Application of Spectroscopic Methods in Molecular Structure Determination

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Lecture - 11
Stereochemistry Determination Using NMR Spectroscopy

Hello, welcome to module 11 of the course on Application of Spectroscopic Methods in Molecular Structure Determination. We will continue with the NMR spectroscopy and look at the use of NMR spectroscopy in stereochemistry determination in organic compounds. Stereochemistry is a very important topic in organic chemistry, and determining the relative stereochemistry or absolute stereochemistry of organic molecules is a very important task in day-to-day research.

Now, in this particular module, we will see how stereochemistry of certain molecules can be determined using the delta values and J values, which can be derived from the NMR spectrum.

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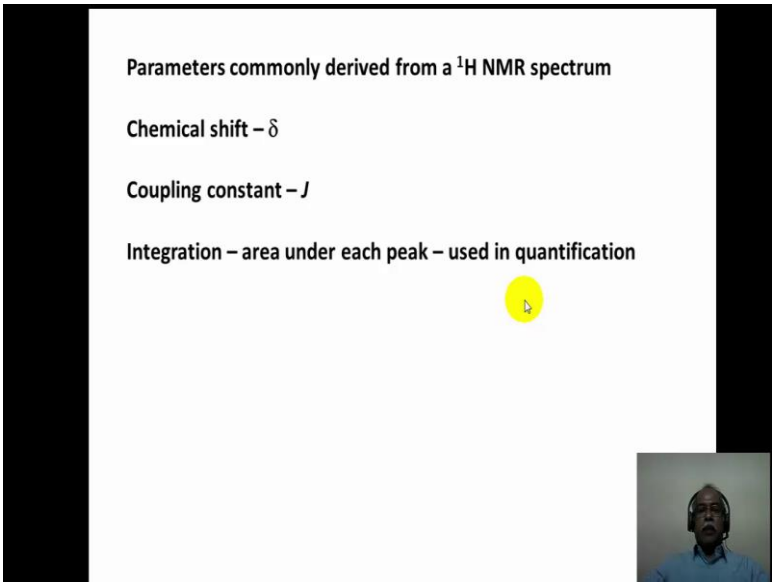

The parameters that are commonly derived from the NMR spectrum are the chemical

shift value - the delta value, and the coupling constant value, which is the J value. Both of these parameters can be extremely useful in deciding the stereochemistry of an organic compound. Of course, the third parameter which is derived from an NMR spectrum is the integration; in other words, the area under each of the peak. This is essentially used for quantification purposes. In pure compounds, of course, it tells you the relative intensity, tells you the number of protons under each of the chemically different hydrogens. Of course, in a mixture of compounds, it tells you the mole ratios of the compound present it the mixture.

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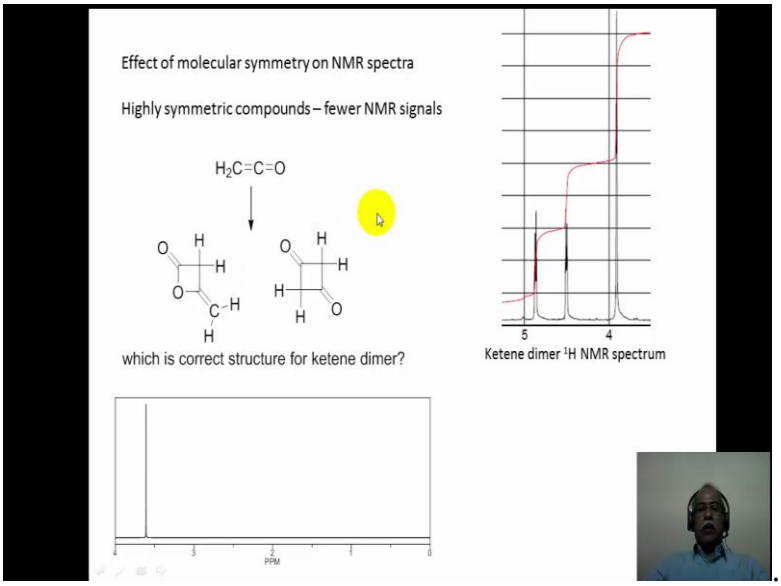

Now, let us look at a very simple example of ketene dimerization. This essentially illustrates how complex an NMR spectrum becomes, when the molecule becomes unsymmetrical, or when the molecule is highly symmetrical, how fewer number of lines are seen in the NMR spectrum. Ketene can undergo dimerization; one can conceptually think of the dimerization in two different ways. In one case, 2 molecules undergo dimerization, essentially at the carbon-carbon double bond in a head to tail fashion, to give this diketone as the product. The other way, 1 molecule C double bond O and another molecule C double bond C can undergo the 2 plus 2 cyclo addition reaction, to give a beta electron structure like this one. Of course, if you look at the 2 structures, this is clearly a

more unsymmetrical structure, compared to this particular structure. The actual experimental spectrum of ketene dimer is shown on the right-hand side, here, and you can see here, it is a fairly complex spectrum, consisting of chemical shift value 1, chemical shift value 2 and chemical shift value 3. Now, if you look at these 2 structures, this structure should have 1 chemical shift value corresponding to this hydrogen, which is cis to the oxygen; another chemical shift value corresponding to this hydrogen, which is trans to the oxygen; and finally, 1 chemical shift value for both the methylene hydrogens in this particular molecule. So, 3 chemical shift value would be anticipated for this structure.

And indeed, this spectrum gives you the 3-different chemical shift value, roughly in the integration ratio, 1:1:2 ratio, is the integration ratio. Therefore, one can confirm that, the ketene dimer actually has this kind of a structure. If you look at the other structure, which is a highly symmetrical structure, there is a plane of symmetry passing through this molecule, and there is another plane of symmetry passing through the molecules. It is also c2 axis of symmetry; that makes all the 4 hydrogens chemically equivalent. So, it is expected to give only a singlet. Indeed, it does show only a singlet around 3.6 ppm, or so, in the NMR spectrum.

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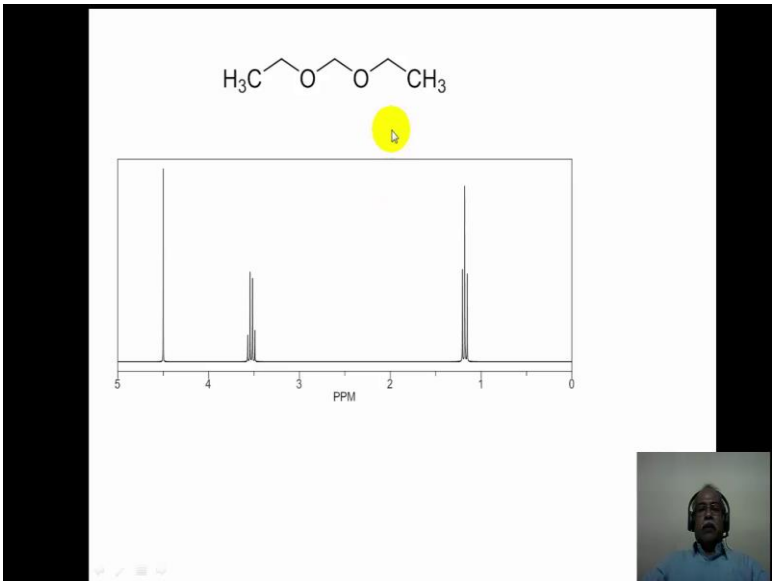

Let us see another example. This is a, diethyl diether is what is shown here. The ethyl groups are essentially appearing as a simple quartet and a triplet in the NMR spectrum; and, this methylene group appears as a singlet around 4.5 p p m in the NMR spectrum. Let us see what happens to the spectrum, when we introduce a methyl group at this position, how complex the NMR spectrum becomes.

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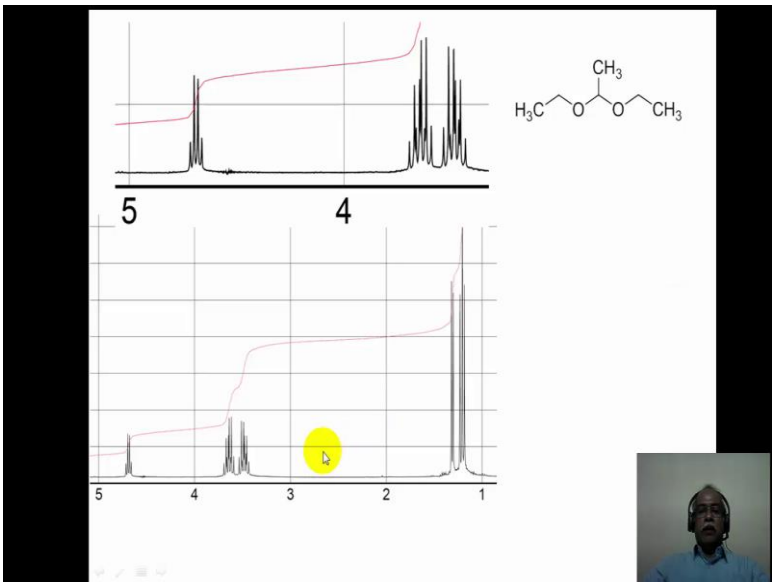

This is the NMR spectrum of the diethyl acetal of acetaldehyde. This molecule is nothing, but the diethyl acetal of acetaldehyde. And, just by the introduction of this methyl group here, this, this methylene groups become diastereotopic. As, a result of that, they split each other into a AB quartet, which is further split by the methyl group into a quartet.

