Introductory Organic Chemistry

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Lecture - 16
Chirality and Stereochemistry
Part - 3

Now, that we had viewed the properties of enantiomers and diastereomers, it is quite clear that it will be difficult to separate enantiomers using standard separation techniques. As you know, separation techniques work on difference in physical properties. For example, filtration works on the difference in the physical state so, you are able to separate a solid from a liquid because they are in two separate physical state, one is a solid; one is a liquid whereas, distillation works on the difference in boiling point. So, you are able to separate two liquids because one of them boils at a different temperature than the other, right.

But since enantiomers are the same physical properties, it is extremely difficult to separate them using these regular techniques. So, now, what I want you to think for a minute is how would you separate the enantiomers? You can imagine that it is going to be highly tedious task. So, now, let us look at different techniques that are used to resolve two enantiomers from each other as we call it or to separate the two enantiomers from a mixture.

Resolution of enantiomers is a pretty critical step especially in drug industry, right. So, when you make a medicine, if it has a chiral molecule in it, right, if it is a chiral molecule, you will have to separate it because as we saw earlier in this class that you have to give enantiomerically pure compounds as medicines because the other enantiomer could have adverse effects.

So, one general scheme for separating enantiomers is to convert them into corresponding diastereomers, okay. This is a very successful strategy because as we saw diastereomers have completely different properties or more often kind of different in their physical as well as chemical properties. So, you are able to separate them using your regular techniques and then later on convert this diastereomers back to the compounds that we started with right.

So, now we are going to look at one such example wherein we try to separate a mixture of enantiomers by first converting them into diastereomers and then converting them back into the compounds that we started from, okay. One of the reactions that you may want to learn for understanding this example is a very standard reaction between an acid and base.

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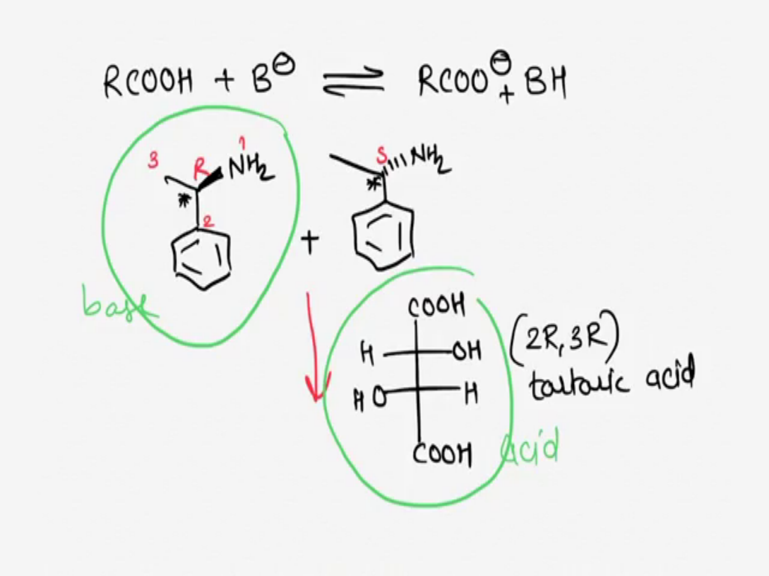

So, I am going to write down a standard acid base reaction here. I am going to take a carboxylic acid and I am going to react it with a base B minus, it is a generic base. Whenever a base reacts with a carboxylic acid, you have corresponding salt prepared which is basically RCOO minus and you have BH formed right, okay.

So, what we are going to do now, is we are going to try and separate these two compounds. Okay. So now, I have a mixture of R and S 1-Phenylethylamine, okay. So, let me draw the R form first. Okay, so, this is R and then this will be S. Let us confirm, we have our chiral center right here, right, that's the chiral carbon. Now, nitrogen will get the 1st priority, this carbon gets the 2nd, this gets the 3rd; the hydrogen is already going away from you; so, you have it rotating like R and it is indeed R and this one will be S, okay.

So, now my task is to separate the R and S even though right now they exist as one liquid. So, you can imagine you have a liquid bottle and that has this 1-Phenyl ethylamine in it, okay. The way I convert it to the corresponding diastereomer is by reacting it with a chiral acid, okay. So, I am going to take Tartaric acid and the Tartaric acid as you know is also chiral so, this is (2R, 3R)-Tartaric acid. Let me draw the structure here and I am drawing this structure using Fischer projections. So, you can kind of revise your Fischer formulas here, so you have tartaric acid, this is (2 R, 3 R)- Tartaric acid.

Now, NH_2 is a basic functional group meaning that it will act as a base more often because that nitrogen has lone pair of electrons and it wants to grab a proton. So, this is basically my base and this is gonna be the acid, right. So, the same acid-base reaction that we wrote on top, very similar reaction is going to happen now and let me draw the products as these two groups react with each other.

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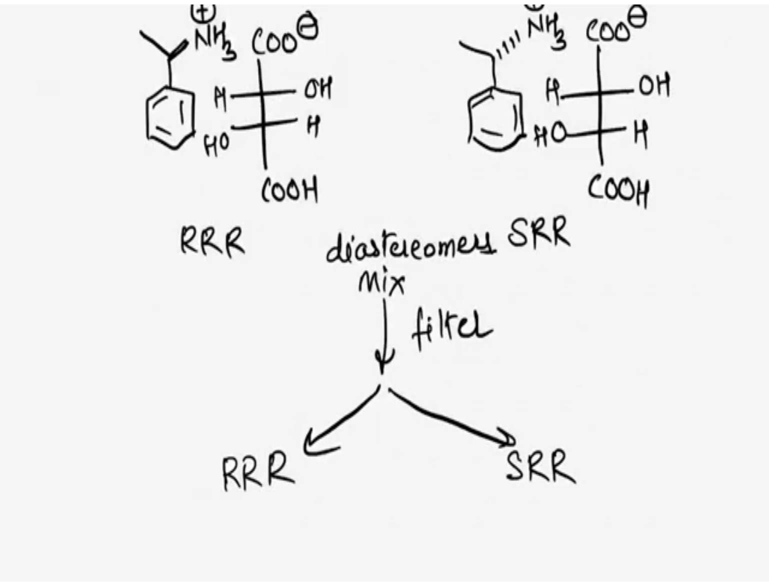

So, I am going to draw the products here. So, I form this particular salt right or I will form the other salts. So, as the R enantiomer reacts, it forms this salt. As the S enantiomer reacts, it forms this other salt.

