Application of Spectroscopic Methods in Molecular Structure Determination

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Lecture – 07
Simplification of second order spectra

Hello, welcome to module 7 of the course on Application of Spectroscopic Methods in Molecular Structure Determination. In module 6 we considered the second order effects on the NMR spectrum. The second order spectra are fairly complex and we saw many examples of the second order spectra. We also realized how difficult it is to get the delta values and j values from second order spectra. In this module, we will consider certain techniques that are used for the simplification of second order spectra.

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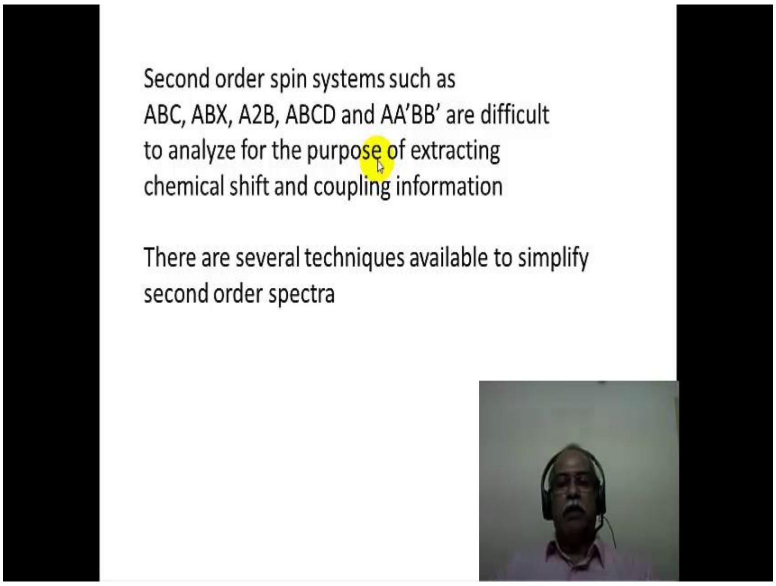

Second order spin systems such as ABC, ABX, A2B, ABCD and AA'BB' are difficult to analyze for the purpose of extracting chemical shift and coupling information

There are several techniques available to simplify second order spectra

Typically, second order spin system such as ABC, ABCD, AA prime, BB prime are difficult to analyze, for the purpose of extracting the information about chemical shifts and coupling constants. There are several techniques available to simplify the second order spectra, some of the techniques we will consider in this particular lecture.

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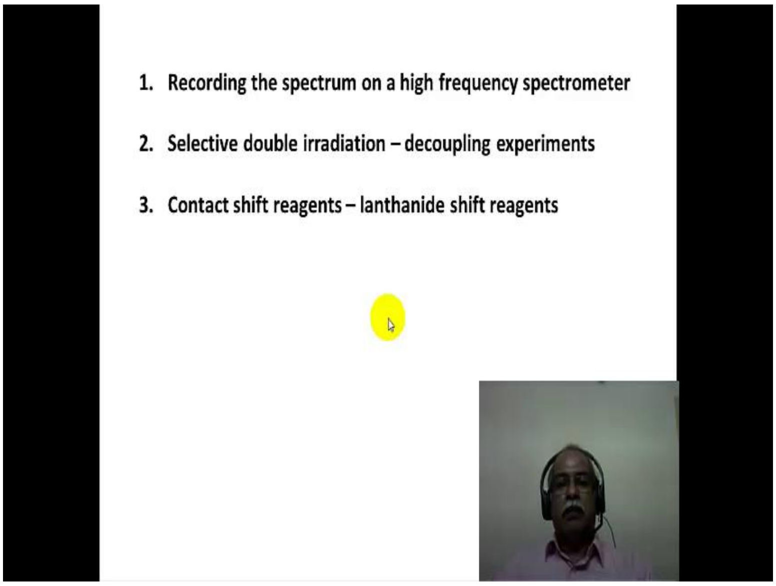

1. Recording the spectrum on a high frequency spectrometer
2. Selective double irradiation – decoupling experiments
3. Contact shift reagents – lanthanide shift reagents

First, one can record the spectrum on a higher frequency spectrometer and make the spectrum look simpler because of the high frequency spectrometer. Secondly, one can do what is known as double irradiation experiment. One can selectively decouple spins so, that from a complex spin system one can reduce it down to simpler spin system. Third point, one can use what are known as contact shift reagents. These are lanthanide based shift reagents which are paramagnetic and these shift reagents essentially spread out the spectral information to a wider spectral width. So, that one can analyze the spectrum much more easily.

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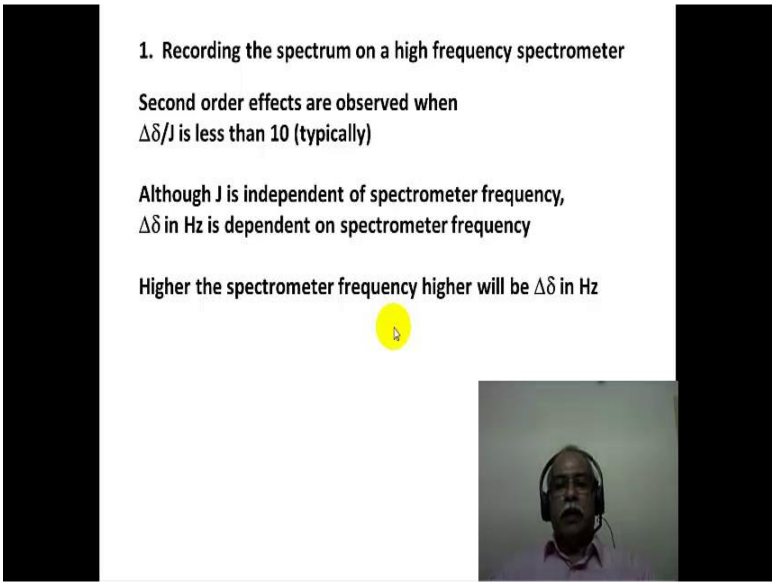

1. Recording the spectrum on a high frequency spectrometer

Second order effects are observed when
$\Delta\delta/J$ is less than 10 (typically)

Although J is independent of spectrometer frequency,
$\Delta\delta$ in Hz is dependent on spectrometer frequency

Higher the spectrometer frequency higher will be $\Delta\delta$ in Hz

.