So, what one sees, is a quartet of, an AB quartet is what is seen here, and this is a signal that is corresponding to the methylene region, methylene hydrogens of this particular molecule, around 3.6 p p m or so; and, this region is expanded to show the complexity of the spectrum that is arising out of the introduction of the methyl group at this position. Now, this quartet, which is a simple first order quartet, is essentially for this hydrogen, the methine hydrogen, which is flanked by the 2 oxygens, and that is further split by the methyl group into a quartet. So, this is an illustration of an unsymmetrical molecule,

giving a fairly complex NMR spectrum, which is enriched with a lot of information about the structure of the molecule.

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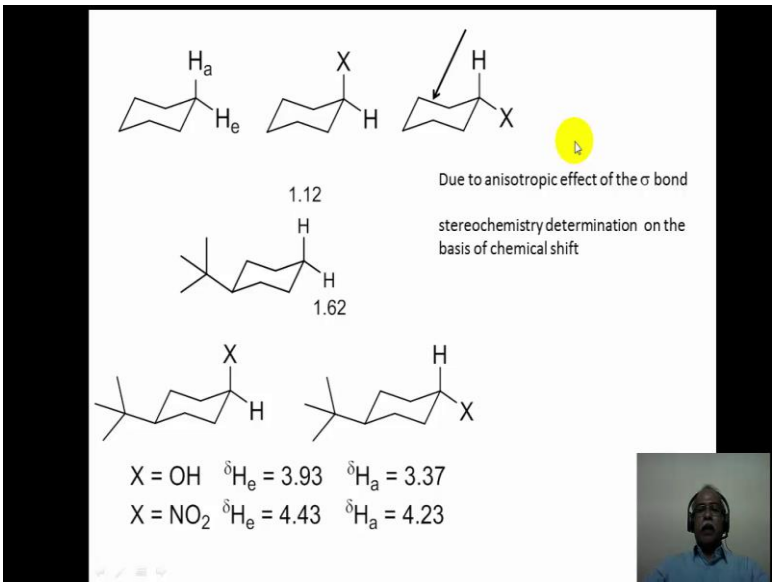

Now, we will take a look at the use of chemical shift value in the determination of stereochemistry with a few examples. Now, due to anisotropic effect of the sigma bond, the axial hydrogen and the equatorial hydrogens appear in different chemical shift value. This is something we have already seen, and we have also explained the phenomena of the anisotropic effect of this particular hydrogen, sorry, this particular carbon-carbon bond on the equatorial hydrogen, and the axial hydrogen.

The equatorial hydrogen is always at a higher delta value, compared to the axial hydrogen, because of the anisotropy of this particular carbon-carbon bond. This is easily reflected in the spectrum of tertiary butyl cyclohexane, for example. Tertiary butyl cyclohexane does not undergo the chair to chair inter-conversion. Therefore, the hydrogen, which is axial and the hydrogen, which is equatorial, are fixed in their position, and the NMR can very clearly tell the difference between these 2 hydrogen.

Now, the equatorial hydrogen appears at 1.62 p p m, whereas, the axial hydrogen appears as 1.12 p p m. Of course, there is no stereochemistry associated with the tertiary

butyl cyclohexane. On the other hand, if you look at 4 tertiary butyl cyclohexanol, or the nitro substituted 4 tertiary butyl cyclohexane, these are the 2 types of molecules one can consider. The OH group, or the nitro group, can be either in the axial positions; this would be the cis isomer of the 4 tertiary butyl cyclohexanol; the X group, namely the hydroxide functional group, or the NO 2 group, can be equatorial in position, and this would be corresponding to the trans isomer of the 4 tertiary butyl cyclohexanol, or the nitro cyclohexane derivative, 4 tertiary butyl nitro cyclohexane derivative.

Now, this would mean that, this equatorial group, which is equatorial hydrogen, which is attached to a carbon directly bearing the electronegative center, namely the oxygen, or the nitro group in this molecule, you should experience higher delta value, compared to all the other hydrogens in the molecule. So, it should be easy to pick out this particular hydrogen in the spectrum, compared to all the other spectrum of the same molecule, for example.

When we do so, we identify this hydrogen to be an equatorial hydrogen, having a chemical shift value of 3.93, whereas, in the axial isomer, namely, the axial hydrogen isomer corresponds to a chemical shift value of 3.37. So, if whenever one encounters this kind of molecules, the one that is showing a higher delta value for this particular hydrogen, would correspond to the axial X, or the equatorial hydrogen isomer. The other isomer, namely, the one with the lower delta value, will have the hydrogen in the axial position, or the substituent in the equatorial position.

This is illustrated by these 2 examples very clearly, showing that, the cis configuration, namely, the tertiary butyl and x being cis, has a higher delta value, whereas, the tertiary butyl and the X being trans with respect to each other, has a lower delta value in the NMR spectrum, which is very useful for the identification of the cis tran sides of the… These are, essentially, diastereoisomers, cis isomer and the trans isomer. They can be easily distinguished, purely based on the chemical shift value of the hydrogens, which are distinguished as equatorial, or axial in nature.

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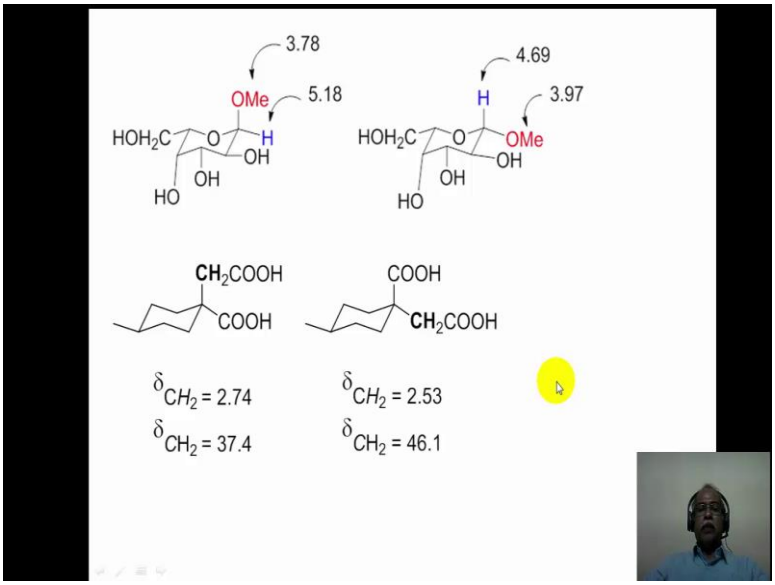

Now, sugar chemistry is rich in stereochemistry and it is important to determine the stereochemistry, absolute stereochemistry, as well as the relative stereochemistry of sugar molecules. Let us take the methyl glycoside of glucose, for example; this is not glucose, I am sorry; this is galactose; this is a methyl glycoside of galactose, is what is shown here, in this particular spectrum. And, if you look at this particular hydrogen, this is the anomeric hydrogen. When the methoxy is in the axial position, the anomeric hydrogen is the equatorial position.

Similarly, when the methoxy is in the equatorial position, the anomeric hydrogen will be in the axial position, in the chair form of the cyclo, chair form of this six membered ring, which is the sugar ring that is shown here; sorry, pyranose ring is what is shown here. Now, we can very clearly see that, the hydrogen, when it is in the equatorial position, it is coming at a higher delta value of 5.18, compared to hydrogen, which is in the axial position, which is coming around 4.69. If you look at the molecule, the blue hydrogen is the one that is going to come at the highest chemical shift value, and hence, we are able to distinguish between the equatorial isomer, and the axial isomer very clearly, from the chemical shift value of the hydrogen.

Not only from the chemical shift value of the hydrogen, the methoxy group also plays a

role in determining stereochemistry. Axial methoxy group, for example, comes at a lower delta value, compared to the equatorial methoxy group, around 3.97; once again, due to the anisotropic effect of this carbon-oxygen bond, which is beta gamma from the position, from where the measurements are being made. This is another example, again, showing that, in the carbon spectrum, the axial CH 2 and the equatorial CH 2 can be distinguished. The axial CH 2 carbon comes at a lower delta value compared to the equatorial CH 2 carbon, which comes as a higher delta value, for example, in the carbon 13 spectrum of the compound, which is this dicarboxylic acid, cyclohexane dicarboxylic acid.