Now, in order to recognize them separately I am just going to name them based on the chiral centers they have. So, this one will be RRR and this one will be SRR, okay. As you can see, these two molecules are now diastereomers of each other, right because they are not mirror images because only one of the chiral center is changed, right, out of the three, only one is changed. So, they are not mirror images; they are non-super imposable; so, they become diastereomers, okay.

Now, it is easier for me to separate so, as I mix these two into a conical flask and I keep these things together, what happens is because they have different solubilities because their properties are now different, one of them will start forming crystals whereas, the other one will stay in the solution, okay. So, as the crystals form that one of the compounds will start getting into the solid form whereas, the other one still stays as a liquid compound.

So, I am able to use filtration to separate the RRR from SRR, right. So, then we filter and we convert this mixture into a separate form of RRR and SRR molecules, okay. Now, as I said we have separated the two enantiomers, but they are not yet in the original form. So, my job was to separate 1- Phenylethylamine right, but right now this is a completely different salt of Phenylethylamine and Tartaric acid. So, now what I do is now I will convert this RRR form back into the R-1-Phenylethylamine, right.

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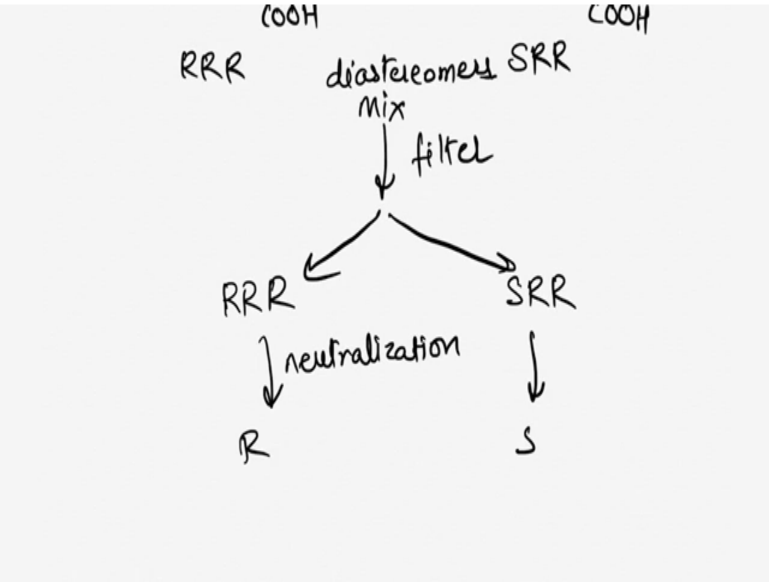

So, what I am going to do is, I will then acidify it or do some kind of neutralization procedures right and we will separate them out to corresponding R and S forms, okay. So, this is something, I am not gonna go over the reactions, but you can imagine that once you have two separate flasks, you can do reactions on those to get back the R and S forms.

There are some other ways of resolving enantiomers and they include either using a chiral column or secondly, they can be using enzymes to separate the corresponding mixture of enantiomers. So, in the case of enzymes, one of the enantiomers selectively reacts with the enzyme whereas, the other enantiomer remains unreacted and it can be separated.

Whereas, in the case of chiral column, the column or the solid phase on which you are going to put the compounds itself is really chiral. So, one of the compounds will selectively interact with the column whereas, the other one passes through the column without interacting with the chiral media and you are able to separate the two compounds.

So, let us now try to combine something that we learnt in the last class with the understanding of stereochemistry. So, in the last class we looked at various cycloalkane derivatives; cyclopropane, cyclobutane, cyclohexanes and so on and now let us try to now see if we can predict if the derivatives of these compounds are chiral or not, okay. So, I am going to start with the cyclopentane derivatives, okay. So, herein I have a compound cis-2-methylcyclopentanol, okay.

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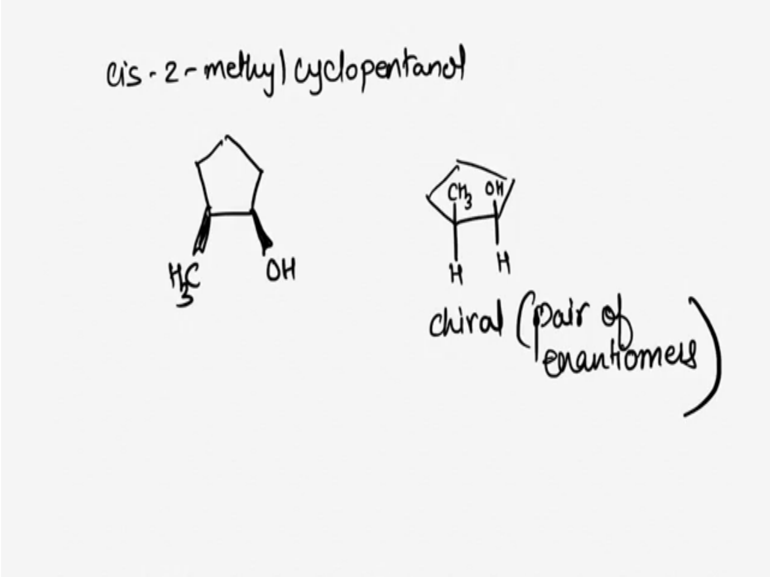

So, cis meaning both the groups have to come in the same direction right. So, I am going to draw the molecule, it’s 2-methyl and cyclo pentanol, ‘nol’ means it has an OH group and 2-methyl meaning, it has a methyl group.

Now, if you look at this molecule, it does not have a plane of symmetry and ideally when you are looking at cycloalkane derivatives, it is a good practice to also try to see it in the 3D manner. So, until cyclopentane it really does not matter, but cyclohexane definitely you want to draw a chair and see how that particular molecule looks in a 3D space.