Now, why does the high spectrometer frequency help in solving the second order spectra because second order effects are typically because of the fact that you have delta delta divided by j being less than 10 which is typically the value that one sees. Although; j is independent of spectrometer frequency. Delta, delta is not independent of spectrometer frequency when it is expressed in hertz. Therefore, a higher spectrometer frequency will help because, it will increase the delta, delta value in hertz and there by decrease j the ratio delta delta divided by j will be also increased. As a result of increase in the delta, delta value with the increasing spectrometer frequency with the increasing spectrometer frequency the delta delta increases in hertz. As a result of that the delta delta divided by j is also increasing j being constant which is irrespective of the spectrometer frequency it will be the same.

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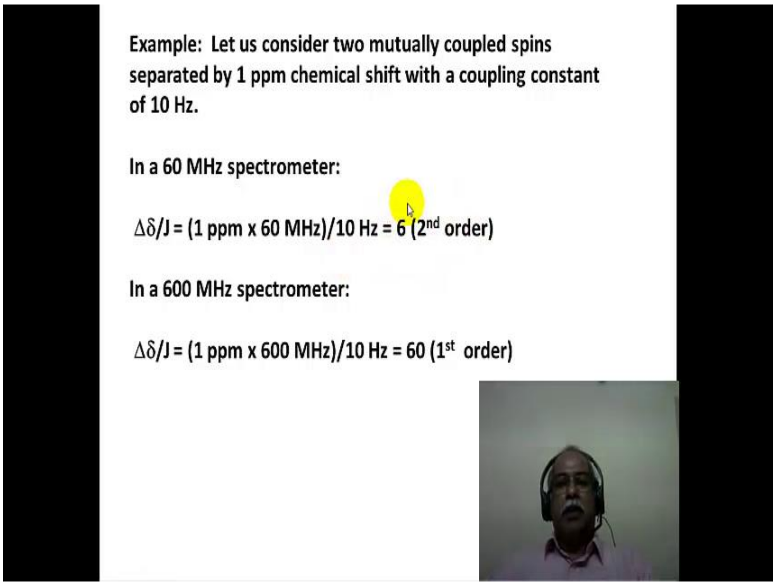

Example: Let us consider two mutually coupled spins separated by 1 ppm chemical shift with a coupling constant of 10 Hz.

In a 60 MHz spectrometer:

$\Delta\delta/J$ = (1 ppm x 60 MHz)/10 Hz = 6 (2^{nd} order)

In a 600 MHz spectrometer:

$\Delta\delta/J$ = (1 ppm x 600 MHz)/10 Hz = 60 (1^{st} order)

Now, let us consider a simple example two mutually coupled spin system, lets called it as A B system. Separated by about one ppm chemical shift with the coupling constant of 10 hertz in a 60 megahertz NMR spectrometer, the delta delta will be about 60 hertz and the j value is 10. Delta, delta divided by j will be around 6, which is typical second order effect is what one would see in the spectrum. However, when you move to a 600 megahertz NMR spectrometer the delta delta would be 600 hertz and when it is divided by 10 you get a number a 60 which is will within the first order domain of the NMR spectrum. So, you can see from this how the change in the delta delta value with increasing spectrometer frequency helps in increasing the delta delta divided by j that ratio delta delta by j to a higher number there by, reducing the complexity of the spectrum.

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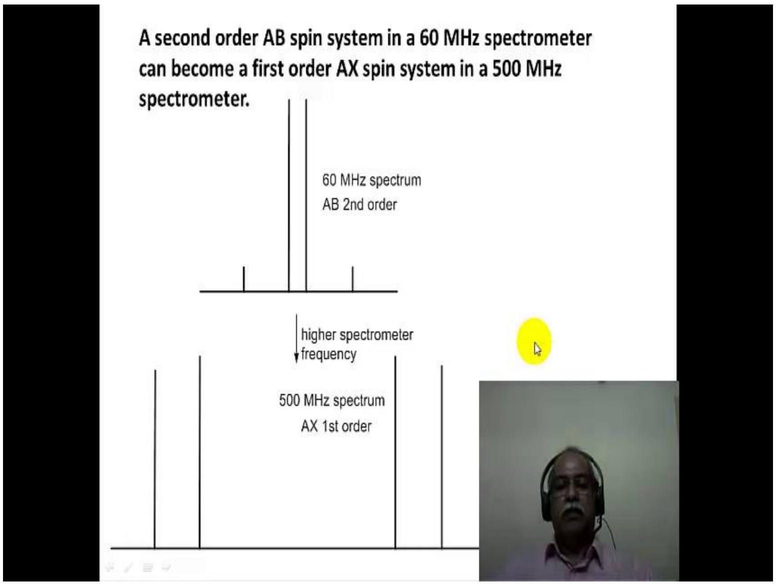

A second order AB spin system in a 60 MHz spectrometer can become a first order AX spin system in a 500 MHz spectrometer.

Now, what I mean is graphically represented in this particular slide. A second order AB spin system in a 60 megahertz NMR spectrometer can easily become a first order AX spin system in a 500 megahertz NMR spectrometer. From a visually inspection one can say this is second order spectrum because, the inner lines are much taller than the outer lines, the intensities are not as per the expectations that one would have per doublet of a doublet. On the other hand if we go to a higher spectrometer frequency, we can see this doublet as almost equal intensity and this doublet also has almost equal intensity. While one cannot easily take the center of the peak as the chemical shift value in the top case, one can reasonably approximate to the center of the peak center of these two peaks which are the chemical shift values for the delta a and the delta b respectively. So, higher spectrometer frequency essentially reduces the complexity of a second order spectrum to a first order spectrum.