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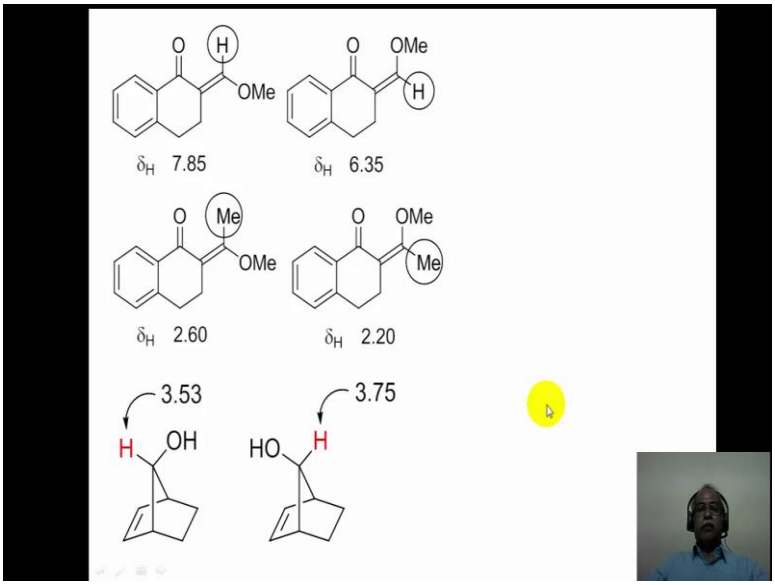

Now, anistropic effect of carbonyl groups can play a very important role in determining the stereochemistry of this kind of exocyclic double bonded compound. This is nothing, but an enol ether of the alpha formyl tetralone, which is the molecule here. This hydrogen, actually feels the anisotropic effect of this particular carbon-oxygen double bond, and comes in the deshielding zone of the anisotropic effect of the carbon-oxygen double bond. So, when it is cis with respect to the oxygen of this particular carbonyl functional group, it comes at a higher delta value of 7.85 p p m; whereas, when it is trans to the carbonyl functional group, it comes around 6.35 p p m. In other words, this does not have the same facility of feeling the anisotropic effect of the carbonyl functional

group, when it is trans, compared to when it is cis compound. The same effect is seen, instead of a hydrogen, if you have a methyl substituted derivative. This is a, 2 acetyl tetralone enol ether is what is shown in this particular spectrum, the, not spectrum, sorry; the particular structure corresponds to the enol ether of the two acetyl tetralone as a molecule. In this particular case also, this methyl, which is cis to the carbonyl functional group, comes at a higher delta value, compared to the methyl, which is trans to the carbonyl functional group, which comes at a lower delta value.

Now, when the hydrogen is placed exactly on top of a carbon-carbon double bond, or an aromatic ring, it gets highly shielded, because of the anisotropic effect of the double bond, which is the shielding zone, above and below the double bond, and deshielding zone, on the periphery of the double bond. So, if you look at this bicyclic alcohol, 2 isomers that are shown here. This would be an exo isomer, with respect to the double bond, and this would be an endo isomer, with respect to the double bond. The exo isomer has the hydrogen lying above the carbon-carbon double bond.

Therefore, this must be shielded in nature. So, that comes at a lower delta value of 3.53 p p m; whereas, the one which is in exo compound, which is the exo hydrogen, with respect to the double bond, that does not have the facility to feel the anisotropic effect of the carbon-carbon double bond, which is further away from the hydrogen. So, this comes at a higher delta value, in relation to this one. In all of these cases, it would be nice, if both the isomers are available, and the stereochemistry can be determined by measuring the spectrum of the 2 compounds, and looking at the chemical shift value of both the isomers. It may not be easy to, if you have only one isomer to decide on the stereochemistry of that particular isomer, purely based on the chemical shift value that we are discussing here.

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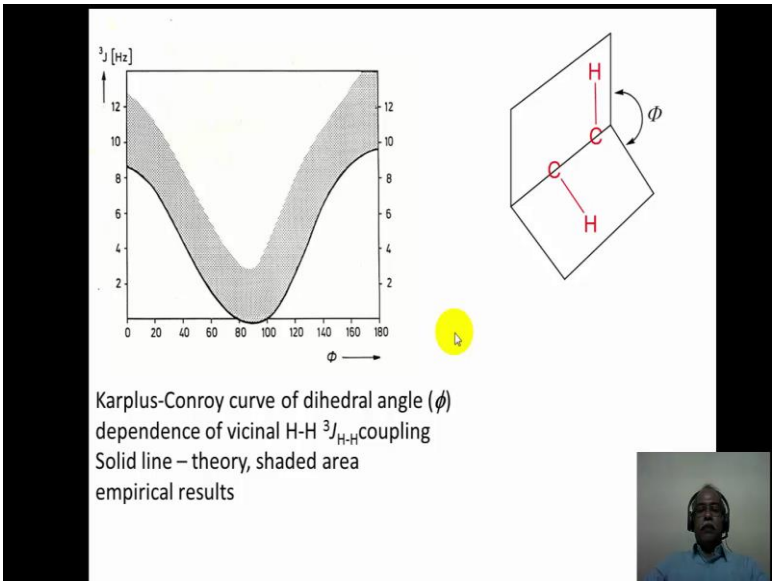

Now, let us move on to using J value for the determination of stereochemistry. It is very clear that, stereochemical aspects arise, because of the orientation of the molecule in certain ways, and, this orientation is, essentially, decided by the dihedral angle, when you have vicinal hydrogens of this kind. So, one can use a vicinal coupling constants as a tool, for determining stereochemistry of certain molecules, and let us see some examples of this. This curve, you are already familiar with. This is called the Karplus - Conroy curve for the dihedral angle dependence of the vicinal coupling constant, which is a 3 bond coupling; and, the vicinal coupling, 3 bond coupling is, what is pictorially shown here. And, this corresponds to the dihedral angle that we are referring to, in the figure, where dihedral angle is plotted against the J value.

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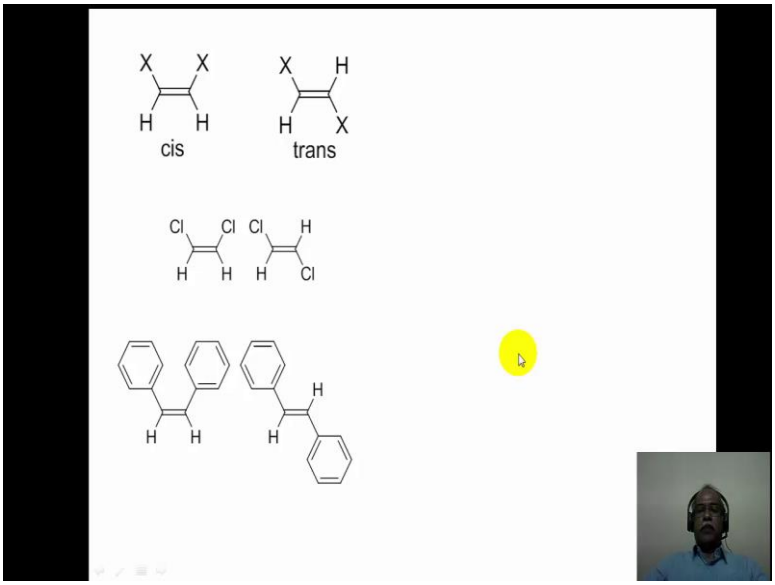

Now, if you take a highly symmetrical molecule like this dichloro ethylene, cis and trans isomer, the dichloroethylene cis and trans isomer, or the cis-stilbene, trans-stilbene kind of molecule, these 2 hydrogens do not couple with each other; as a result of that, we are not able to use the J value to determine the stereochemistry of this class of molecules.