So, for cyclopentane, I am going to draw a different projection, okay and you can see that it’s like these CH_3 and this OH are both going up top and both the hydrogens are going down. As you can see this molecule does not have a plane of symmetry, right. So, this will be a chiral compound, okay; it has chiral centers, it does not have a plane of symmetry. In fact, it will exist as a pair of enantiomers, right. So, cis-2-methylcyclopentanol really means that I have both the enantiomers with me; if I have to specify which one then I may have to specify whether it is R or S.

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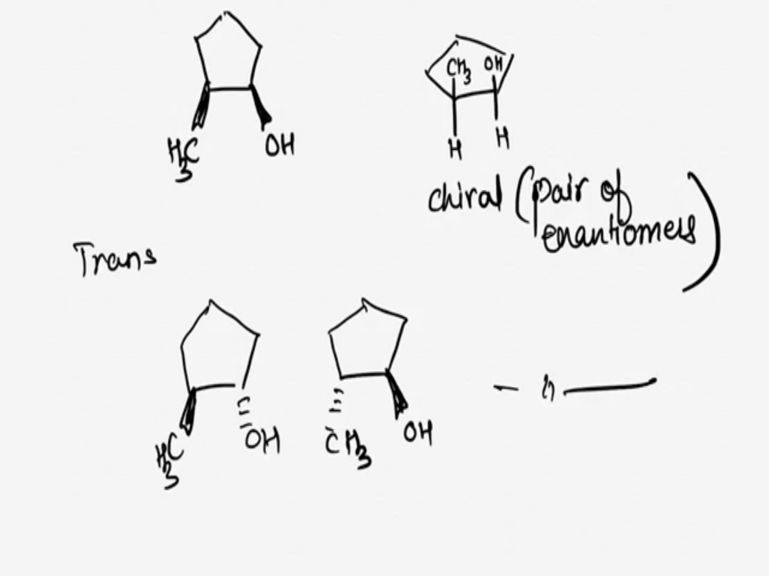

Let us go to the next one. Now, if I take the trans compound; now in the case of trans-2-methylcyclopentanol, trans meaning they are going in opposite directions. So, either the methyl is coming towards you and the OH is going away from you or it could be such that the OH is coming towards you and the methyl is going away from you, right? Both of these are possible representations of the trans compound.

Again there is no plane of symmetry. So, you are not going to have it as a meso compound, right? Remember meso compounds, when you have a plane of symmetry, the compound cannot exist as a chiral compound because the molecule can really fold in on itself, right. So, in the case of trans compounds, in this case particular, you cannot have a plane of symmetry. So, this will also be a chiral compound right and it will exist as a pair of enantiomers. Now, let us go to the next one; now, I want to talk about cis-1, 2-cyclopentanediol, okay. So, let's write that down.

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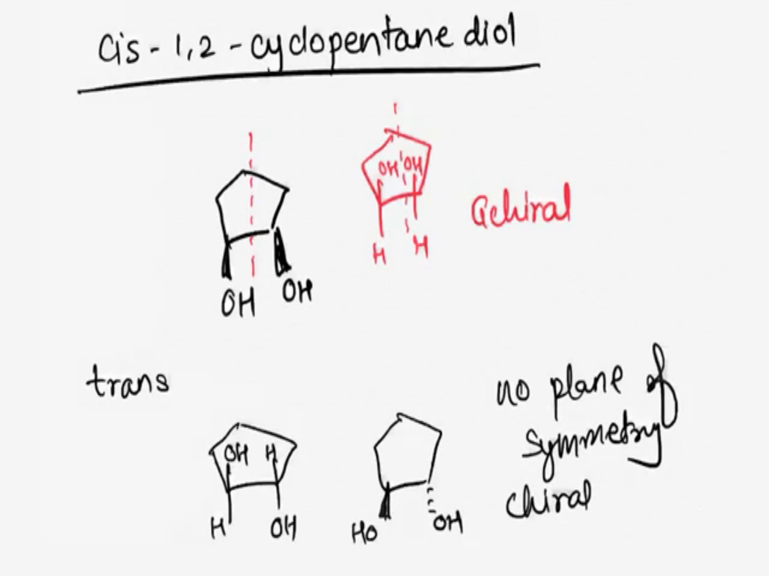

Okay. Now, in the case of cis-1, 2-cyclopentanediol, imagine this, so now, let me draw the molecule, it's cis, so both of the OH's are either coming towards you or going away from you.

Now, you can clearly see that plane of symmetry so, if I draw this line because both the groups are OH's, there is a clear plane of symmetry and this molecule becomes achiral right. So, you can even try drawing the other representation, you can see that line of symmetry going through the molecule right.

If I make this trans so, instead of cis if we now talk about trans-1, 2-cyclopentanediol, one of the OH's is coming towards you whereas, the other OH is going down right, something like this. As you can see in this particular molecule because the OH's are going in opposite directions there is no plane of symmetry and in fact, this particular molecule will exists as a pair of enantiomers, okay. So, there is no plane of symmetry so, this will be chiral and it will exists as a pair of enantiomers.

Now, let us go further now I want to talk about cyclohexane derivatives. Now, as I said when you are dealing with cyclohexane derivatives, it is very very important that we convert the 2D structure into a chair so that it helps us visualize how the molecule exists in a 3D state, right.

