Introductory Organic Chemistry II
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Indian Institute of Science Education and Research, Pune
Module 08
Lecture 55
Rearrangements - Part 2

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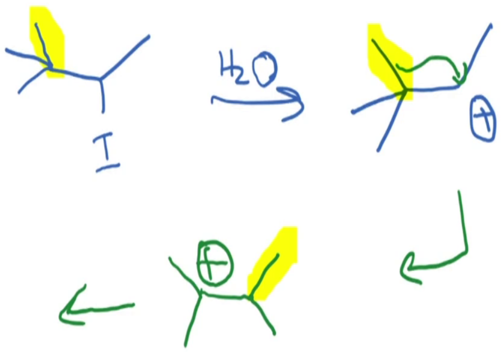
CARBOCATION REARRANGEMENTS



So, now, let us look at the some of the rearrangements that involve carbocation. This has been briefly looked at in the previous part of the course, but imagine that you have a leaving group such as this and basically in the presence of water or some highly polar solvent, you do a reaction which facilitates the formation of a carbocation. And the carbocation that we have sort of looking at would be this.

So, you have a compound like this and then you could have a possibility of a carbocation being formed here and we have a prior understanding that this is possible that this can migrate over here and generate a tertiary type carbocation which can of course, undergo elimination or it can undergo substitution to give you the corresponding product. So, the rearrangement is the situation where this carbon-carbon bond has now moved to form a new carbon-carbon bond here and which results in a molecular rearrangement.

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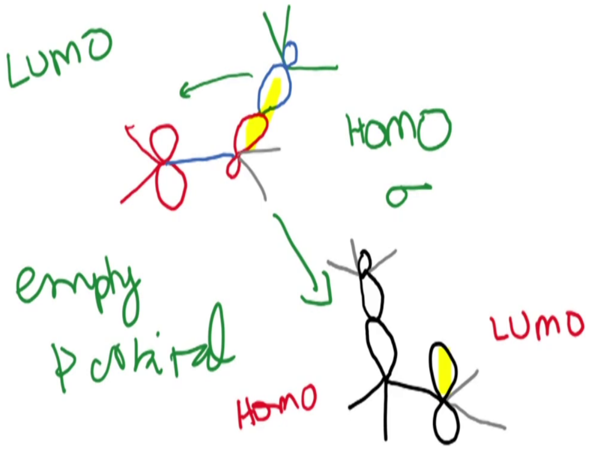

So, we have already looked at some of the orbital aspects of this but let me just quickly go through this. So, basically the carbocation is an empty p-orbital. So, this is the empty p-orbital and here is the let us say the carbon-carbon bond that is going to rearrange. So, this is the way the orbitals are denoted and you have the three hydrogens over here.

And so, what ends up happening is the HOMO, the highest occupied molecular orbital of the sigma bond now migrates to the LUMO which is the empty p-orbital. So, once it migrates then you will generate a new carbon-carbon bond and an empty p-orbital. So, just to be clear, there are groups here as well. And so, this is basically the three hydrogens as shown here.

So, therefore, this sigma bond that was here has now transformed into an empty p-orbital. So, this is the LUMO now, and this is the HOMO, if you are going to look at the another reverse rearrangement in this process. So, this is how the, from an orbital standpoint, the reaction occurs, or our understanding of this reaction is from the orbital standpoint.

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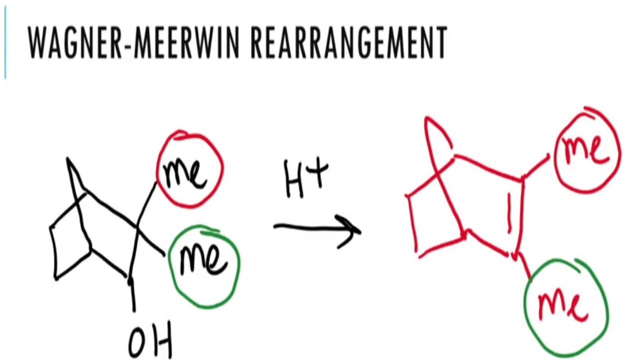
WAGNER-MEERWIN REARRANGEMENT

Now, let us look at another a very interesting rearrangement which is called the Wagner-Meerwin Rearrangement. So, this is of the following reaction. So, if you recall, we had discussed these kinds of norbornane type compounds earlier, you have a methyl group here, you have a methyl group here, and you have an OH.