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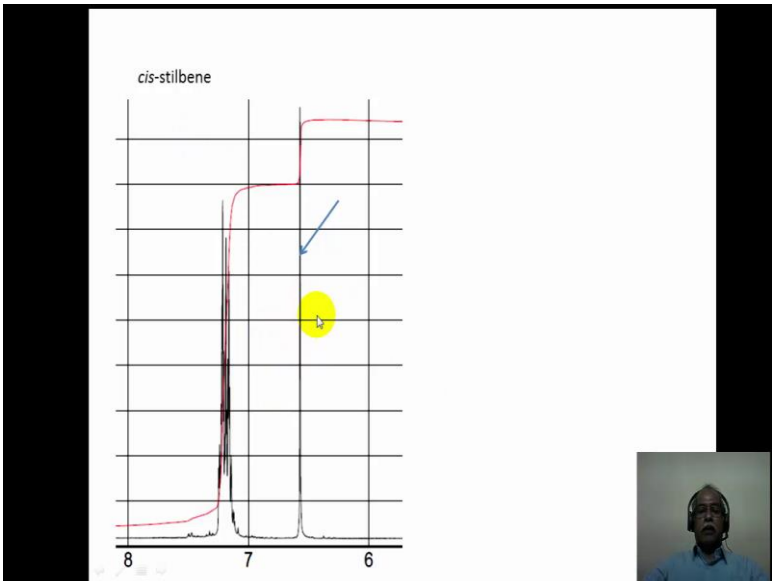

Let us have a look at the NMR spectrum of the cis-stilbene. cis-stilbene, the olefinic hydrogen comes as a sharp singlet, and does not have any kind of a signature of coupling with other hydrogen.

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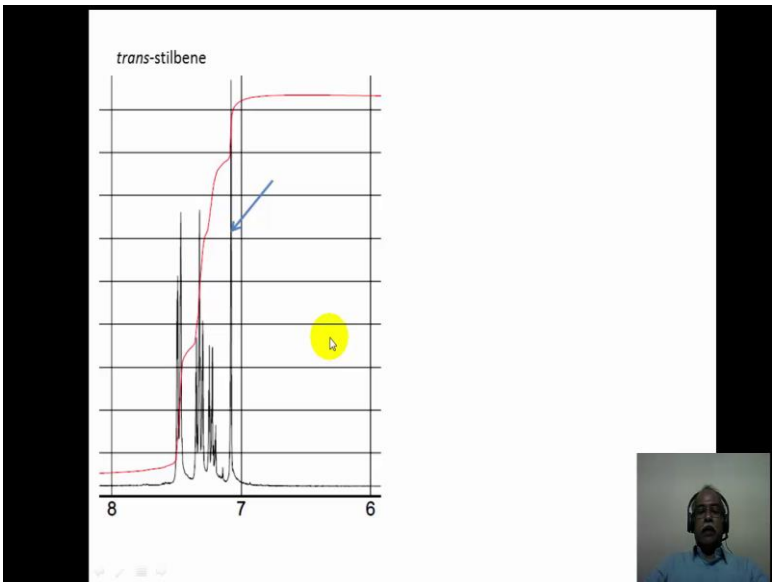

Similarly, in the trans isomer also, the trans-stilbene, the olefinic hydrogen come as a singlet in the trans stilbene also. Nevertheless, the cis-stilbene and trans-stilbene can be distinguished, based on the chemical shift value. The cis-stilbene has a lower chemical shift value, around 6.6 p p m, whereas, the trans-stilbene has a higher chemical shift value for the olefinic hydrogen, which comes around 7.1 p p m or so. It may not be easy to do this with the dichloro derivative, which is dichloro ethylene, for example, because, dichloroethylene does not have this kind of an anisotropic effect to distinguish those 2 hydrogens, from the cis and the trans isomer.

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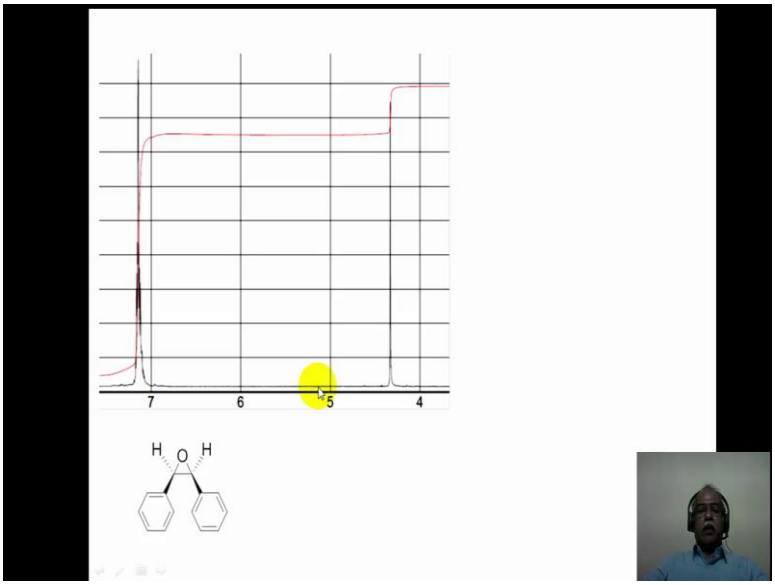

Now, if you look at the cis-stilbene oxide, as well as the trans-stilbene oxide, again, essentially, one cannot determine based on the J value, because, there is no coupling between these 2 hydrogen, because of the symmetrical nature of this molecule.

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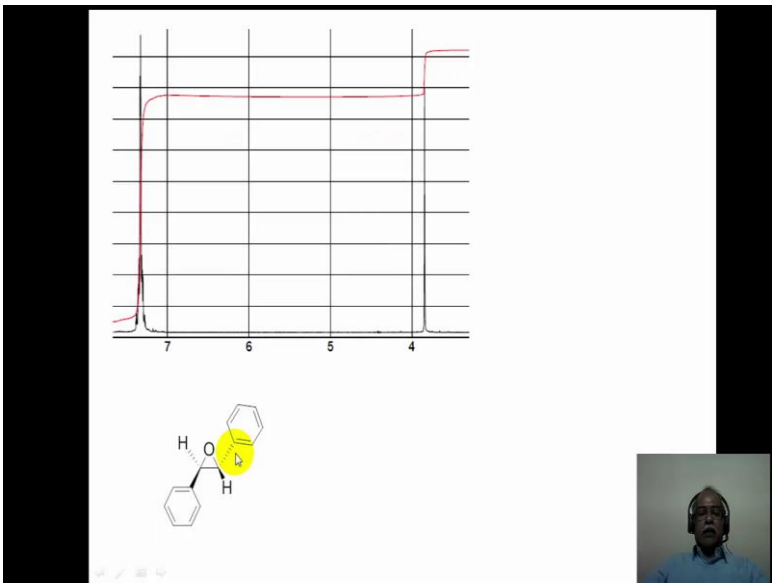

In the trans isomer, the 2 hydrogens come at 3.9 p p m, or so, whereas, in the cis isomer

here, it comes around 4.2 p p m or so, in the NMR spectrum, for the 2 hydrogens, which are the epoxy, epoxide ring hydrogen in this molecule.

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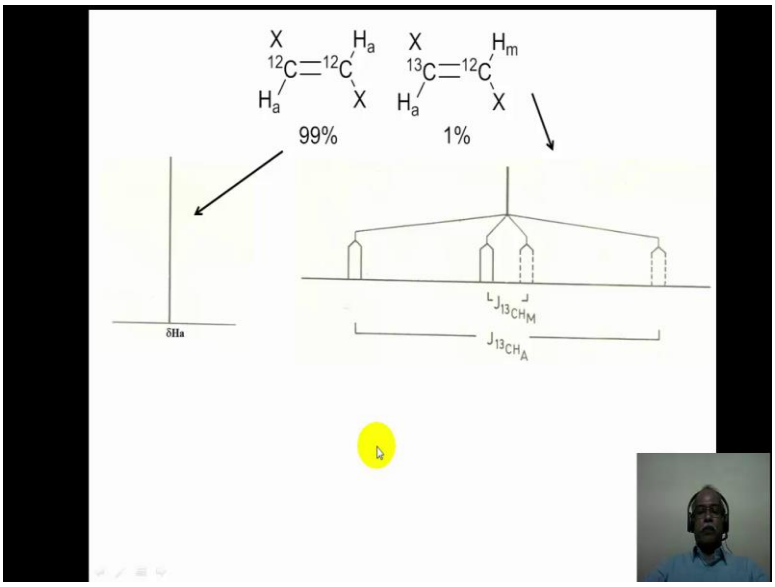

That is why, we use the carbon 13 satellite spectrum. This is something we have already discussed earlier, but let me refresh your memory that, the carbon 13 satellite spectrum is nothing, but a proton spectrum of the compound, where the carbon 13 is in it is natural abundance. So, since a natural abundance of carbon 13 is 1 percent, if you take a molecule like dichloroethane, this would be 99 percent of the molecule that we take, whereas, 1 percent of the molecule will be naturally labeled by a carbon 13 labeling in this position. The carbon 13 label makes this molecule unsymmetrical, in terms of the magnetic equivalence, as well as, chemical equivalence of these2 hydrogens, for example.

These 2 hydrogens are chemically equivalent still, but magnetically non–equivalent, because, we have introduced another magnetic nuclei, which is the carbon 13 nucleus, in this particular case. So, what happens to this molecule, the NMR spectrum of this molecule? Will, this hydrogen, if you take, it will be split by the carbon 13 by a large coupling constant of nearly 100 hertz, or more; it will be a large coupling. And, this coupling, this hydrogen will be further split by the trans, the trans hydrogen, because,

these 2 hydrogens are now magnetically non-equivalent.