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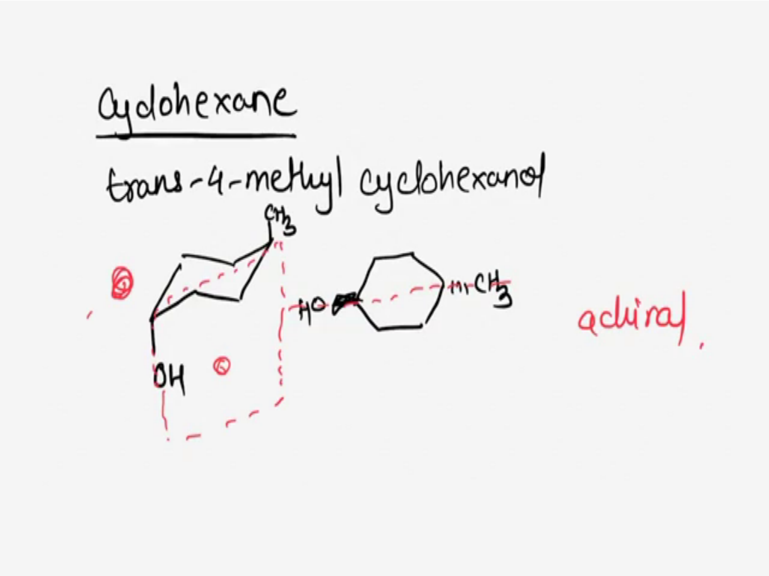

So, first let's take the first cyclohexane derivative, I want to start with the 1, 4 derivative of cyclohexanes, okay. So, for example, I can take trans-4-methylcyclohexanol, right, so let me draw, the, both the things so that you can see that this is an OH and since it is trans, you have one group coming towards you, one group going away from you, right.

As you can see in the case of trans molecule, you still have a plane of symmetry, right, because you can cut through that OH and CH_3. Even in this case, the plane of symmetry will kind of be like this; whereas, this portion here and this portion they two are kind of symmetrical with respect to each other and the molecule will be achiral, okay.

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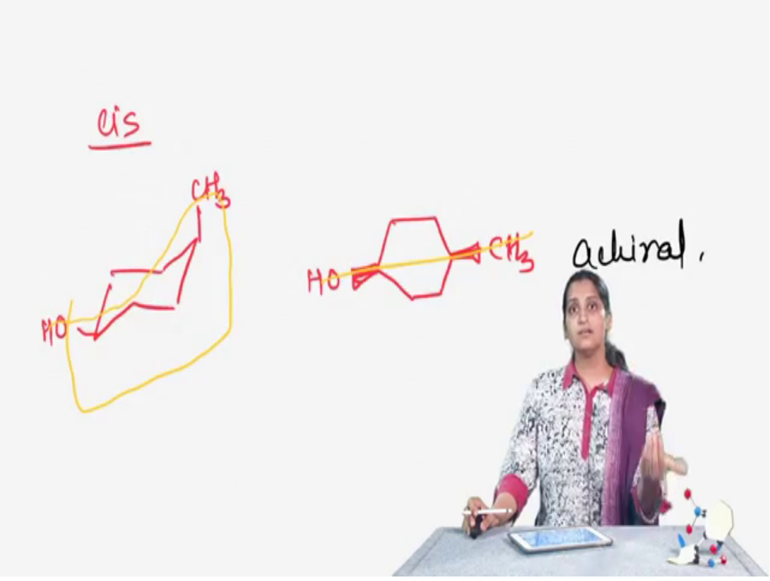

Now, let us do the same thing for cis. In the case of cis molecule, you are going to have both of these groups coming towards you. So, there is a CH_3, there is a OH; same thing here, CH_3 going up, OH going here up, right; cis meaning both of them are going up; so, not equatorial or axial. So, this is a good revision of what we learnt in the last topic right. So, cis meaning both of them are either going up or going down, right?

So, in this case, this is a cis molecule and as you can see that still exists a pair of a plane of symmetry such that you can divide the two molecule, the molecule into, half, two half such that they overlap with each other. So, then this molecule also becomes achiral, okay. Now, let us go further and now let's look at the 1, 3 derivatives right. So, now this is cis-3-methylcyclohexanol.

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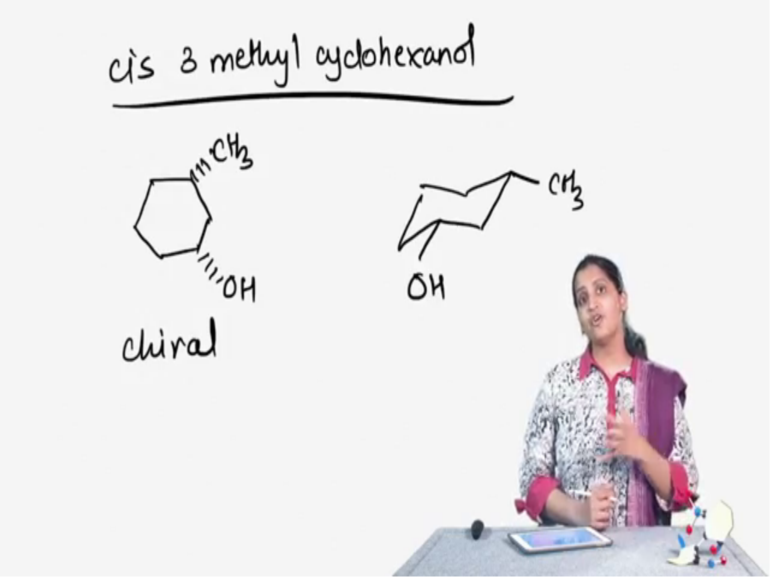

Right? So, in this case, cis meaning both of them are either going away from you or both of them are coming towards you, right. There is no plane of symmetry as you can see because one is a methyl, one is a OH right. So, there is no plane of symmetry this is gonna be a chiral molecule; it's gonna exist as a pair of enantiomers, okay and this is gonna be a chiral compound.

You can even draw the chair and look at it so; this is cis meaning both of them have to go in the same direction. So, I am going to draw it going down; this one also goes down, this is CH_3, this is OH. So, even in the chair form, you can see that there is no plane of symmetry, okay. Now, let us take a different molecule, now, I want to draw cis-3-hydroxycyclohexanol, right.