So, when you expose this to an acid, what you would expect is that this gets protonated, and it gets lost and I mean, we look at the product, but this is something that you can expect right away. And so, the product that you obtain in fairly large yield is this methyl, methyl, the double bond. Now, let us spend a little bit of time and understand what has happened in this reaction. So, if you see here, this methyl group here remains this methyl group.

Whereas this methyl group seems to have moved to the neighbouring position and therefore, this does qualify as a rearrangement. And now, let us look at the mechanism. The rest of the molecule remains the same, I would urge all of you to number the carbons, when you are looking at rearrangements so that it is easy for us to follow it.

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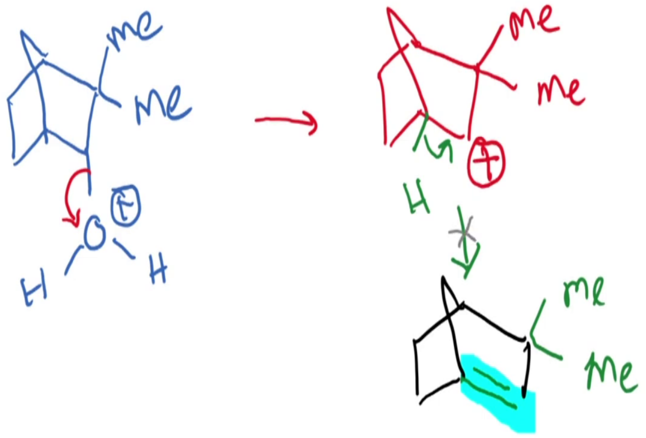

Let me draw out the structure again, and let us see how best we can propose a reasonable mechanism. So, here are the two methyl groups and this is the OH. And so, you can straightaway propose that the oxygen gets protonated and then there is a loss of water which is fairly straightforward for us to propose. And so, the methyls remain here and then you have carbocation that can be produced.

So, now, clearly there is a hydrogen next to it. And so, if this is undergoing loss of a proton, then the product that you would get be this. So, this is a fairly straightforward reaction for us to propose except that this type of double bond on the bridgehead is not favoured. And so therefore, this reaction is not favourable. So, now let us move back and try and understand what happens with this carbocation, which is going to be the key intermediate for us.

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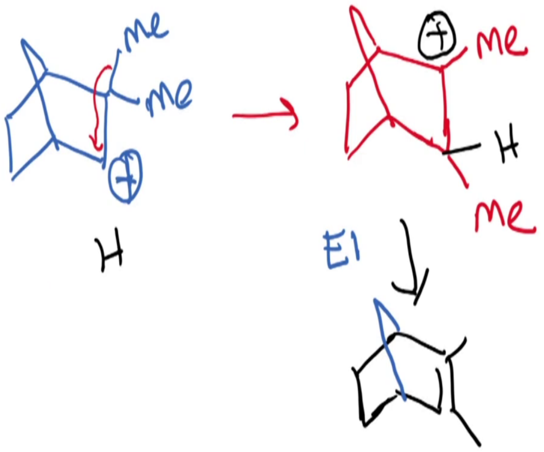

So, here is the carbocation again, methyl, methyl and positive charge. And so, what you can propose is that this methyl group migrates over here. And that results in the movement of the methyl group from one carbon to the other. So, this methyl remains here and you have another methyl over here. And keep in mind that there is a hydrogen that is sticking out here. So, that continues to be here.

And there is a full positive charge that is going to be formed. Subsequently, this hydrogen can be lost, and you get the product that we observe. So, this kind of shift is called the Wagner-Meerwin Rearrangement. And it is a very powerful way for us to understand how carbocations can rearrange. Now, there are several variations of this which can occur, especially in norbornane systems.

And there is some really cool reactions that happen which unfortunately, we will not have time at this point to look at. And just to remind you, this is the E1 elimination that we are all quite familiar with. So, this would be another example of a carbocation-based rearrangement.

