation. If it is happening on this side, you can see this is also a 3 degree carbocation, but here it contains two phenyl groups.

So, it is diphenylic system. So, there are two phenyls attached to this carbon. So, that will make this carbocation more stable. So, that will allow the formation of this particular carbocation, and then there will be a ring expansion. There is another thing that is the formation of another carbocation and the second thing is that there is a ring expansion happening that is also you know favor to get to this particular product.

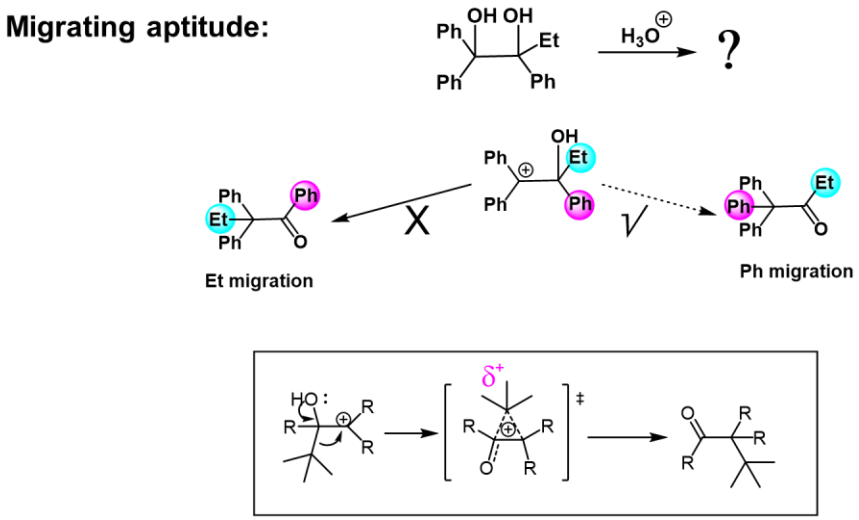


So let's go to some other examples here. So now there is another thing happening here. We have a diphenyl on one side and on the other side, we have a phenyl ethyl. So by looking into it, you might say, sir, I have already learned in the previous slide that this carbocation will be in our favor. But the question comes, once you form this carbocation, which group is getting migrated? I didn't talk about that till now. You have a phenyl and ethyl. Who will be the winner? So what we find out is that this is going to be the product where phenyl migration is going to be better compared to the migration of ethyl.

So now we have to try to understand what is happening here and why phenyl is a better migrating group. Now, if you try to understand the reaction, a lone pair is coming here,

pushing this electron density. Then this particular group, suppose I put this here as a tertbutyl one, this tertbutyl group is migrating to this corresponding carbocation. we have learned that in the Wagner-Marwin shift, they will form some kind of transition state where this migrating group migrates to that carbon, which carries a δ+ charge. And so it means that in the transition state, there will be things which groups will migrate? The groups that can able to stabilize the positive charge more are better migrating groups.

That means if I try to compare the tertiary butyl group versus the isopropyl group, it will be a better migrating group compared to the isopropyl group. Because you know that the tertiary carbocation will be more stable compared to the secondary carbocation.

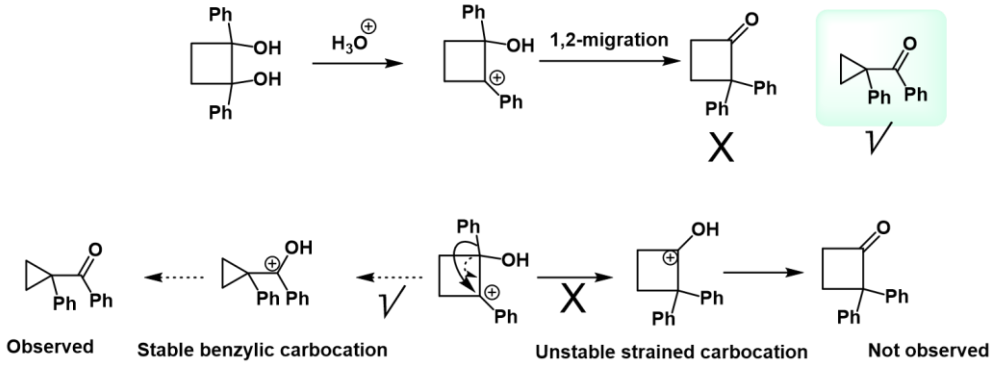


we have some other examples here, and you can see that there is another important thing I'm going to bring here that is always not like that we will find somewhere and protonate diol. If you think this particular vicinal diol you make this carbocation, but the next thing is might be thinking about it, ok, then the next thing will be to say I can draw this there will be phenyl migration, and I am going to end up getting this product, but that is not the thing that is happening here what is happening here, so we end up getting this as a product. because what is happening, if you think about it, the formation of this particular carbocation is not going in favor because you are trying to make a carbocation on top of this cyclobutane molecules, which are already strained molecules. Now you are trying to make it a carbocation on the cyclobutane it is not going to get you much favor here.