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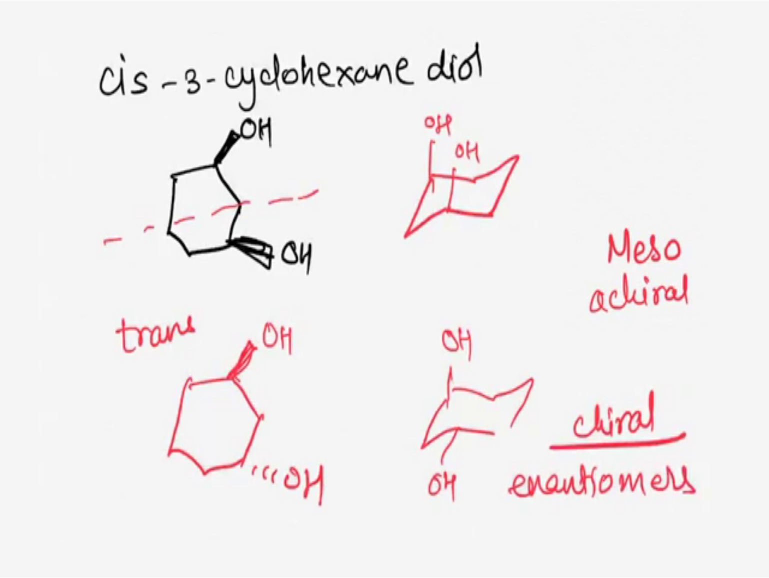

Or cis-3-cyclohexanediol meaning both the groups are now OH's, right. So, in this case, you can clearly see the plane of symmetry going through the molecule since both of them are OH's, there is a plane of symmetry and the molecule in fact, becomes a meso compound and we talked about meso compounds, these are the molecules that are achiral in nature, right. So, they are achiral even though they have a chiral center because there is a plane of symmetry, they will not rotate the plane of plane polarized light towards one direction or the other, okay. You can even draw the chair and have a look at the same thing.

So, in the case of chair what you are going to see is, let's say, right, something like this; you can even still see the plane of symmetry cutting through the molecule, okay. Now, instead if you take the trans molecule, let us look at trans. In the case of trans now, there is no plane of symmetry because they are going in opposite directions, okay. Right? The two OH's are going in opposite direction and trans-3-cyclohexanediol will actually exist as a pair of enantiomers so, this is still chiral, okay. So, now we are done with the 1, 3 derivatives now let us have a look at the 1, 2 derivatives ,okay.

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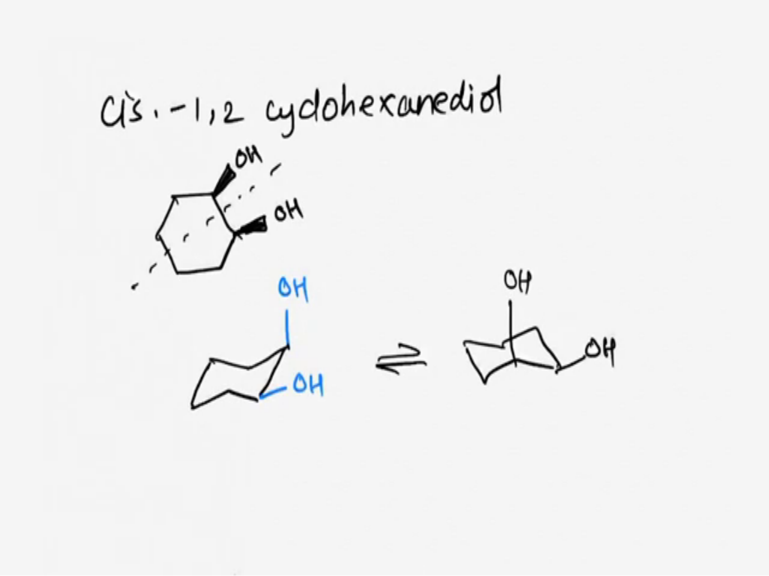

So, now what I am going to take is cis-1,2-cyclohexanediol, right. So, in this case, right, now you can imagine, right, there is kind of a plane of symmetry, but as I said always try to convert it into the chair and see if it really exists as a plane of symmetry in a 3D form. In the case of 1, 2 positions being going on the same side meaning it will be somewhat like this, right.

There is no plane of symmetry now in the 3D form; there is no plane of symmetry and I can even draw the chair flip of this to check, so, what will this be? Right. So, these two are actually the chair flips of each other, this seems chiral, but because the chair flips are constantly going through each other and in fact, you will be able to see that these two are enantiomers of each other.

So, the chair flip of the molecule is itself an enantiomer of the molecule. So, what happens is at room temperature it becomes very difficult to separate the two compounds. So, at room temperature what's going to happen is that they are going to exist as an achiral molecule. So, even though this molecule does itself have chirality because the chair flips and the flip in fact, is an enantiomer of the same compound, you cannot really have them existing as a pair of enantiomers, two separate enantiomers and they really become achiral in nature. Okay.

So, one of the crucial questions to ask is, can molecules be chiral without a chiral center in them. So, for this I want to go back to the conformational isomers of butane. Remember, when we looked at the Newman projections of butane and when we said that the carbon-carbon bond rotates.

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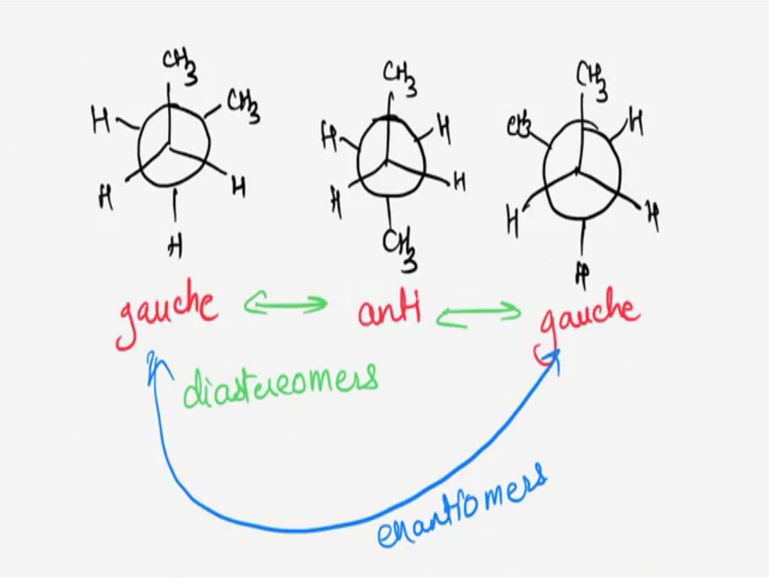

So, now I want to go through three different conformational isomers of the same compound, butane, I want to redraw them here, okay. So, I want you to focus on these particular conformations one of them is a gauche conformation then it goes through an anti-conformation and then it goes through the other gauche conformation.