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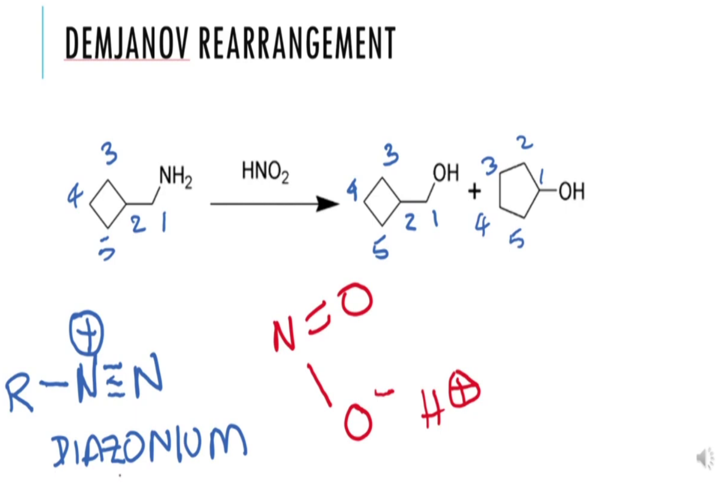

DEMJANOV REARRANGEMENT

Now, let us move on to the next rearrangement, which is called the Demjanov Rearrangement. So, here, you expose this amine to nitrous acid, nitrous acid is $^{-}$ON=O. So, this is nitrite, and then you have H^+ that can be formed. And this is nitrous acid. And nitrous acid can actually produce diazonium ion, so diazonium ion is nothing but N triple bond N, and this is nitrogen.

And so, when you have a group that is present here, this is called the diazonium group. We have looked at this in the past when we are doing functional group transformation on a benzene ring. So, aliphatic compounds can also produce a diazonium ion. And so, this diazonium ion is an excellent leaving group. So, with this background, now let us look at the mechanism.

So, if you see here, the product that is formed, this product which is the expected product, let us say there is 1, 2, 3, 4, and 5, 1, 2, 3, 4, and 5, this is fine. But if you see this other product that is formed this clearly some sort of rearrangement is occurring, because that is not the product that we would have expected from this reaction. So, instead of the 4-membered ring you now have a 5-membered ring. Now, let us look at the mechanism.

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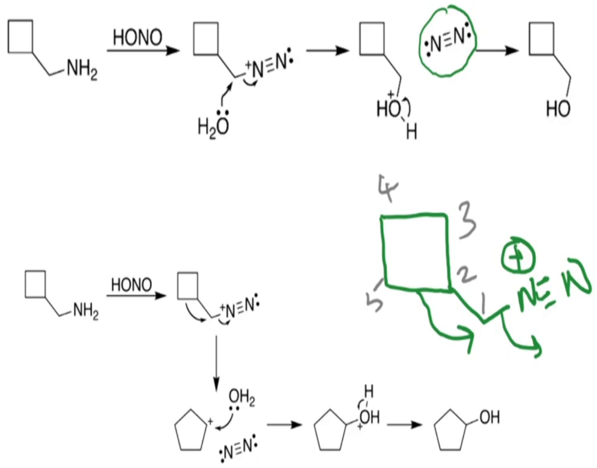

The mechanism is the formation of the diazonium ion as I indicated to you, and subsequently this diazonium ion can lose nitrogen, which is a gas and so this is an irreversible reaction. And the loss of this nitrogen occurs with the attack of water and then you produce this kind of product which is quite straightforward for us to understand.

The second situation is where you produce the same diazonium ion intermediate. And now, diazonium ion intermediate, the loss of nitrogen can precede the attack of water. That means that you have this ring expansion that can occur before the attack of water, so you have the movement of this bond and kicking out of nitrogen to produce 5-membered ring.

So, if your number this the same way we will number it 1, 2, 3, 4, 5. So now, there is a bond between carbon-5 and carbon-1, and carbon-2 has the positive charge on it. Now, the remaining mechanism is fairly straightforward. So, attack of the water on this 5-membered ring gives you the desired product.

So, when you are looking at these rearrangements, you need to keep in mind that the basic understanding of chemistry that we have looked at so far will all those rules apply and once you have a strong foundation of those rules you will be able to figure out the mechanism.

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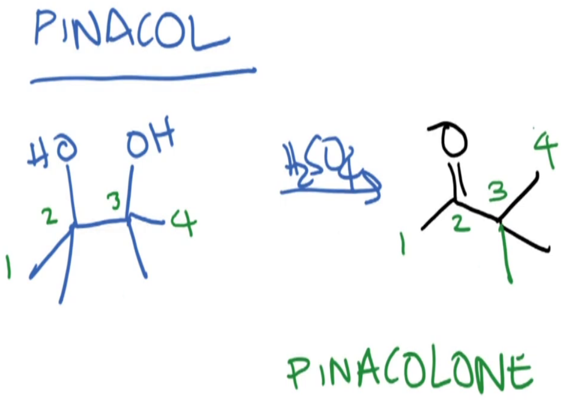

Now with that, let us move on to the next rearrangement which is called the Pinacol Rearrangement. So, this is one of the very popular rearrangement that occurs, it is called Pinacol Pinacolone Rearrangement, as well. So, Pinacol is the following you have two OHs here and this compound, and when you react this with acid H_2SO_4, the product that you get is this.