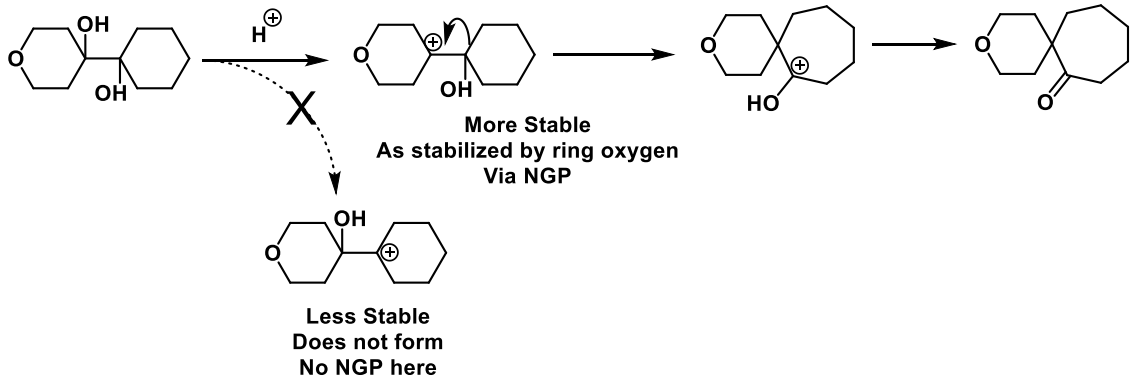
So, what is going to happen instead of that? There will be some sort of carbocation like this okay so if you form this type of carbocation then it you can observe this particular product here okay we are not going to observe this particular product here So, what is

happening here instead of forming instead of going for this carbocation here the first thing that is happening is a breakage of this bond. So, literally this bond is migrating from here to here to make a carbocation character after releasing of this water. So, after releasing this water from here, it will migrate this sigma bond from here to generate a carbocation, which is forming.

In situ formed carbocation stability:

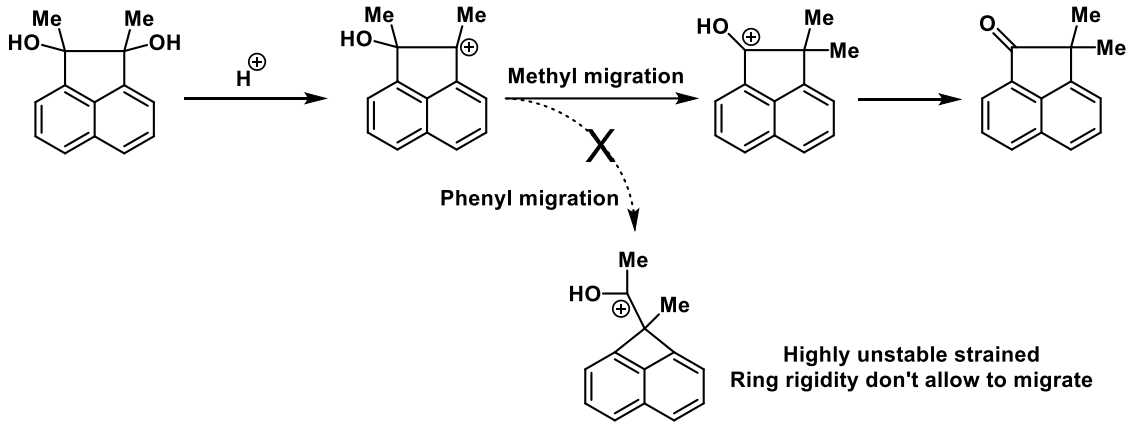


So, here we have example where we have a cyclohexyl group here in the one side, another side with oxygen. Now, what is happening? Now, you know, what will be the competition here? Of course, there will be more stability compared to this because you have this oxygen lone pair that can give electron density that will allow this 1,2-migration to form this particular product.