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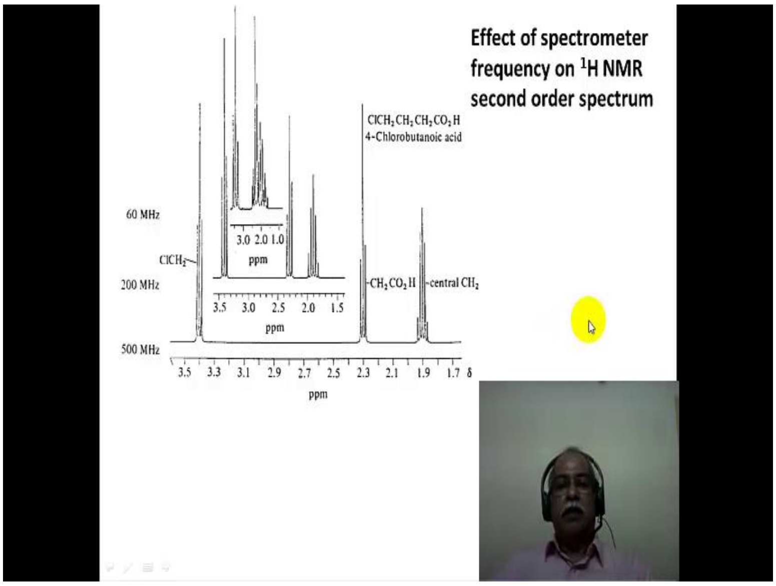

Effect of spectrometer frequency on ^{1}H NMR second order spectrum

This is clearly illustrated in the case of the four chlorobutanoic acid. If we consider four chlorobutanoic acid 60 megahertz NMR spectrum, which is the top spectrum that is shown here the CH 2, CH 2 signals are essentially merging on top of each other and there is very poor resolution this is the typical second order spectrum for any alkyl chain of this kind. The CH 2 that is attached to the chlorine has higher chemical shift value because of the electro negativity of the chlorine.

However, the other two; CH 2 are essentially merged on top of each other. Where, when we go to a 200 megahertz NMR spectrum, There is a better resolution as well as there is a separation of chemical shift values in this NMR spectrum. The chemical shift value expressed in delta is essentially same, but the spectrum is spread because of the scan width will be higher for the same, chemical shift of ppm expressed in the scale here. Now, when you go to even higher spectrometer frequency, namely; the 500 megahertz NMR spectrometer. The spectrum is well spread out and this is a very characteristic first order spectrum.

So, what is originally a CH 2 CH 2 appearing as a second order spectrum in this top case, 60 megahertz case. As now resolved into a well-defined the first order spectrum for example, the central CH 2 which is flanked by two other CH 2's appears as a nice squinted with the intensity ratio that one would except for a first order kind of a squinted in the NMR spectrum.

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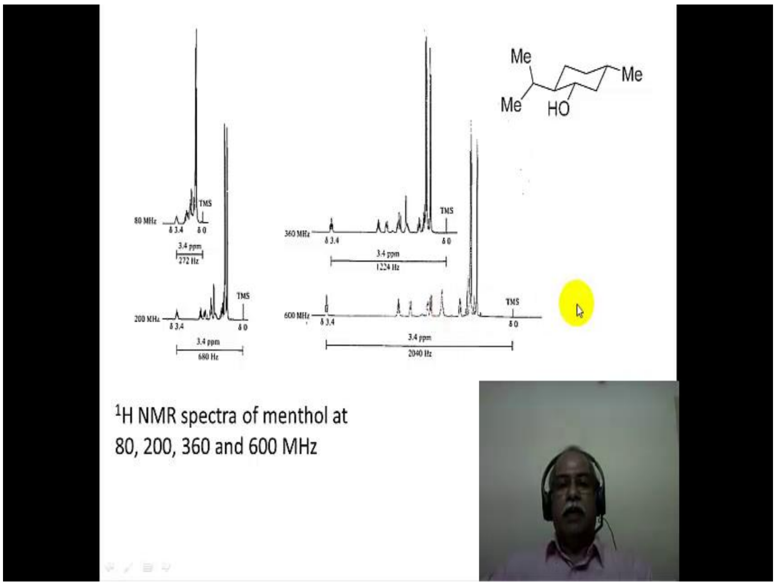

^{1}H NMR spectra of menthol at
80, 200, 360 and 600 MHz

Now, let us take another example this is the spectrum of menthol, menthol is a terpene it is alcohol and except for this particular hydrogen which is attached to the OH carbon. All the other hydrogens are essentially aliphatic hydrogens and they appear as a bunch of peaks in the region between 1 to 1.5 ppm and so on. So, this is the 80 megahertz NMR spectrum of menthol. This is a 200 megahertz NMR spectrum of menthol. This is a 360 and a 600 megahertz NMR spectrum of menthol. As you go from 80 to 600 megahertz NMR spectrum you can see it for the same chemical shift width expressed in parts per million the spectral width is much larger here.

For example, a 3.4 ppm spectral width is about 200 and 72 hertz in the case of the 80 megahertz NMR spectrum. The same spectral width of 3.4 ppm is about 2040 hertz in the case of your 600 megahertz NMR spectrum. So, the spectrum is well spread out which means the delta delta between any two hydrogen's will be much larger, j values being constant going from 80 megahertz to 600 megahertz the delta delta divided by j ratio is keeps increasing as you go from 80 to 600 megahertz NMR spectrum. This is advantage of recording the NMR spectrum in a high frequency spectrometer, because it simplifies a second order spectrum into a first order spectrum.