Now, let us just number these carbons so that it is easy for us to follow this. So, this is let me just start from the left 1, 2, 3, 4, 1, 2, 3, and 4, so carbon-3, which had two methyl groups on it now has three methyl groups and carbon-2 which had an oxygen now has a carbonyl compound. So, this product is called Pinacolone. So, sometimes this rearrangement is called Pinacol Pinacolone Rearrangement.

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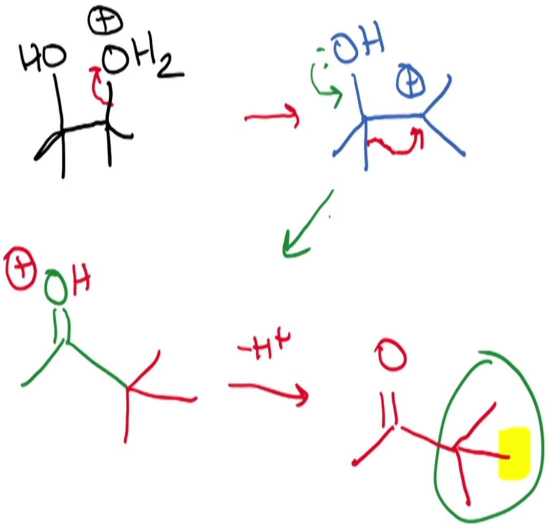

Now, let us try and understand the mechanism, let us again stick to the basics. So, when you have an alcohol one of the first things that happens when you have an alcohol in acid is it gets protonated. And then you can straightaway propose that the loss of water to give you OH, a carbocation over here. And just to be clear, the yield of Pinacolone is 70 percent.

So, it is not a low yielding reaction. And therefore, we are discussing the formation of the major product. Sometimes rearrangements can occur which gives you a minor product and those are very interesting from a mechanistic standpoint, but here we are looking at the formation of the major product.

Now, what we know is by looking at the product as shown here. So, we know that one of the methyl groups has migrated. So, this migration can occur in the following manner. So, you can propose that this methyl group moves to this position which will satisfy the three methyl groups present here and what that leaves us is basically a full positive charge on carbon which can be readily accommodated by this lone pair of electrons.

So, what we can propose from this is that the formation of a carbonyl with the new methyl group here and the two old methyl groups over here. So, this is possible. So, minus H^+, loss of proton gives you the final product. So, I will go through this mechanism once again. So, the diol gets protonated and you form $^+OH_2$ and then the second step is the formation of the carbocation which we already are quite familiar with.

And the next step is a migration of a methyl group which also we are okay with. The only minor difference here is that you do not get a full-fledged carbocation but you get a protonated carbonyl type intermediate which can then subsequently lose H^+ to give you the final product.

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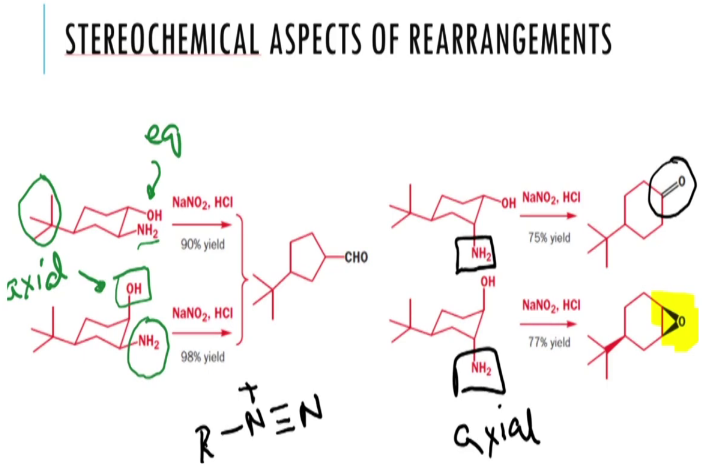
STEREOCHEMICAL ASPECTS OF REARRANGEMENTS

So now, let us look at some of the stereochemical aspects of rearrangements. And this is really nicely highlighted by this set of reactions that have been conducted. So, I want you to look at the structures a little closely and try to understand what is going on here. So, if you see, let us start from the left. So, if you see this compound, this has a tertiary butyl group at the equatorial position.