What was originally magnetically equivalent, becomes magnetically non-equivalent. This should be a AA prime system, rather than a AM kind of a system. There is a mistake here, please correct it. And, essentially, a doublet that is split by the carbon 13, splitting of this H a hydrogen into a doublet, will be further split by H m into a doublet. So, this will be, a doublet of a doublet is what you, one sees. This is the centers, where the, this compound spectrum, essentially comes as a singlet at the center of this spectrum here, which is shown here, for example; whereas, this molecule spectrum, essentially, will be split into a doublet by carbon 13 coupling, and further doublet into this H-H coupling, which is this particular coupling.

Similarly, if you take this hydrogen, this will be split by the carbon 13 into a smaller coupling constant, because, it is a 2 bond coupling, now. And, it will be further split by the H a into a doublet. So, doublet of a doublet is what is seen for H m, which is this spectrum here. And H a, which is this part, and this part of the spectrum, corresponding to H a. So, if you measure the coupling constant between these 2 lines here, that would be, essentially, J AM. Similarly, if you measure the coupling constant between this 2 lines here, that will also be J AM.

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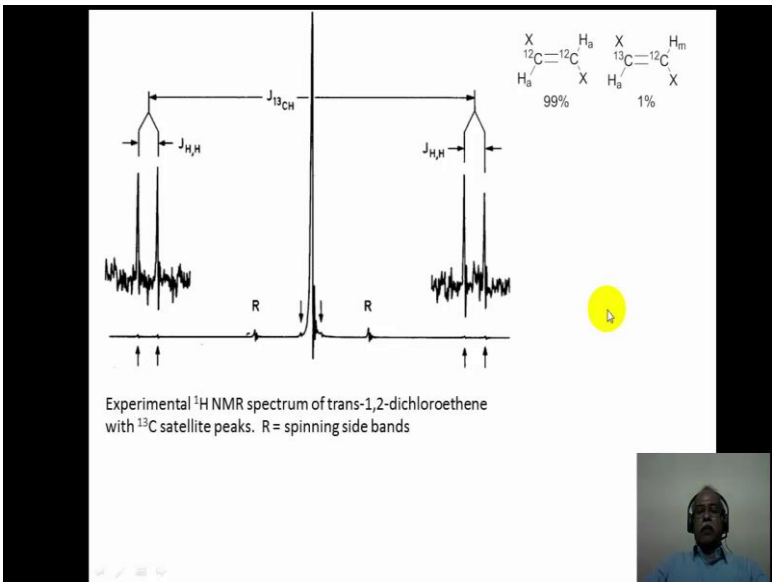

The experimental spectrum is shown here, nicely. Here, the carbon 13 lines are very very weak, because, it is only 1 percent of the sample that contains the carbon 13 labeling. So, one need to do a large number of scan, to minimize the signal to noise ratio, and look at, very carefully, on either end of the main spectrum. This is the main spectrum corresponding to this compound, which does not have any carbon 13. And, the satellite peaks are shown, and it is zoomed into a larger peak, in terms of the visibility of this doublet of a doublet, that we see here.

So, the carbon 13 J value is this gap, and the hydrogen-hydrogen J value is this gap. Once you have the hydrogen-hydrogen J value, one can easily tell, whether it is a cis isomer, or trans isomer, because, trans isomer should have, typically, between 15 to 18 hertz as a J value; whereas, the cis isomer will have a J value of roughly around 10 to 12 hertz, or so. So, here is another example, indirectly deriving the J value from the carbon 13 satellite spectrum, to decide on the stereochemistry of compounds, which cannot be determined, purely based on the delta value alone.

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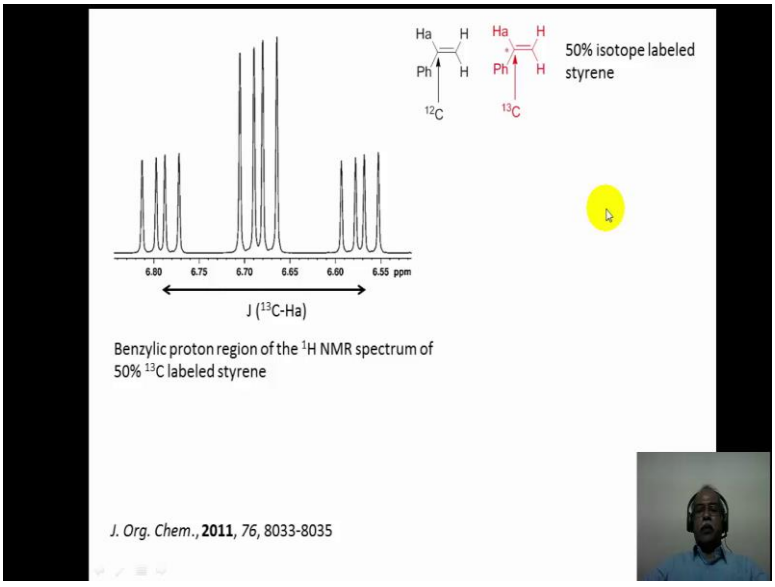

As long as we are speaking about carbon 13 spectrum, one can also label the compound with carbon 13. This is an example which appeared recently in the Journal of Organic Chemistry, for example. We are looking at, only the benzylic hydrogen of styrene; this is

not ordinary styrene; this is a styrene, which is labeled 50 percent by carbon 13 labeling, at this position here; that means, you have a 1 is to 1 mixture of carbon 12 and carbon 13 styrene, where the labeling is very specific to this particular carbon, which is the alpha carbon in this molecule.

Now, what happens to the hydrogen a is, what is shown here; the benzylic hydrogen, which is hydrogen a, that is a spectrum; this is a spectrum corresponding to the carbon 12 molecule, because, H a should be split into a doublet by the trans hydrogen, and further into a doublet by the cis hydrogen. So, what you see for H a is, the doublet of a doublet, which is the main spectrum, as far as this molecule is concerned. The satellite spectrum which is specifically labeled to an extent of 50 percent, that is the reason, you have very high intensity of the satellite peaks here, because this is a labeled compound.

So, 50 percent of the molecule has this carbon, which is carbon 13; that should couple with H a into a doublet. So, you see this large coupling, which corresponds to the carbon 13 H a. Further down, the H a should be split by this hydrogen, which is the cis hydrogen, and this hydrogen, which is a trans hydrogen. So, because of carbon 13, it will be a doublet; because of the trans coupling, it will be a doublet of a doublet; because of the cis coupling, it will be a doublet of a doublet of a doublet. So, essentially, what you see is, a 8 line pattern, which is a doublet of a doublet of a doublet, for this particular hydrogen, in this molecule. This is essentially, illustrate the point that, one can synthetically make samples with carbon 13 labeling, and look at the satellite spectrum in a much more prominent way, compared to the natural abundance carbon 13 spectrum.

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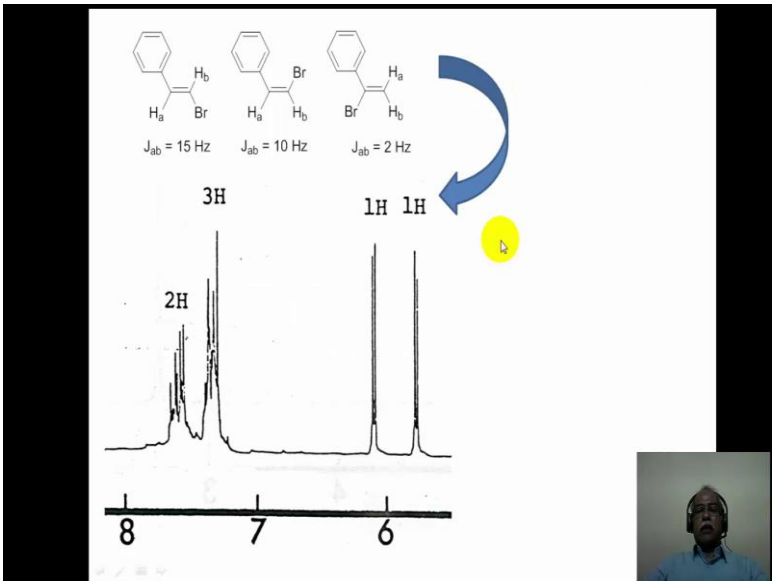

The bromo styrene can exist in 3 different forms. This is a trans isomer; this is the cis isomer, and this corresponds to the alpha isomer. These two are beta isomer, whereas, this is alpha isomer. This is the spectrum of the alpha isomer that is shown here. The olefinic hydrogens, which are H a and H b, comes very nicely as a AB quartet in this molecule. And, if you look at the coupling between these 2 lines here, or these 2 lines, it should be identical. There is a very small coupling. This small coupling is essentially indicating that, this is the particular isomer spectrum that is shown in the picture, here. The spectrum, the J value, essentially, corresponds to 2 hertz, and the 2 hertz, essentially, corresponds to an s p 2, substituted with a geminal di-hydrogen, this kind of a di-hydrogen derivative, which is geminal, and it is also a s p 2 in nature, essentially, gives the coupling constant value of 2. If it is cis isomer, coupling should be around 10, whereas, the trans isomer, typically, coupling should be around 15.