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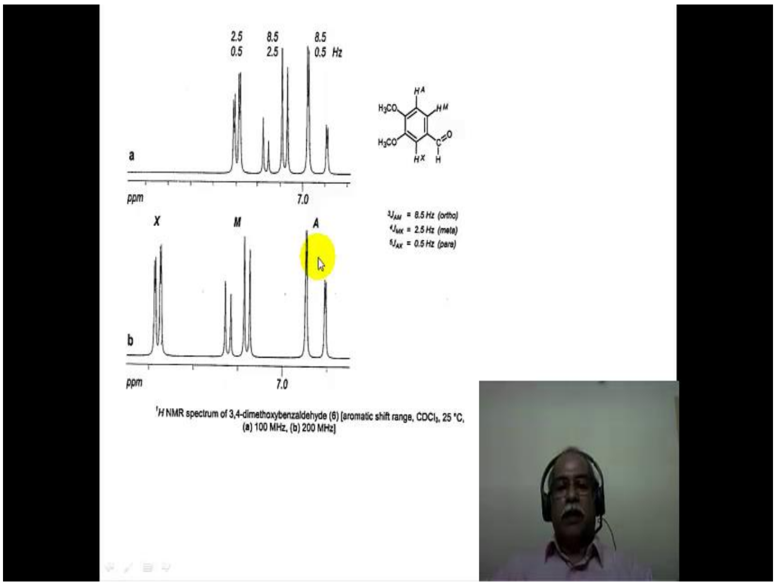

${}^3J_{AM}$ = 8.5 Hz (ortho)
${}^4J_{MX}$ = 2.5 Hz (meta)
${}^5J_{AX}$ = 0.5 Hz (para)

${}^1H$ NMR spectrum of 3,4-dimethoxybenzaldehyde (6) [aromatic shift range, $CDCl_3$, 25 °C, (a) 100 MHz, (b) 200 MHz]

Another example is shown here, this is a spectrum of dimethoxybenzaldehyde. The spectrum we have already seen in the earlier module also, this is a 100 megahertz NMR spectrum and this is a recorded in a 200 megahertz NMR spectrometer. As you can see here the peak intensities are much better here, they are more or less equal intense between the doublets unlike in this case. For example, with the intensities are very different. So, the spectrum tending to be not exactly a first order spectrum, but it is trending to be a first order spectrum as you go from 100 to 200 megahertz the same sample if one where to record it in a 600 megahertz spectrum, it would be typical for starter spectrum.

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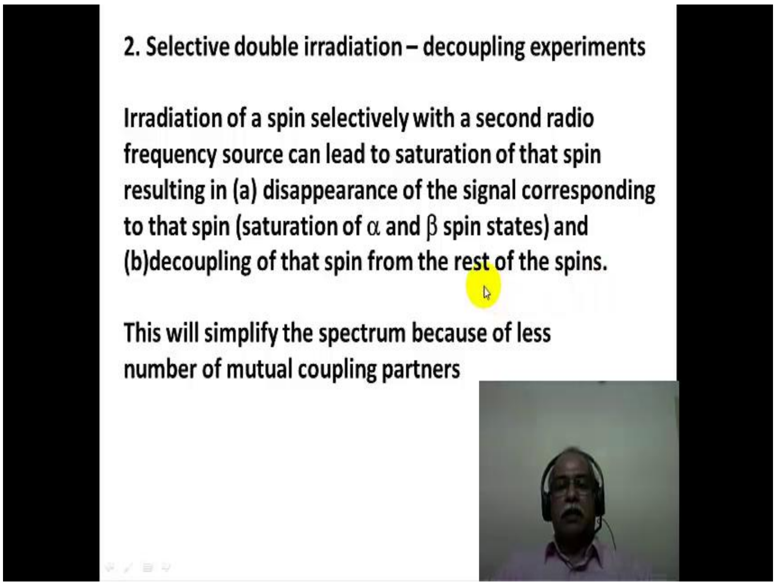

2. Selective double irradiation – decoupling experiments

Irradiation of a spin selectively with a second radio frequency source can lead to saturation of that spin resulting in (a) disappearance of the signal corresponding to that spin (saturation of α and β spin states) and (b)decoupling of that spin from the rest of the spins.

This will simplify the spectrum because of less number of mutual coupling partners

Now, the second technique has to deal with the selective irradiation or the decoupling experiments. What happens in this experiment is, irradiation of a particular spin selectively using a second radio frequency source can lead to the saturation of that particular spin. In other words, you are promoting the spins from the ground state to the excited state, where was from the alpha state to the beta state and in the process if we continuously irradiate the sample at that particular frequency that spin will get saturated.

In other words, the population becomes equal and it is different from the equilibrium population that one excepts. Now this will result in two things. One; is the disappearance of the signal because there is no longer excess population in the ground state so the signal will vanish essentially, because of saturation of the alpha, beta spin states. Second thing; that will happen is the decoupling of that particular spin from the rest of the spin in a mutually coupled system in other words, under equilibrium condition the spins will be mutually coupled then we saturate one of the spins that undergoes a decoupling with the rest of the spins and as a result of that the spectrum simplifies with less number of mutually coupling partners.

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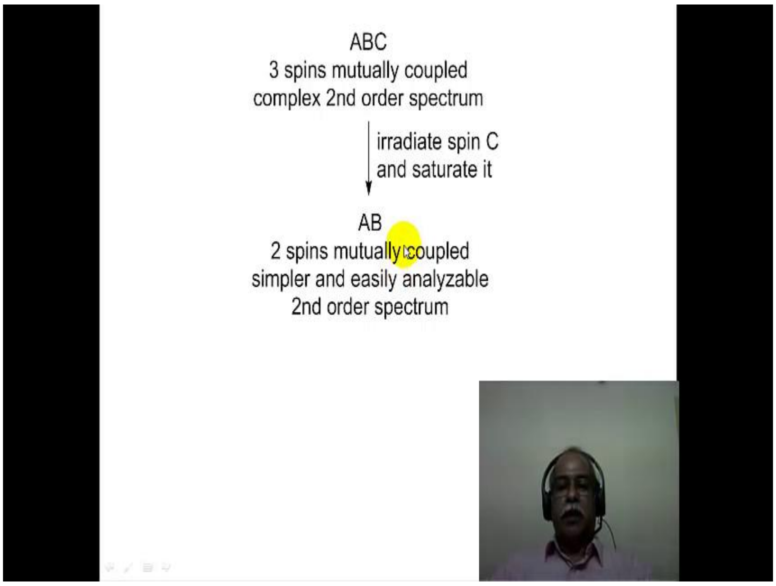