And as we know, the presence of a tertiary butyl group is going to push the equilibrium towards the conformer, where tertiary butyl group is present in the equatorial position. So, one can assume that nearly 100 percent of the population is going to be in this conformation. So, therefore, if you see the common thread in all of these examples is the presence of a tertiary butyl group.

So, what has been done here is we take this 1,2-amino alcohols, so you have an amine group, and you have an alcohol here. So, the first two examples on the left, you have an amine group in the equatorial position. And the difference between these two molecules is that you have a hydroxyl group, here in the axial. And here, the hydroxyl group is in the equatorial position.

So, therefore these two compounds are structurally very similar, only the stereochemistry is different. And when you expose them to sodium nitrite, and HCl, and we have already looked at it, an amine under these conditions will form a diazonium ion. And the diazonium ion as you know is an excellent leaving group. And so therefore, it is a useful way to eliminate amine or convert an amine to something else.

So, when you add sodium nitrite, and HCl, you know these two compounds on the left, they give you this 5-membered ring aldehyde, cyclopentane aldehyde with a tertiary butyl group on it. And they both give you the same compound. And the yields are excellent, 90 percent, and 98 percent. Now, moving to the examples on the right; if you see that the difference between the ones in the left and the right is that the amine is in the axial position.

And the hydroxyl group now can occupy either the equatorial, or the axial. But when you do these reactions with the equatorial hydroxyl and the axial hydroxyl, you do not get the compounds on the left, but you get very different products and they are also in pretty good yield in excess of 75 percent. So, when you start with this compound, you end up with the ketone.

And in the last example, where they both are axial, you get an epoxide. So, now the question is, how do we explain this? But before we answer that question, what I want you to understand is that any rearrangement reaction such as this, stereochemistry is very important. And there are only certain kinds of rearrangements that can occur because others are not favourable both from the stereochemical standpoint as well as the orbital standpoint. So, now let us move to the first example and let us see how this reaction occurs.

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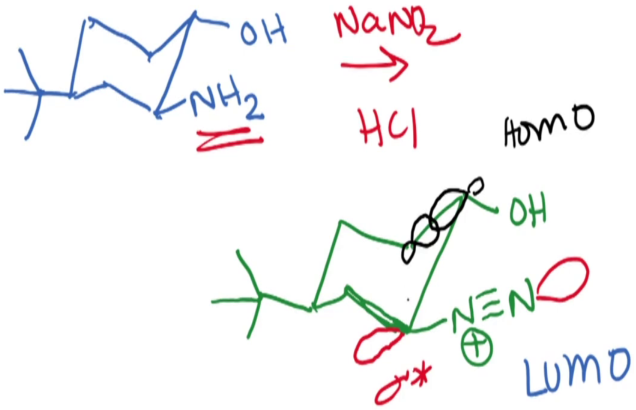

So, let me just draw out this compound and explain to you the way in which this rearrangement occurs. So, the first example here, a tertiary butyl group is in the equatorial position in all the examples as well as the first and the amine is in the equatorial position, and the hydroxyl group is in the equatorial position. So, as I had alluded to earlier, so when you add NaNO2 and HCl, this is going to be converted to the diazonium salt.

And clearly there is no change in stereochemistry during diazotisation process. This remains the way it is. And the hydroxyl group is in the equatorial position. Now, the important thing to note here is that the diazonium salt is a linear molecule, this bond angle is 180 degrees, this nitrogen is sp hybridized. So, now, this is the antibonding orbital of the carbon-nitrogen bond and the nitrogen bond here.

And what we need to understand here is that this is the σ^*. It is also the LUMO that we are interested in because that is where the electrons are going to be transferred to. And in this bond, if you consider it, this is going to be the highest occupied molecular orbital or HOMO. And this is the bond that is going to break.

So, what we have to consider is that these orbitals are aligned in a way that just movement of this bond in this direction towards this σ^* will result in the formation of a new bond, and also the breaking of this carbon-nitrogen bond. So, in the next slide, what I am going to draw is I am just going to draw out this structure once again.