If you focus on the gauche and anti-conformations, okay, what you will see is that these are two molecules which are not super imposable and non-mirror images of each other, right. So, they are really diastereomers of each other, right. So, these two are diastereomers of each other and these two are diastereomers of each other. But now if you focus on the two gauche conformations, you can see that they are mirror images of each other, but they are non-super imposable.

So, these two in fact, are enantiomers of each other, right. So, there is no chiral center in butane still because of the conformational isomers of butane are different in the 3D arrangement, it can lead to the rise of chirality in the molecule. But if you really think this through you will realize that butane cannot be chiral right because at room temperature what is going to happen is that the molecule is constantly spinning right and it is going from one gauche to the anti to the other gauche, it's constantly rotating; the carbon-carbon bond is constantly rotating such that it is impossible to isolate one of the gauche conformations from the other gauche conformations.

So, overall the molecule becomes achiral because it is going through all of these transformations and some of the intermediate transformations like the anti is an achiral molecule because it has a plane of symmetry right. So, even though the conformational isomers, are, can be written such that they are chiral overall butane becomes achiral because of the rotation being so fast and there is no barrier to rotation at room temperature. The other type of diastereomers, which we really have not focused on are the diastereomers in the case of cis and trans double bonds, okay.

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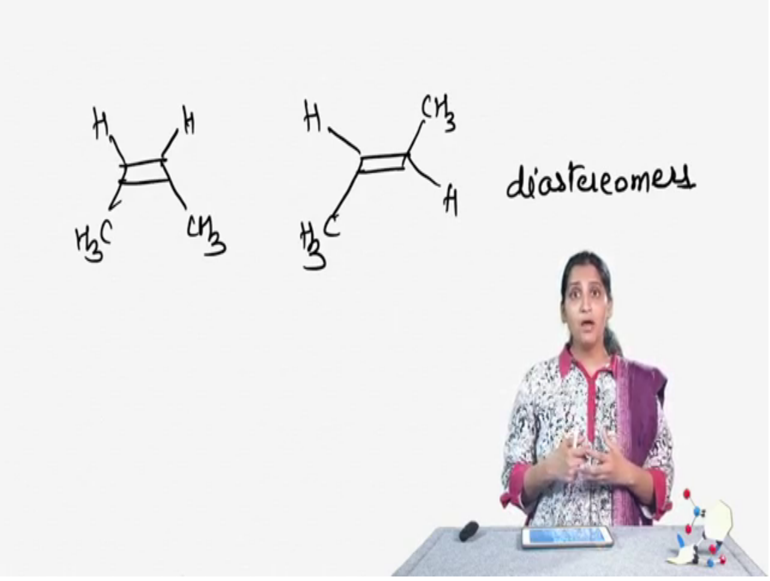

So, now I am going to draw a cis molecule, a cis double bond and this one is a trans double bond, okay. So, the cis and a trans molecules here, you can imagine are non-super imposable and they are non-mirror images of each other. So, these two actually exists as diastereomers and it is in fact, possible to isolate them completely, separately and you are going to have these two compounds separate.

So, in the case of double bonds because there is a barrier to rotation, right, if I rotate the carbon-carbon double bond, the bond will break, right. So, rotation along the carbon-carbon double bond is not possible. So, the diastereomers can exist as a cis and a trans double bond.

We are gonna see one more example, where unlike butane the barrier of rotation is so large that the enantiomers cannot interconvert at room temperature through a planar form and the molecule in fact, remains chiral.

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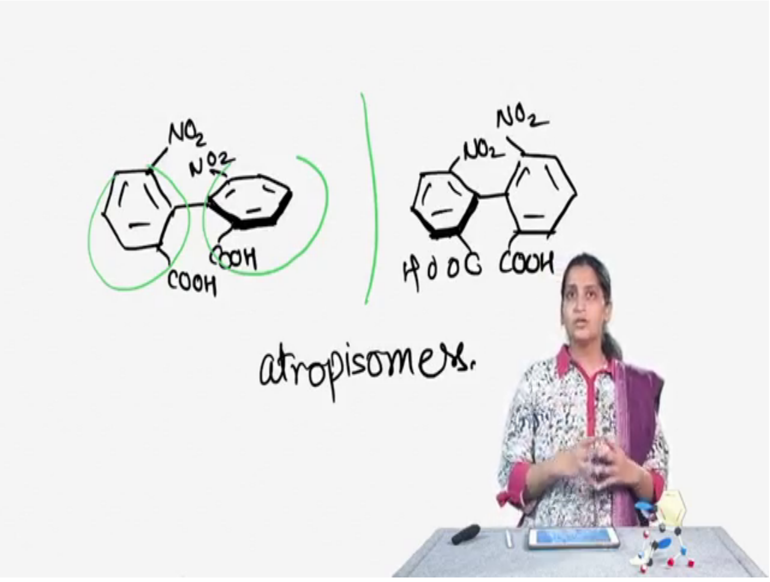

So, I am going to draw the compound here. Okay. So, now, let us look at this particular compound and in fact, I have also made a model of this particular compound. You can see these two benzene rings and they are not in the same plane. So, one of the benzene ring is kind of flat like this, the other benzene ring is like this, right.