ABC
3 spins mutually coupled
complex 2nd order spectrum

irradiate spin C
and saturate it

AB
2 spins mutually coupled
simpler and easily analyzable
2nd order spectrum

To illustrate; an example here, if we take an A, B, C system. This is the 3 spin system which is mutually coupled to each other. So, it will present as a second order spectrum fairly complex spectrum. Suppose, if one irradiates the spin c in other words; use a second radio frequency corresponding to the frequency of spin c. Hydrogen c Let us say for example, it will saturate the particular hydrogen spins and as a result of that decoupling takes place. So, as a result of that A, B, C system simplifies to an A, B system which is a 2 spin system which is mutually coupled. An a b system is much easier to analyze. We know the methodology to analyze an A, B spectrum much better than analyzing an A, B, C spectrum. So, as a result of that although it is still a second order spectrum, it becomes a more easily unleasable second order spectrum in terms of the less number of chemical shifts and coupling constant that one has to deal with to obtain this information from the spectrum.

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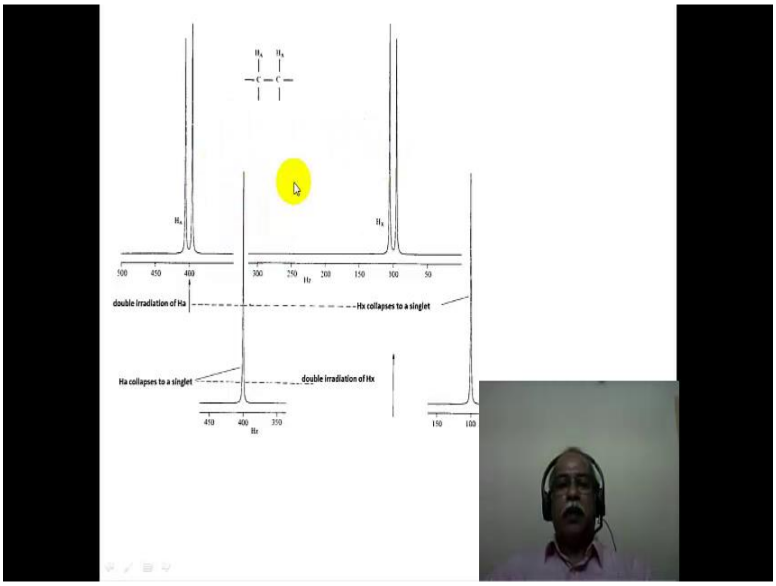

Now, this is illustrated in this particular example, if you take a 2 spin system essentially. You have an A, B kind of a pattern that you see in the NMR spectrum. Now, when a double irradiation frequency is applied to this particular signal here. That signal completely disappears and this signal collapses to a singlet. Similarly, if one applies a second radio frequency corresponding to this particular spin here this hydrogen here that signal collapses completely and this signal reduces to a singlet. An A, B quartet can essentially become a singlet spectrum. When B is the coupled or A is the coupled this is even more useful.

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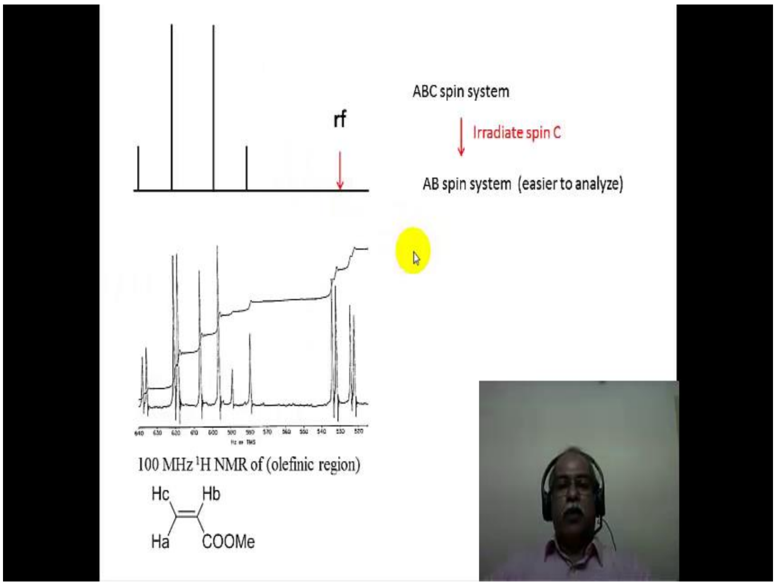

ABC spin system

Irradiate spin C

AB spin system (easier to analyze)

100 MHz ^1H NMR of (olefinic region)

When you have an A, B, C spin system going to an A, B kind of a spin system alkynic hydrogen's will present a fairly complex spectrum. The spectrum we have seen already earlier. This is a spectrum of methyl acrylate this is an A, B, C spin system. The c is coming, shown separately in this right-hand side of the spectrum. This is a fairly second order complex pattern is what one sees here.

Suppose if one applies a radio frequency corresponding to the frequency of c which is approximately in this region here. That will essentially result in decoupling of the C with A and B. So, A and B will present simply as an A, B spectrum. A, B spectrum with the 4 line pattern like this, is much easier to analyze and they extract the information corresponding to delta A, delta B and j AB.

Now if one applies a frequency over here, the second frequency when it is applied here, then it will become A, B, C spectrum which is also a second order spin spectrum, two spin spectrum. So, it is easy to analyze such 2 spin spectrum much more readily compare to a three spin system which will be a fairly complex spectrum like it is shown here.