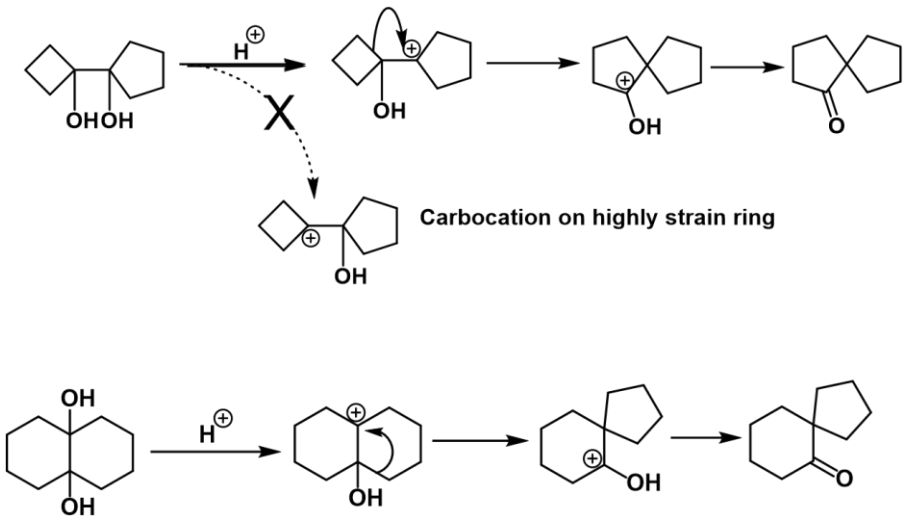
And then there is another example here. We can get a protonation here very easily, but the problem is the migration. So, here, the methyl migration will occur. If you migrate the

phenyl, you end up making a very unstable strain molecule. So that is why the methyl migration will be favored to give to you these corresponding products.

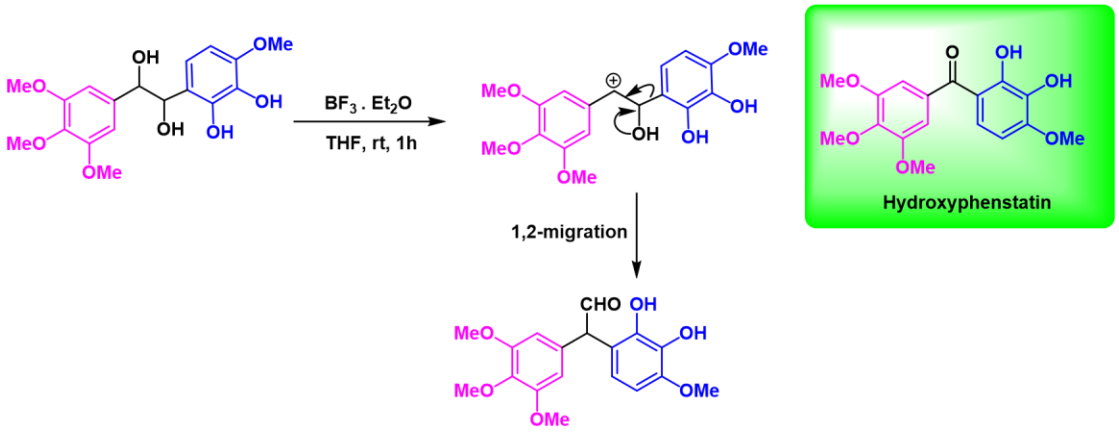


There is another example here: if you have two different size rings, as I told you before, there will be more possibility of the formation of a charge on the bigger ring compared to the smaller ring because there will be more strain.

That is why this product will be the major product. If you have an intramolecular case that can also go through this type of expansion and release water, then there will be a 1,2-migration which will end up forming this particular product.



So, this is an example of an important molecule. As you can see now you have a diol on both sides and you have a phenyl with 3 different methoxy or 1-Ome and 2-OH, in the presence of $BF_3{\cdot}Et_2O$ it can form this carbocation. Now, there is a 1,2- migration. You can see this particular group will participate in 1,2-migration to form this particular product.



And this can be further used to make this type of important bioactive compounds. So, in this class, you have learned about the Wagner Maroon rearrangement and the Pinnacol rearrangement, and several examples of them. I hope you guys like it and if there are some references here, you can follow. Thank you all, and now thank you for coming to the class.