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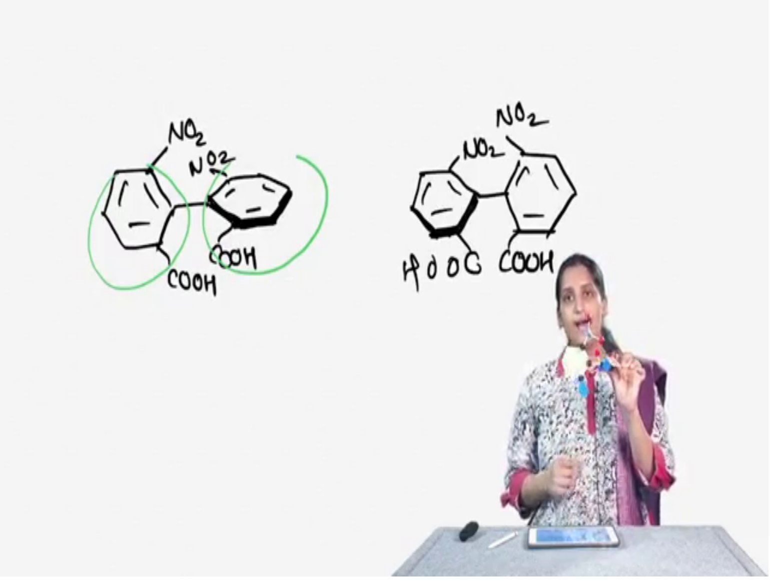

So, the two benzene rings here are not in the same plane; you can see this 3D model here; it is somewhat like this where one benzene ring is in this plane the other benzene ring is in the other plane. Now, what happens is because these two nitro groups and the two COOH groups are extremely bulky what happens is as I start rotating as you can see if this bond between the two benzene ring wants to rotate, it has to go through a state wherein the two nitro groups are clashing with each other. And as a result of this what happens is that the molecule does not show rotation at room temperature. Because of this the molecule can be termed as chiral because it now has a directionality, right. And it is chiral because now I can really create an enantiomer of the same molecules.

So, I have drawn the enantiomer also and the enantiomer of the same molecule can exist as two separate compounds at room temperature and they cannot interchange. However the moment I increase the temperature, what's gonna happen is that the barrier to this rotation is gonna go down and slowly as we go on increasing temperature, you may see that the chirality is lost because now there is no chiral center present, but this can only happen at a very high temperature.

So, at room temperature this molecule will be existing as a chiral molecule and such compounds where the barrier of rotation matters, where, in order to determine the chirality of the molecule are termed as Atropisomers, okay. You can also think of a rise of chirality in a tertiary structure. So, for example, each of the DNA bases does not have a chiral center, but as it arranges to form the DNA, the DNA itself has a helical chirality meaning it can rotate either clockwise or anticlockwise, right.

So, you have two different types of helices that can exist. So, even though the individual bases are not chiral when we combine them in a particular manner, the structure, the structure that is formed overall can have a handedness to it and in fact, we see these type of compounds a lot in biology. So, proteins for example, you can have a compound that does not have a chiral center in it in the molecular state right, but as it folds to form a particular protein, the protein can have a very directional property or can have the handedness, okay.

So, so far we have looked at the structural properties of molecules be it in the case of bonding or the kind of conformations that they do or the nature of chirality etcetera. So, all of this plays a crucial role in how molecules react. So, the next class, when we begin to look at reactions of organic acids and bases all of these things are going to be very important to us.

So, we are going to use this tool box that we have created in understanding the reactions of organic compounds, but before we go ahead I want to summarize all of this entire tool box because I feel it is very very important for us to really put everything in its place before we go and look at the reactions. So, what we are going to do is we gonna create a concept map of the different isomers that we have seen or the different type of molecules that we have seen so far, okay.

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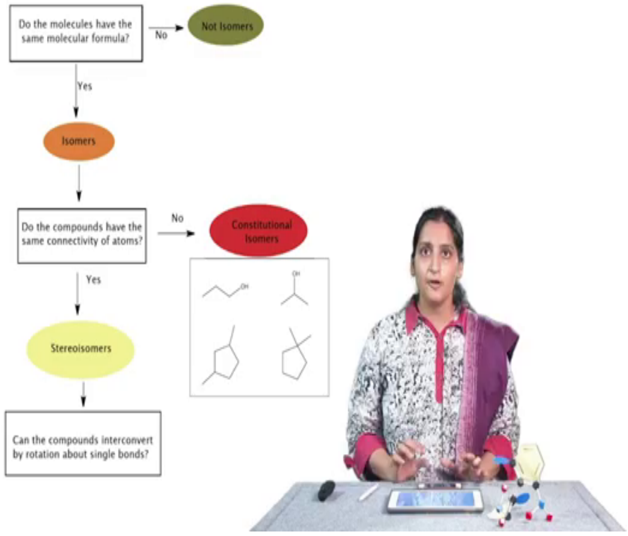

Do the molecules have the same molecular formula?

No → Not Isomers

Yes → Isomers

Do the compounds have the same connectivity of atoms?

No → Constitutional Isomers

Yes → Stereoisomers

Can the compounds interconvert by rotation about single bonds?

So, given two molecules how do I understand what kind of isomers they are or whether they are even isomers or not. Okay, so, the first thing we ask is, do the compounds have the same molecular formula? If the answer to this question is No, then they are two, simple, simply different molecules. So, there is no connection between them, they are two different molecules, okay. But if the answer to this question is yes; that means, they have the same molecular formula then they are some kind of isomers of each other, okay.

Now, our job is to look at what kinds of isomers. So, the next thing you do is you look at the connectivity; do they have the same connectivity of atoms as the molecule is structured? If the answer to this question is No, then what we have is a pair of constitutional isomers. So, for example, as I have it here, these are propanol constitutional isomers. So, one of them is 1-propanol, one of them is 2-propanol and they are constitutional isomers of each other.

However if the connectivity is also the same then we have to go further because now if the molecular formula is same and the connectivity is same then they are stereoisomers of each other, okay. So, now, we will go further and look at if the molecules are actually stereoisomers of each other and what kinds of stereoisomers. So, the question then you ask is, can the molecules rotate and interconvert between each other? So, can they interconvert and convert from one molecule to another through a rotation of a single bond?