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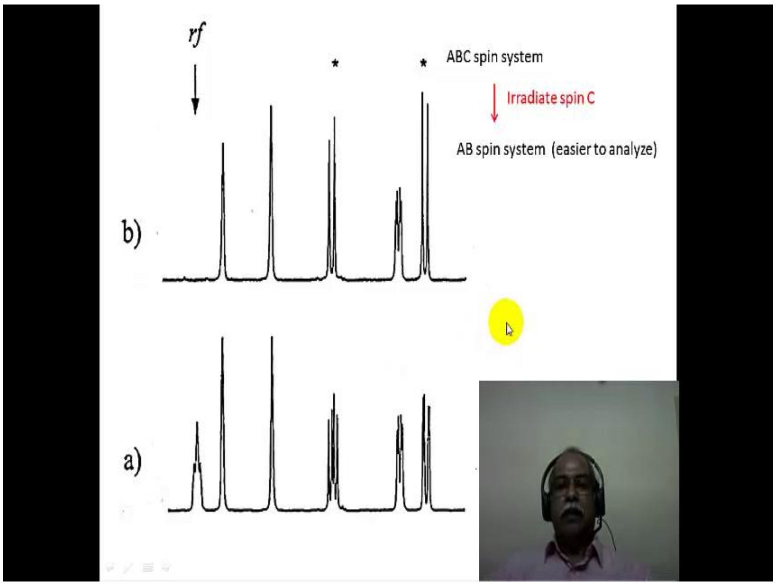

ABC spin system

Irradiate spin C

AB spin system (easier to analyze)

Another example of A, B, C to A, B spin system, if you observe this particular multiplet which is appearing in the left-hand side. That is mutually coupled to this multiplet here and this multiplet here. So, when a second radio frequency is applied and this multiplet is decoupled or saturated that signal completely vanishes and also we can see that two stared multiplet which are originally a multiplets. Second order effect multiplet is what is seen now it appears as an AB quartat, A B quartat can now easily be solves because it is easy to extract the information from AA B quartat rather than a complex multiplet pattern like this one.

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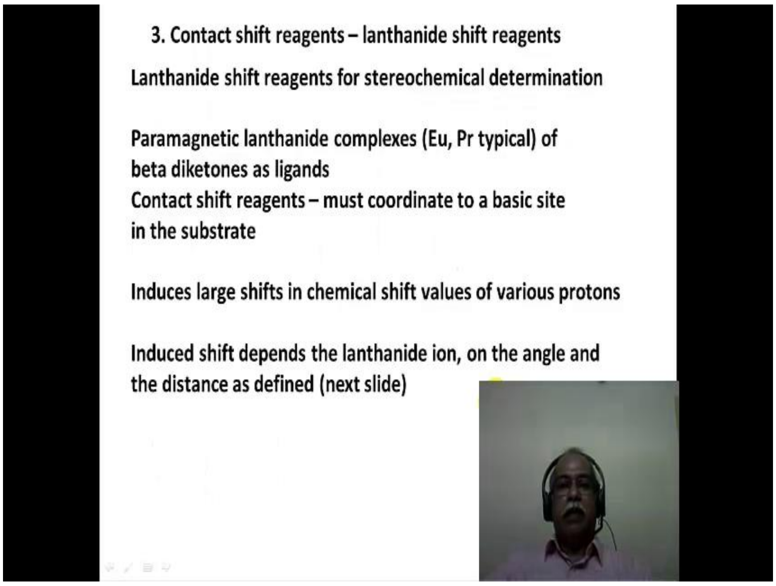

3. Contact shift reagents – lanthanide shift reagents

Lanthanide shift reagents for stereochemical determination

Paramagnetic lanthanide complexes (Eu, Pr typical) of beta diketones as ligands

Contact shift reagents – must coordinate to a basic site in the substrate

Induces large shifts in chemical shift values of various protons

Induced shift depends the lanthanide ion, on the angle and the distance as defined (next slide)

Lastly, we see the effect of contact shift reagents. Otherwise; known as lanthanide shift reagents. Lanthanide shift reagents are very useful for stereochemical determination. We will deal with this aspect of the lanthanide shift reagents in a different module. But for the present purposes it a Paramagnetic lanthanide complexes with beta diketones as the ligands.

In other words, they are kelating ligands these are contact shift reagents they must coordinate to a basic site in the substrate. In other words, they must coordinate to either an oxygen, lone pair nitrogen, lone pair or a sulfur lone pair kind of a functional group must present in the molecule in order for the shift reagents to work. Because they form a weak complex with the substrate and then effect the shifts which are induced to sifts as a result of the contact. Then the induced large shifts in the chemical shift values of various proton is what one measures the contact shift reagents studies. Induced shifts depends on the lanthanide ion concentration. It is a angle and the distance as defined in the next slide we will show in a minute.

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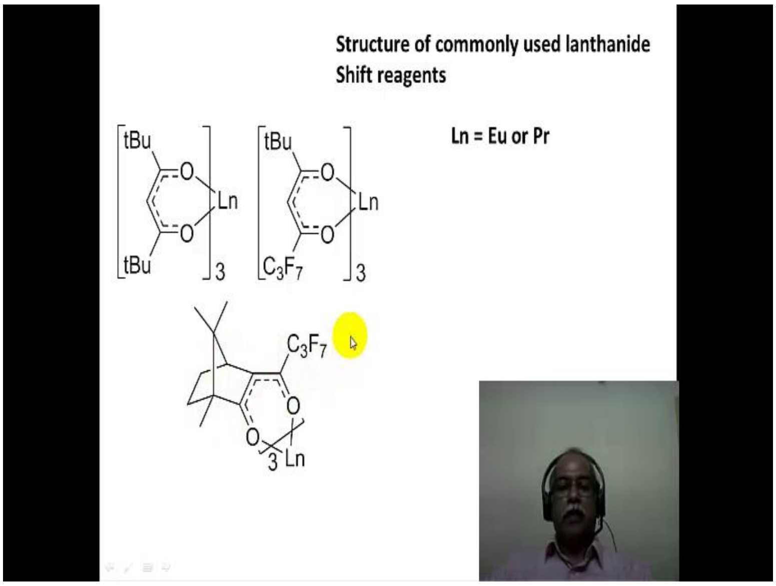

Structure of commonly used lanthanide Shift reagents

Ln = Eu or Pr

These are the structures of commonly used lanthanide shift reagents. You can see here each of this ligand is a beta diketonate kind of a ligand and 3 such ligands are kelating to the lanthanide ion the usual lanthanide ions that are used are europium 3 plus, praseodymium 3 plus or the ions that are normally used in the case of lanthanide shift reagents. This is a chiral lanthanide shift reagents, this is extremely useful when one wants to analyze enensumeric mixtures of compounds.