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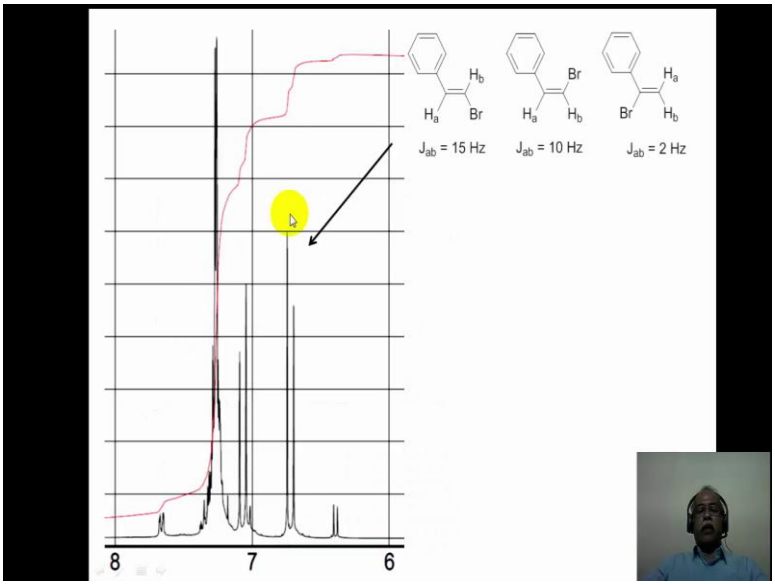

You can see the trans isomer in this particular case, with the larger coupling; you can see the, compare the spectrum, this spectrum, with the smaller coupling, and this spectrum, with the larger coupling; this corresponds to the trans isomer of the beta bromo styrene in this particular case.

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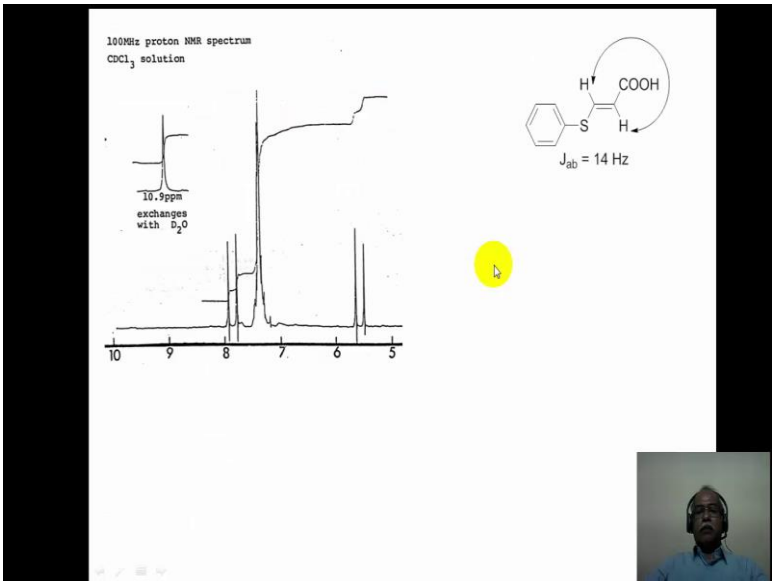

Another example to illustrate the use of the coupling information, namely the trans coupling, is what is seen here. This hydrogen should be a doublet; this hydrogen also should be a doublet; and, this hydrogen, essentially, which is right next to the carbonyl functional group, this will be, this is actually a push-pull kind of a system; the sulphur lone pair can be delocalized on to the COOH group. So, this hydrogen, which is in the beta position, and also close to the sulphur, comes at the higher delta value, around 7.9 p p m or so; whereas, this hydrogen, comes, which is the alpha hydrogen, comes around 5.6 p p m or so. And, this trans coupling is measured by measuring the gap here, or measuring the gap here, which corresponds to 14 hertz, and the 14 hertz is typically, 14 to 18 hertz, is typically the trans isomer; anything less than 12 hertz is taken as the cis isomer.

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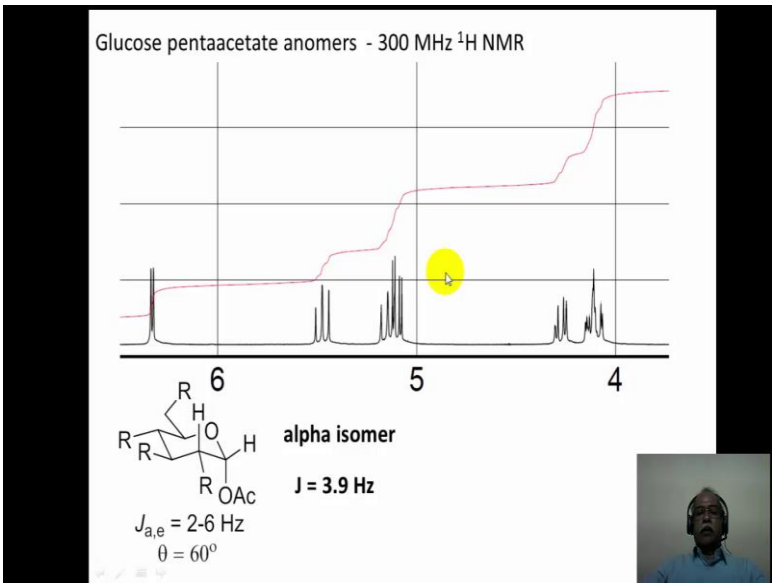

Now, earlier, we saw the glucose derivative, which is identified on the basis of the chemical shift value of the anomeric hydrogen. One can also use the coupling constant of the anomeric hydrogen to determine the stereochemistry of this molecule.

Let us take glucose pentaacetate, both the alpha anomer, as well as the beta anomer. This is the beta anomer of the pyranose ring that is shown here, and this is the anomeric position carbon. So, if you look at this particular hydrogen, this has a coupling partner

which is in the adjacent carbon. So, it is a vicinal coupling between these two. The dihedral angle between these 2 hydrogens, are about 60 degree. So, one would expect around 2 to 6 hertz is the coupling constant value between axial and equatorial hydrogen, in the terms of the vicinal coupling that one can see. The spectrum is shown here. The spectrum is fairly complex, because, this hydrogens are second order pattern hydrogen. But, what is easy to identify is, the anomeric hydrogen, which comes at the higher delta value, which is around 6.2 or 6.3 in this particular case; and, this is appearing as a doublet, because of the vicinal coupling. And, the coupling constant that is measured, is the gap between these 2 lines, that is shown as a doublet here, in this region of 6.3; and, that corresponds to 3.9 hertz. So, as a result, we conclude that, this would be the, this is actually, the alpha isomer of the, alpha isomer of the pentaacetate of glucose.

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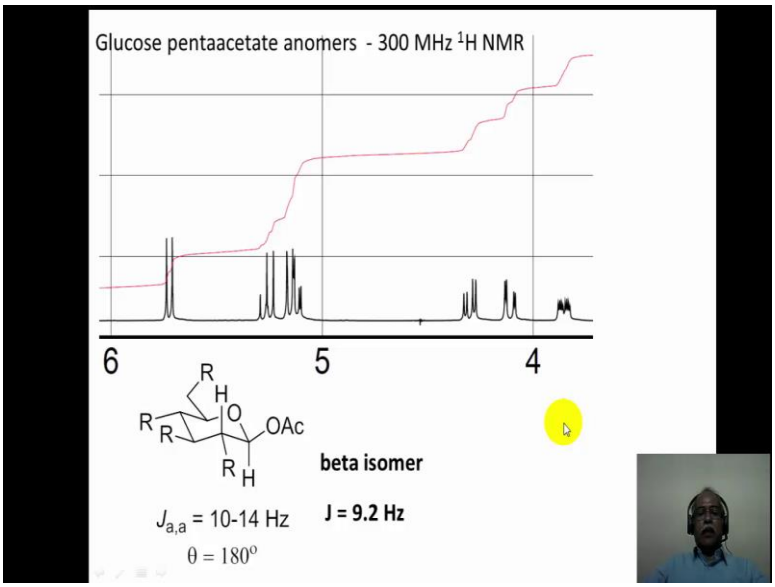

If you look at the beta isomer, which is this particular isomer, the dihedral angle between these 2 hydrogen should be 180, because they are trans, and they are diaxial in nature. The dihedral angle is 180, which will have the maximum coupling constant in the range of 10 to 14 hertz or so. This is the anomeric hydrogen in this molecule, which is coming at a lower delta value, because, remember, the axial hydrogen will come at a lower delta value, compared to the equatorial hydrogen, which comes at a higher delta value. So, in addition to using the delta value, which is high for the equatorial hydrogen, and low for

the axial hydrogen, one can also use the vicinal coupling between the anomeric hydrogen and the adjacent hydrogen, if the adjacent hydrogen is present in the molecule. Then also, one can derive at the stereochemistry. In this particular case, the gap between these 2 lines which corresponds to the diaxial coupling, corresponds to about 9.2, which is expected in the range of about 10 to 14; 9.2 is close enough.