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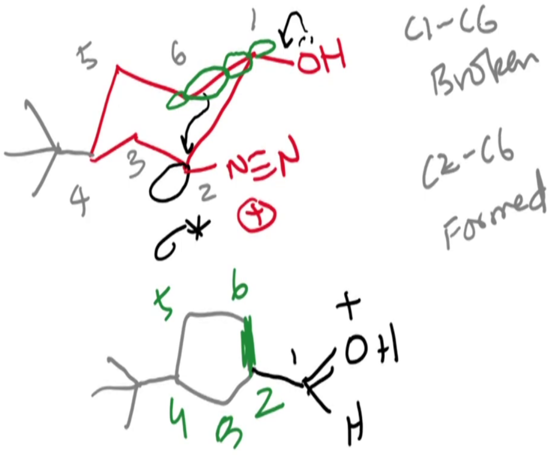

So, here is the hydroxyl group, here is the diazonium ion. And here is the orbital that we are interested in. And now, what we are suggesting is that this is the σ^*. So, this bond is going to move here. But in the process, there is also a lone pair on the oxygen which can assist this process by forming a double bond.

So, let me now number these carbons so that we are clear about the positions, this is 2, this is 3, 4, where there is a tertiary butyl group, this is 5, and this is carbon-6. So, the bond between carbon-1, and carbon-6 is broken. And the new bond between carbon-2, and carbon-6 is formed. So, this is important for us to note down. And so, this gives us a 5-membered ring.

So, I am just going to draw the 5-membered ring as shown here. And this is the tertiary butyl group. And this is the new bond between carbon-6 and carbon-2, this is 3, 4, and 5. And now, the bond between carbon-1 and carbon-2 is intact, and there is a new protonated aldehyde that is produced, and this is carbon number 1.

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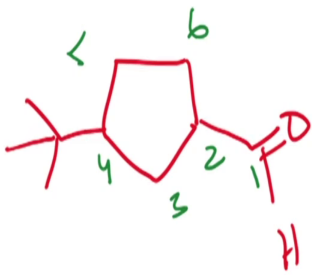

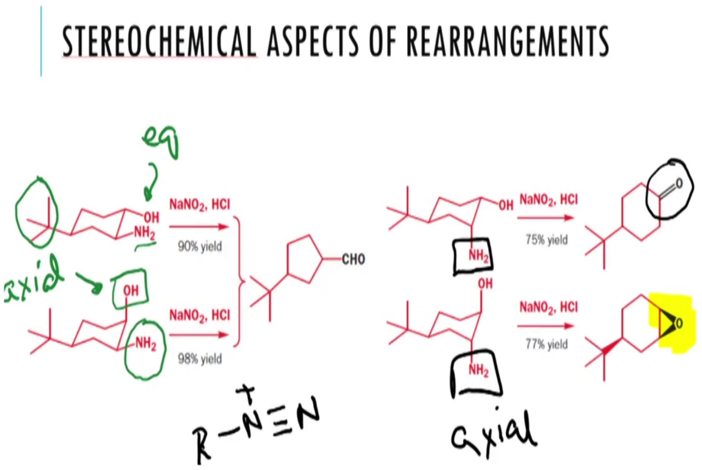
STEREOCHEMICAL ASPECTS OF REARRANGEMENTS

So, once this loses a proton, then you get the final compound, which is the aldehyde, which we are producing as shown here. So, this is 1, 2, 3, 4, 5, 6. So, there is no loss of carbon, here is just that the alcohol is now getting converted to an aldehyde. And the amine is getting converted to a diazonium salt, which then leaves as nitrogen gas. So now, this helps us understand the first reaction that we were interested in.

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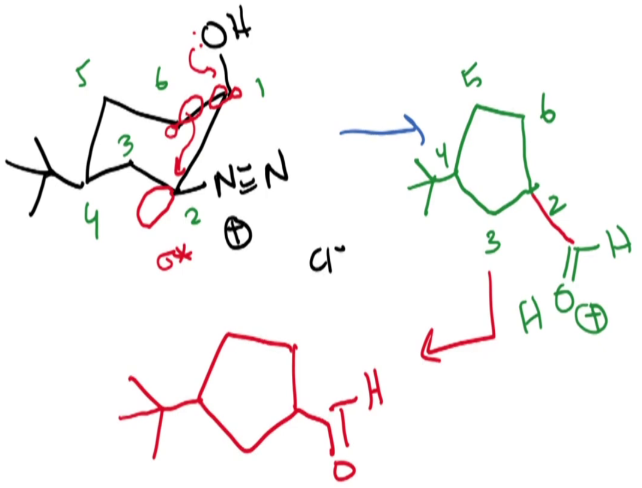

Now let us look at the second example, which is, the amine continues to be in the equatorial position. And so that is going to give you N≡N$^+$, and usually there is a chloride as a counter ion. So, again, this is the important concept here, which is the σ^* orbital. And, again here, this is aligned in such a way that this is going to come here, and the lone pair is going to assist. And, again, let us keep the numbering the same.