In other words, racemic mixture of compounds can be analyzed using a chiral shift reagent. We will some examples of use of chiral shift reagent when we talk about stereochemical aspects by NMR spectroscopic.

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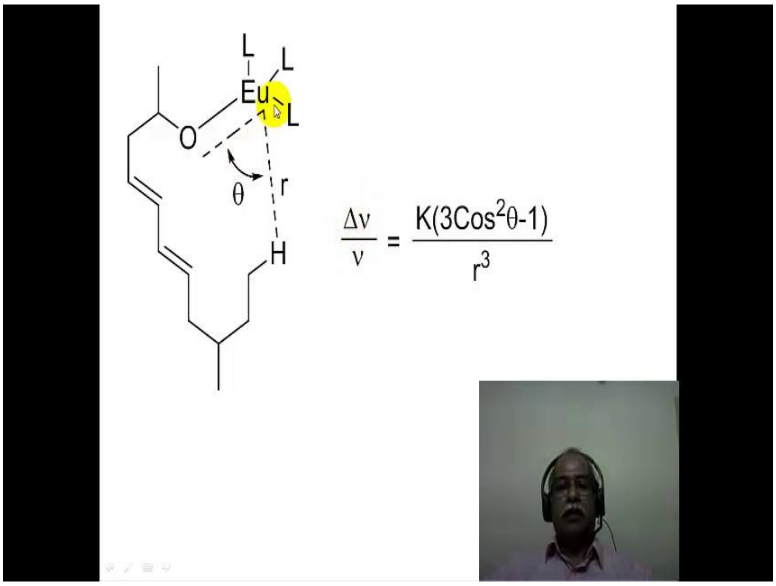

$$\frac{\Delta\nu}{\nu} = \frac{K(3\mathrm{Cos}^2\theta - 1)}{r^3}$$

Now, this is the relationship which is called the Maternal Relationship. The delta mu is the difference between the chemical shift value without the shift reagent added to the chemical shift value with the shift reagent added, and mu is the frequency without the chemical shift reagent being added. Now these parameters the k is a constant, 3 cos square theta minus one by r cube essentially relates to the ratio of the induced shift which is, delta mu divided by mu. r is the distance between the lanthanide ion and the contact to the hydrogen which is under observation, for example.

Now the lanthanide ion is complex to an oxygen lone pair and it is now at a distance of r from the hydrogen which is under observation and this is the angled between the oxygen, europium and the hydrogen is the theta which corresponds to the theta in this particular equation. So, one can readily see that the lanthanide shifts is essentially inversely proportional to the power 3 of the distance in other words as the distance increases, the induced shift falls of quiet rapidly. in other words closer the hydrogen to the europium center larger will be the shift of the induced shift of the chemical shift as a result of the lanthanide sift reagents.

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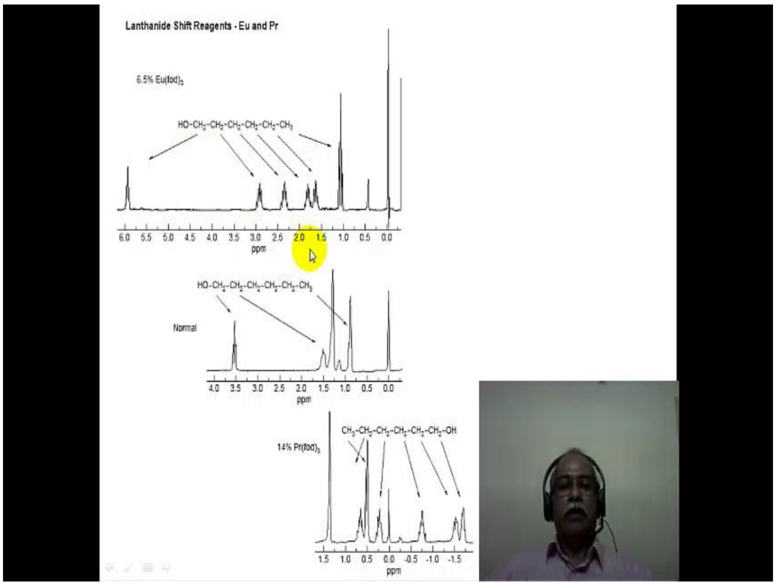

Lanthanide Shift Reagents - Eu and Pr

Here is an illustration of the effect of lanthanide shift reagents on hypotonal. I am sorry this is hexanal. You can see the hexanal spectrum being shown without any lanthanide shift reagents being added as a normal spectrum essentially; except for the CH 2 OH functional group. Where the CH 2 is attached to a oxygen which is an electronegative element. Which comes around 3.5 ppm all the other aliphatic hydrogen essentially appear as fairly complex multiplet as a bunch of peaks. Which are unresolved peaks for example, in the region between about 0.08 ppm to about 1.5 ppm or so. The whole bunching of the aliphatic hydrogens cannot be resolved without addition of the shift reagent when shift reagent is added about 6.5 percent of europium fod 3. fod 3 is the beta diketonate, one of the beta diketonate ligands.