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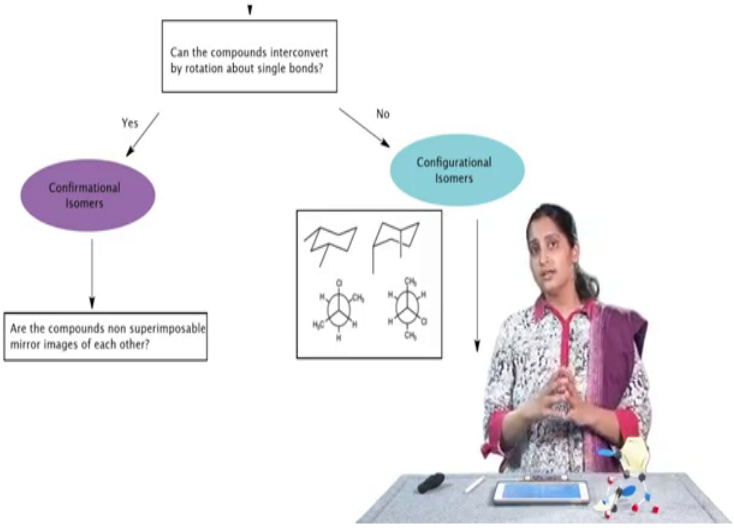

Can the compounds interconvert by rotation about single bonds?

Confirmational Isomers

Configurational Isomers

Are the compounds non superimposable mirror images of each other?

If the answer to this question is Yes, then they are conformational isomers, okay. So, the way in the case of butane for example, the way we looked, they were able to rotate and convert from gauche to anti to gauche and they were really the conformational isomers of each other.

But if they cannot rotate along a carbon-carbon single bond and cannot interconvert between each other, then, if it’s a No then we get to configurational isomers. So, they are either pair of enantiomers, they are a pair of diastereomers and you cannot inter convert them based on the rotation of the carbon-carbon single bond.

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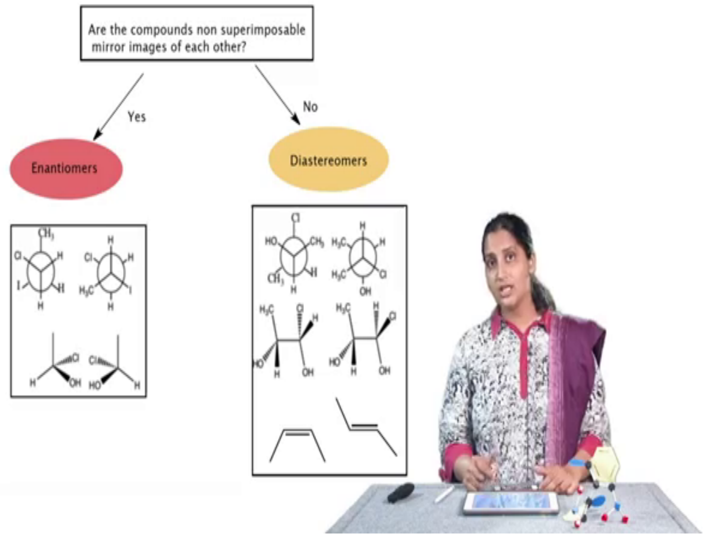
Are the compounds non superimposable mirror images of each other?

Yes

No

Enantiomers

Diastereomers

So, further in configurational isomers, you do have either enantiomers or diastereomers. In the case of enantiomers, these are non-super imposable mirror images. So, they are mirror images, but they cannot lie on top of each other such that they coincide with each other. Whereas, in the case of diastereomers what you have, is, are two compounds which are non-super imposable, non-mirror images of each other.

So, for example, the way I have shown here the double bonded compounds are diastereomers of each other, they cannot interconvert between each other very easily at room temperature and also they are non-mirror images.

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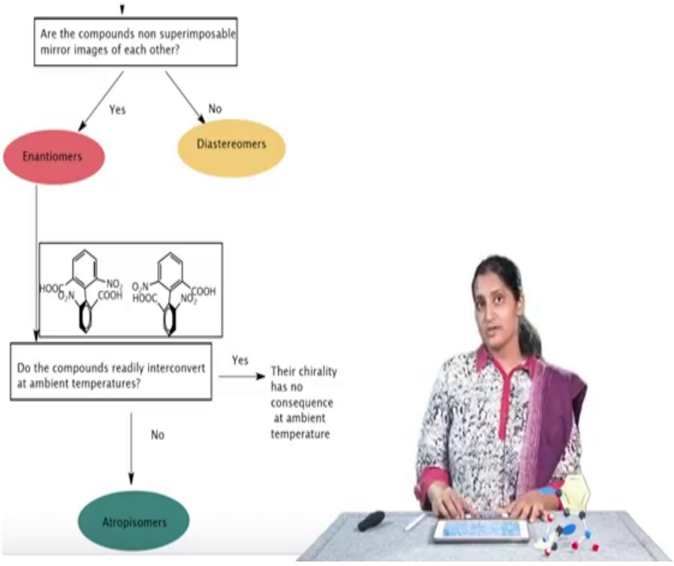
Are the compounds non superimposable mirror images of each other?

Yes

No

Enantiomers

Diastereomers

Do the compounds readily interconvert at ambient temperatures?

Yes

Their chirality has no consequence at ambient temperature

No

Atropisomers

So, the next question to ask in the case of conformational isomers as well as you saw in the case of butane for example, we saw that there was a pair of enantiomers, as well as a pair of diastereomers when the conformational analysis. So, the same question we will ask for the conformational stereoisomers as well and the question is, are the compounds non super imposable mirror images of each other? If Yes, then they are enantiomers, if the answer is No, then they are diastereomers.

So, further in the case of enantiomers, we can ask one more question is that, do the compounds interconvert between each other readily at room temperature? If the answer is No, then you have a pair of Atropisomers; if the answer is Yes, they can interconvert, then it is more like the two gauche conformations of butane wherein they can easily interconvert and their chirality really plays no effect because you are not able to separate the compounds at room temperature very effectively. Okay.

So, now that we have put all of these compounds and all of these information that we have learnt in the first three chapters together on one paper, now, in the next class we will begin with the chemistry of acids and bases mainly organic acids and bases, but before even we go to organic acids and bases, it might be very good for you to look at the general properties of acids and bases, and, such that the inorganic acids HCl, H_2SO_4 or the inorganic bases NaOH, KOH just have a look at your acids and bases chapters that you have seen before we go ahead and look at the organic compounds. So, in next class we will actually start with the reactions.

Thank you.