So, this is 1, 2, 3, 4, 5, and 6, so there is a bond form between carbon-2 and carbon-6. And rest of the molecule remains the same, carbon-4 has a tertiary butyl group. The old bond between carbon-2 and carbon-1 remains intact. And this gives you the protonated aldehyde, just like the previous case, and now this can lose a proton and gives you the final compound as shown here as the product.

So, the concept here that we need to understand is that the σ^* of the carbon-nitrogen bond plays a crucial role in determining the outcome of the reaction. So, these two we can propose a mechanism. But now the question is, does it hold for the other two examples.

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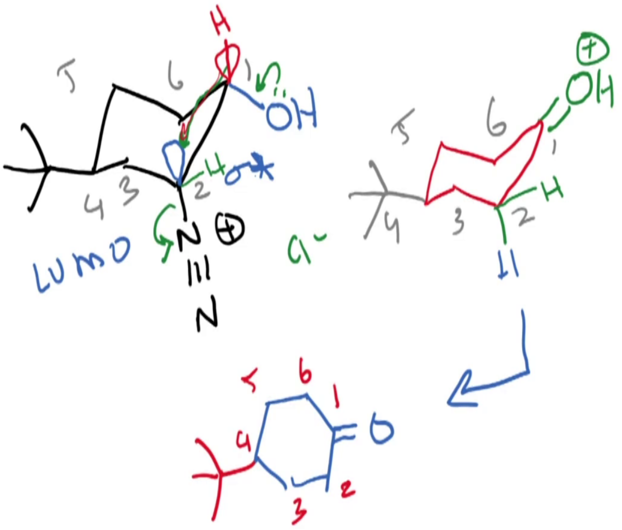

So, now let us look at the third example, which is the formation of ketone. And so, this is where we need to draw out the structure again. And let us look at the compound once again. So, here, NH_2 is in the axial position. And the first example that we are looking at is the OH is in the equatorial position. So, here is the OH. So now again, the important point here is that the σ^* for this bond is here.

This is the LUMO σ^*, which is the important orbital here. And what we can propose here is that the carbon-hydrogen bond as shown here is the most important bond because again this has a HOMO of this carbon-hydrogen bond is now in up situation where it can interact with this σ^* orbital. And that is going to result in the migration of this carbon-hydrogen bond from here to here.

So, once that migrates, what we are going to see is that this N≡N is going to be lost. And this of course, chloride as the counter ion, and the product that we will get has the following structure. So, again, let us keep the same numbering, this is 1, 2, 3, 4, 5, and 6, so the 6-membered ring remains intact.

And now you have a new bond between this carbon and this hydrogen. And like we have proposed previously, one of the driving forces for this reaction is the formation of this ketone. So, you have a C double bond O, that is formed in carbon-1, it is a protonated ketone. And now this hydrogen that is moved here, there is already another hydrogen here, this hydrogen moves here, there is going to be an inversion and stereochemistry and you have the original hydrogen as shown here.

So, therefore, this is consistent with the mechanism that we are proposing in that the σ^* of the carbon-nitrogen bond plays a very important role in the outcome of the reaction. So, this is going to give you, just drawing it out in a planar form. So, this is going to give you cyclohexanone. And the relationship between the ketone and the tertiary butyl group is 1, 4. So, let us see whether that also holds good. So, here, this is 1, 2, 3, 4, so this is 1, 2, 3, 4, 5, 6, so it is correct. So, this mechanism is again consistent with the product that is formed.