So, this is a larger coupling, compared to the earlier example of the alpha isomer. So, the alpha, beta anomers can be easily distinguished, based not only the chemical shift value, but on the coupling constant values as well.

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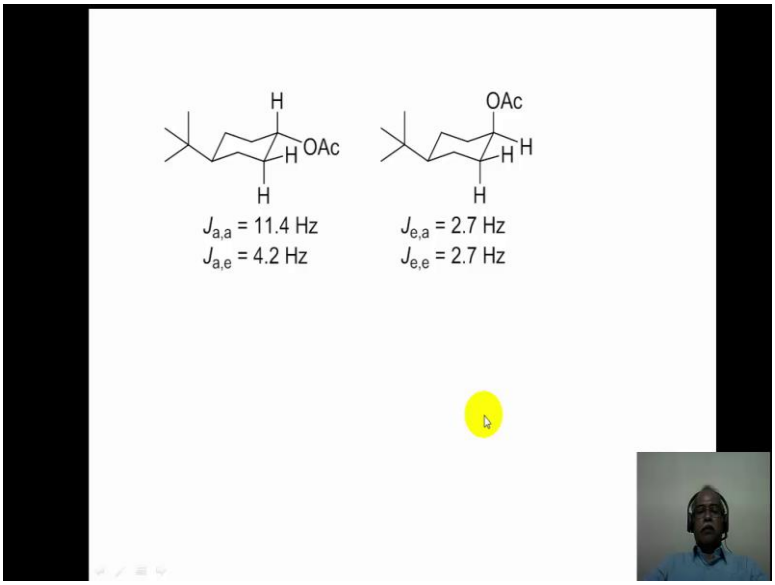

Some more examples of the cyclohexyl derivative, the corresponding… Earlier, we saw the alcohol; here, we are seeing the acetate. But, we are looking at the coupling constants here, rather than the chemical shift values of this hydrogens.

Now, you are looking at the coupling between this hydrogen and this hydrogen, or this hydrogen and this hydrogen. The axial-axial coupling is about 11.4. The axial-equatorial coupling is 4.2, whereas, in this case, for example, there is no axial-axial coupling; there is only a equatorial-equatorial, and equatorial-axial coupling, which are much less than 10 or so. So, one can easily distinguish between these 2 molecules, based on the coupling

that one sees for this particular hydrogen, which will be a doublet of doublet, in this particular case, because of these 2 hydrogens splitting it into a doublet of doublet; that spectrum is not available. So, I am just putting the values that are given in the literature, as far as the coupling constants are concerned. So, this is another example, a molecule, where the stereoisomers, namely the trans isomer and the cis isomer of the 4 tertiary butylcyclohexanol acetate is distinguished, based on the, purely on the coupling constant values, rather than the chemical shift values.

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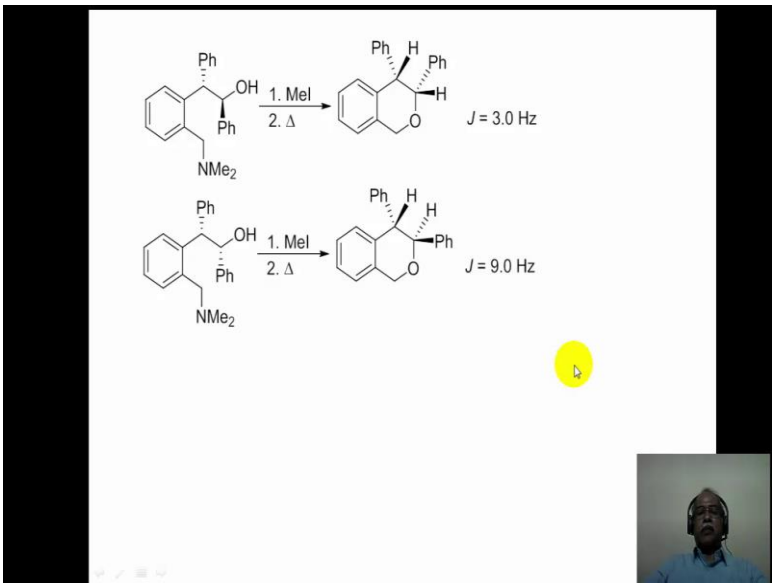

Let us look at an interesting example of cyclisation by means of a nucleophilic substitution reaction. This amino alcohol is treated with methyl iodide; upon treating with methyl iodide, methyl iodide reacts with this tertiary amine, and forms a quaternary ammonium salts. So, will have NCH 3, 3 NCH 3 3 times. The iodide, the iodide will be the counter ion. When the molecule is heated, the oxygen lone pair essentially attacks this benzylic position, and trimethylamine is eliminated in the process. So, essentially, nucleophilic substitution, followed by the trimethyl amine as a leaving group, is the reaction that you are looking at. But, in order for the oxygen to substitute at this position, this carbon-carbon bond should undergo a rotation, and that is why you see the stereochemistry of this two, in this particular case, the threo isomer, for example. In the product, you see the 2 phenyl cis to each other, whereas, if you take the opposite

diastereoisomer, namely the erythro isomer of the molecule, oxygen, when the carbon-carbon bond rotates, these 2 phenyl group becomes trans with respect each other in the product.

So, if you observe the stereochemistry of the starting point and the end point, essentially, there is a carbon-carbon bond rotation that is taking place. This is a freely rotating bond. So, the oxygen, in order to attack this particular carbon, should undergo a carbon-carbon bond rotation, and the oxygen should come here, in order to attack this particular carbon. So, what happens in the stereochemistry of the product that is formed? How do we find out which isomer is formed? This is the cis isomer, where the 2 hydrogens are cis with respect to each other. This is the trans isomer; the 2 hydrogens are trans with respect to each other. The dihedral angles are clearly very different in these 2 cases. This will have a larger dihedral angle. As a result of that, it has a larger coupling constant. So, one can look at… This would be a doublet, and this also would be a doublet. This will be a AB system in both cases, and the AB system, the coupling constant is based on the coupling between these 2 hydrogen. One can easily identify the trans isomer to have their larger coupling constant, compared to the cis isomer, which has a lower coupling constant.

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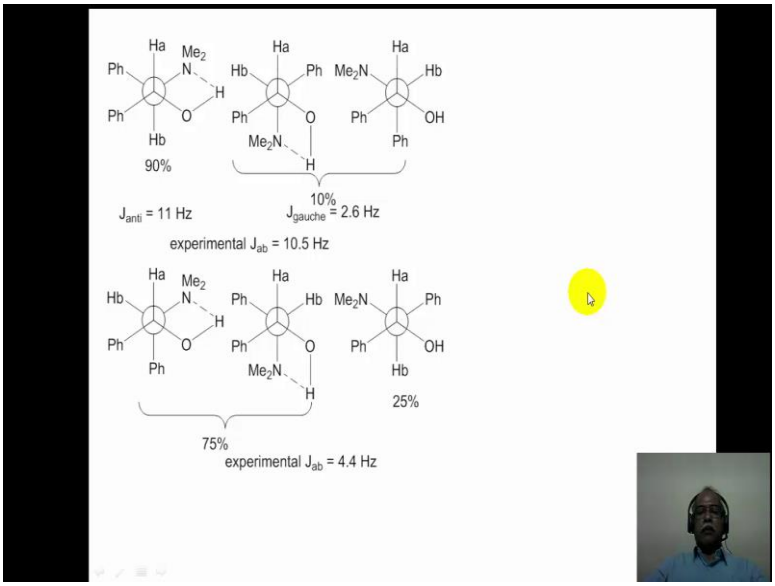

So, in the case of aliphatic system, where there is a free carbon-carbon bond rotation, this

is the example of the erythro and threo isomer of the amino alcohol that is shown here. This particular isomer is a threo isomer, and this particular isomer is the erythro isomer of the molecule. In the threo isomer, if you look at, there are 3 conformations that I have written here. These 3 conformations, 2 of the conformations have intra-molecular hydrogen bonding facility between the nitrogen and the OH. And, that will give added stability to that particular conformation.