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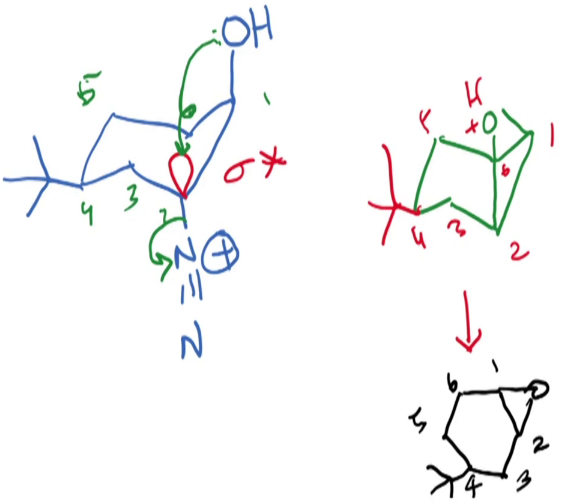

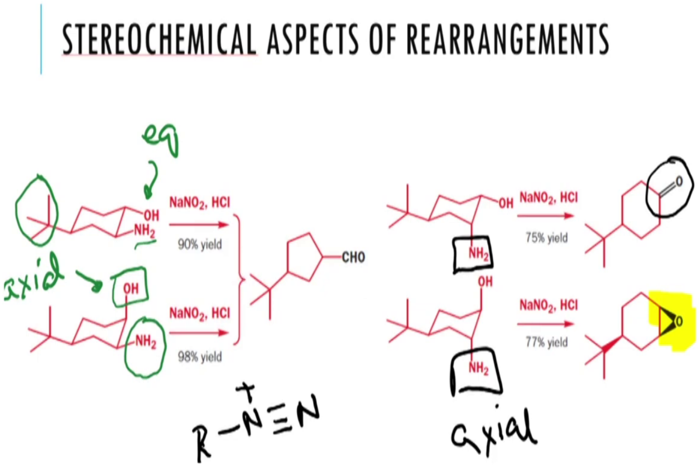
STEREOCHEMICAL ASPECTS OF REARRANGEMENTS

Now to the last example, here, you by now you know how these reactions are going to happen. So, here the last example, your N≡N is going to be the same, the difference is that now your OH is in the axial position. And so again, the important player here is the σ* orbital. So, let us number these carbons again, 1, 2, 3, 4, 5, and 6.

So, there is in this case, what happens is that the lone pair on the oxygen is going to play a role, like in the previous cases, but the difference is that the lone pair is going to directly attack on the σ* orbital here and resulting in the loss of nitrogen, and the product that we would get is the epoxide, and the rest of the molecule remains the same.

So, this is 1, there is a protonated epoxide 2, 3, 4, 5. And that last carbon is number 6. So, this is nothing, this is going to lose a proton. And the final structure that we would get is the 6-membered ring with an epoxide between carbon 1 and carbon 2, 3, and 4, 4 has the tertiary butyl group on it, 5 and 6. So, if I go back to this, this is the compound that I get so 1, 2, 3, 4.

And so, this is the product that is formed in 77 percent yield. So, therefore, the stereochemistry of these reactions is quite important. And you need to pay attention to the migrating group and the orbitals that are in play during migration. So, just to recap here, let us go back to this reaction and try to explain this.

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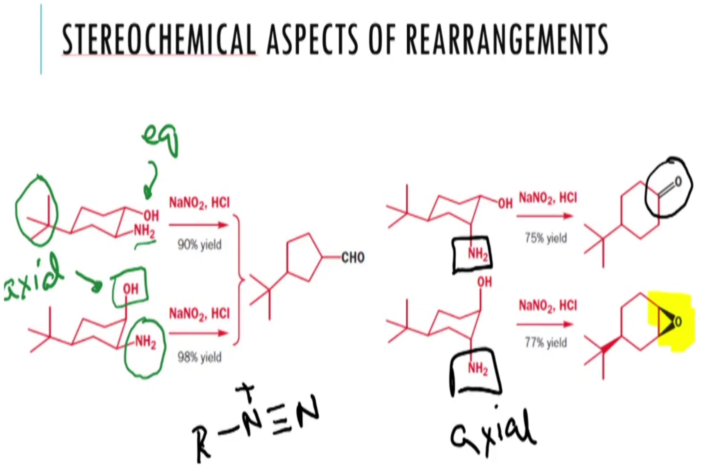

STEREOCHEMICAL ASPECTS OF REARRANGEMENTS

So, here, in this case, the diazonium salt is going to be formed here. And the bond that really moves here that is close to the σ*, and is aligned properly to attack the σ* is this bond.

Similarly, here, again, it is the same situation, the alignment of the orbitals is going to be in favour of this bond migrating.

Whereas here in this case, there are two possibilities, the σ^* is over here. And the carbon-hydrogen bond prefers to migrate, of course with assistance from the lone pair here. And lastly, there is no scope for migration of a carbon-oxygen bond. But instead, the lone pair attacks and you form an epoxide.