Finally, this is a conformation, where the amino group and the OH are anti with respect to each other. So, there is no possibility of formation of an intra-molecular hydrogen bonding facility, in this particular case. If you look at this particular conformation, here, the bulky groups are farther away from each other. This is the best possible configuration that one can have, including the stabilization, because of the hydrogen, intra-molecular hydrogen bonding; and if you look at the dihedral angle between these 2 hydrogens, this is anti, is 180, with respect to the 2 hydrogens being anti to each other. So, as a result, one would expect a large coupling constant, if this were to be the most populated state among the three conformers that you have shown here. Clearly, this particular conformer will be the least stable conformer, because all the bulky groups are right next to each other; gauche interactions are very severe in here. And, this is,

relatively also speaking, unstable isomer; nevertheless, it has a contribution from the intra-molecular hydrogen bonding. So, among the three, this is expected to be the most stable. Indeed, if this were to be the most stable, this vicinal coupling should be a large coupling. The experimentally observed coupling is about 10.5 hertz and this is anti coupling. Expected coupling, theoretically based on the Karplus- Conroy equation, it is about 11 hertz or so. And, this is being close to the experimentally observed 10.5, one concludes that, this isomer, this conformer is the major conformers in the mixture of conformers that you can have in the solution phase. It is estimated to be about 90 percent populated, compared to the other 2 isomers, which are about less than 10 percent populated. But, when you come to the erythro isomer of the molecule, the possibility of having all the three equally populated exists in this particular case, because,

of the intra-molecular hydrogen bonding, intra-molecular hydrogen bonding in these 2 systems. And, if you look at this one, this is the anti conformer. The anti conformer

essentially derives, no stabilization whatsoever from the intra-molecular hydrogen bonding, just as in the case of this. So, one can expect these three, which are relatively speaking, less stable, compared to these three, to be equally populated in this particular case of erythro isomer.

The experimentally observed J value between these 2 hydrogens, vicinal hydrogen, is about 4.4. So, this is estimated to be about, contributing to about 75 percent of the mixture of these two, with internal hydrogen bonding interaction; and, to an extent of about 25 percent of the non-hydrogen bonded gauche isomer, in this particular case. So, essentially, this tells us that, the thermodynamically more stable isomer is the threo isomer, with the anti conformation of this 2 hydrogen, resulting in a large J value, compared to the erythro isomer, which has a smaller J value. So, you are using the J value, not only to determine the stereochemistry, but also to predict the relative concentrations of the various conformers in solution. In fact, NMR spectroscopy is one of the most widely used spectroscopic technique, to not only identify the conformers, but look at the relative populations of conformers in equilibrium, in solution.

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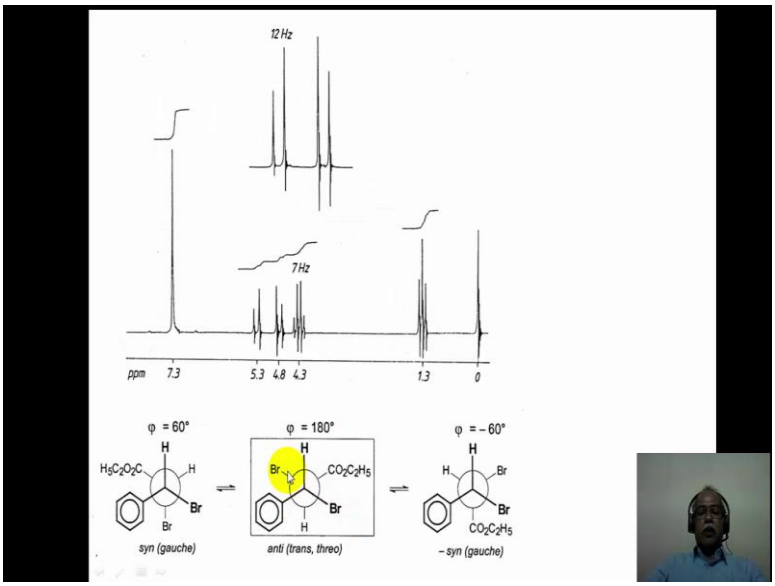

Another example, this is a dibromo cinnamic acid derivative, dihydro cinnamic acid derivative. This molecule again, the most stable conformation, where the 2 bromines are

anti with respect to each other. Hence, the 2 hydrogens are also anti with respect to each other, in the threo isomer. And, the experimentally observed chemical shift, the coupling constant value between the vicinal hydrogen is about 12 hertz. This is the NMR spectrum of this compound. This hydrogen and this hydrogen, forms an AB quartet, which is shown here; and, the CH 2 of the ethyl ester group is a simple quartet, which is this particular signal here. So, essentially, from the coupling information, you come to the conclusion that, this is a most predominant isomer in the solution of the 3 conformers that are written in this particular molecule.

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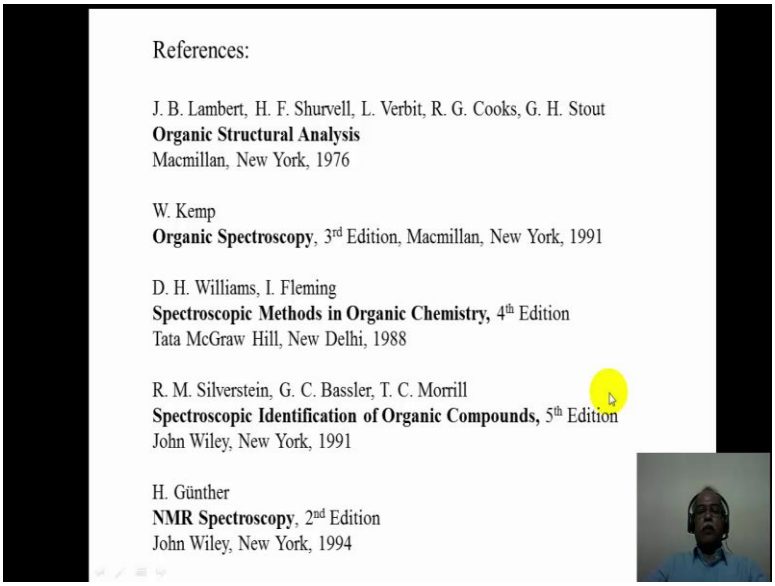

So, what we have seen here is a few examples of identifying stereochemistry, particularly, cis trans isomer stereochemistry, or diastereomeric isomer stereochemistry, or conformational isomers, using NMR spectroscopic technique. And, we have used, in some cases, the delta value, or the chemical shift value, to distinguish the stereoisomers. In some other cases, few examples, are also shown, where J values, namely, the coupling, vicinal coupling information is used as the tool for identifying the relative stereochemistry of organic molecules. These are some reference text books that I have used to collect information for this particular lecture. If you want to refresh your memory on this stereochemistry of organic compounds, I recommend that, you read the book by Nasipuri. It is an excellent source of information, as far as organic stereochemistry is

concerned.

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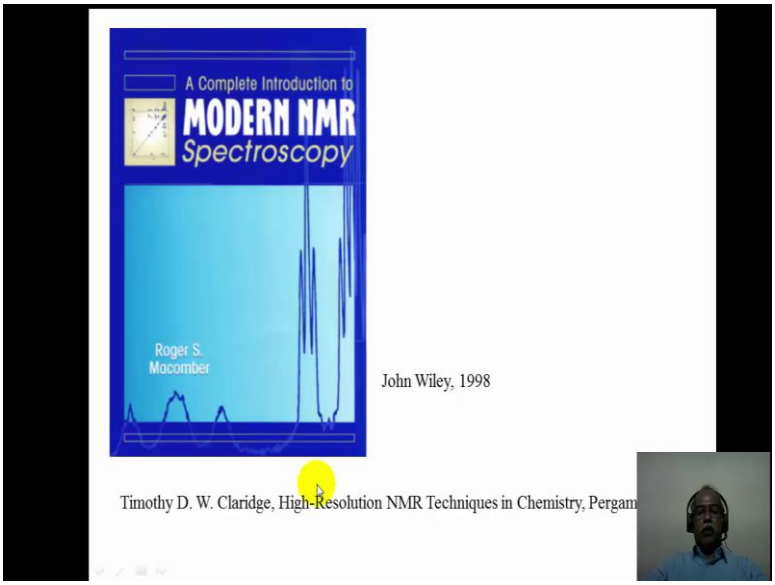

Finally, these are again two more books that are available readily for reference, in terms of looking at some NMR spectra, and looking at stereochemical aspects of NMR spectra. Finally, I would conclude the lecture by thanking all of you, for your kind attention.

Thank you very much.