The europium complex, when it is added it complexes to the oxygen and you can see here the shift of the hydrogen of the CH 2 OH from 3.5 ppm to about 6 ppm. This is the induced shift that we are talking about delta delta and this can be expressed in hertz if you know the spectrometer frequency of the spectrum that is being recorded. Now you can see also all the other peaks which are bunched up together here. Now they are getting resolved as result of the induced shifts of the various hydrogen. Once the europium is coordinated here, with respect to the europium each of this hydrogens are having different distances as we go further away and away from the europium. The shift is going to be reduced in other words the CH 3 which will appear as a triplet which is appearing here, essentially reminds the same possession a very little shift is taking place. Whereas, the CH 2 to OH where the CH 2 which is attached to oxygen as well as europium as the largest shifts. In other words, as a distance increases the induced shift falls of quite rapidly.

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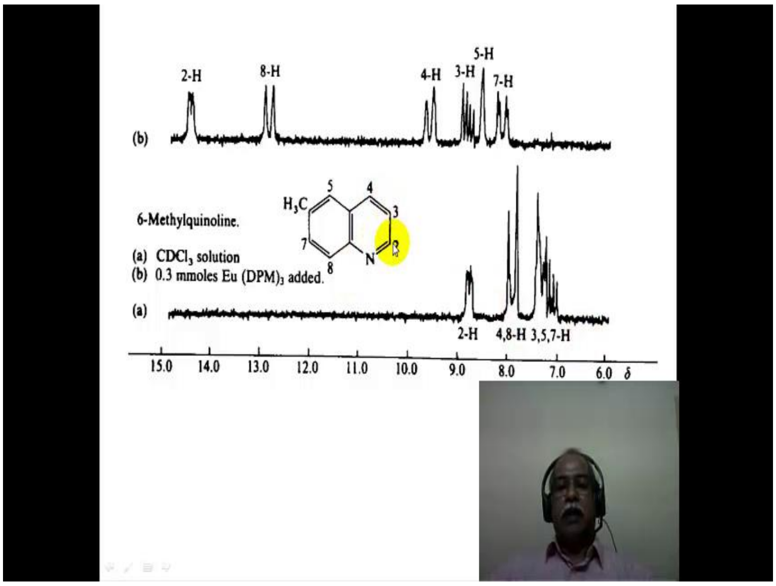

Here is another example; this is 6 methylquinoline is the example that is given the bottom spectrum is essentially without the addition of the europium shift reagent. The spectrum is measured in series l, 3 as a solvent. You can see here the hydrogen of the aromatic ring. Here hydrogen 3, 4, 5 and 7 they all bunched together and appear as a multiplet in the region between 7 ppm to 8 ppm. Only the hydrogen which is adjacent to the nitrogen, because again because of the electron withdrawing effect of the nitrogen, it appears separately as a multiplet around 8.9 ppm or so.

Upon addition of the shift reagent, the shift reagent will coordinate to the nitrogen lone pair here, as a result of that hydrogen 2 and hydrogen 8 which are close approximately to the europium. They get shifted further down field in the NMR spectrum. For example, the hydrogen 2 now comes around 14.5 ppm. Whereas the hydrogen 8 now comes around 13 ppm also not only that hydrogen 8 is now resolved. You can also see the multiplicity very clearly, one can obtain constant information fairly, readily from this one cannot the chemical shift value because the induced shifts are now very different in each of the spectrum depending upon how much of the europium shift reagent is added. So, the chemical shift information is not very useful. Never the less one can see the multiplicity pattern emerging to a simpler multiplet passion which is easily analyzable.

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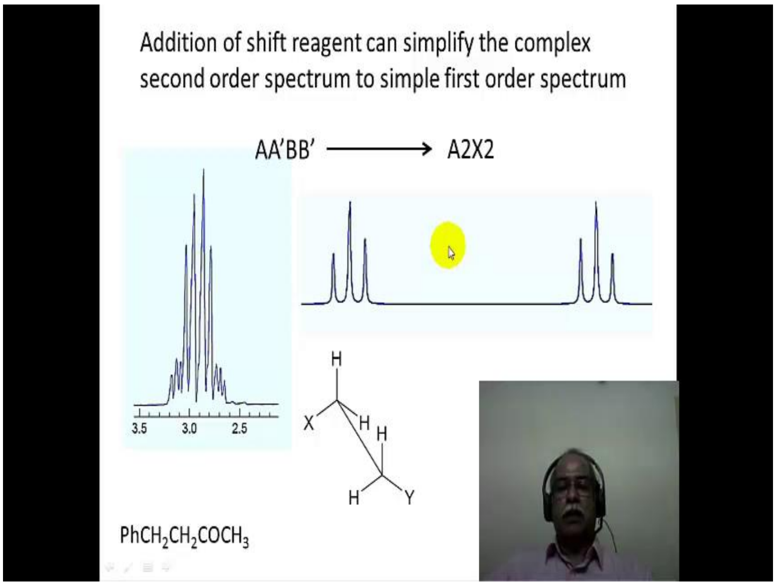
Addition of shift reagent can simplify the complex second order spectrum to simple first order spectrum

AA'BB' ⟶ A2X2

$PhCH_2CH_2COCH_3$

So, the addition of shift reagent can actually simplify a second order spectrum to a simple first order spectrum. Another example would be an A A prime, B B prime spectrum. Which is a fairly complex spectrum take the example of the CH 2, CH 2 which would appear as the A A prime, B B prime spectrum in this particular ketone indeed, it appears has a multiplet as shown in the spectrum here. When shift reagent is added it will complex to the oxygen lone pair.

As a result of that now the chemical shift is going to be spread out and this will essentially; now become, a first order system because the chemical shift difference between the 2 CH 2 are going to be much more when the shift reagents is added. This j reminds constant irrespective of the shift reagent. So, as a result of that the delta delta divided by j is going to be much higher after the addition of the shift reagent. So, what was originally a complex multiplet, now as a result into 2 triplets, which are much easier to analyze in terms of extracting the j value information from this spectrum rather than from this spectrum. So, essentially what has happened is after the addition of the shift reagent. What was originally an AA prime, BB prime system has simplified itself to an A2X2 such that, the A2 appears as a triplet and the X2 also appears as a triplet in this particular instance.

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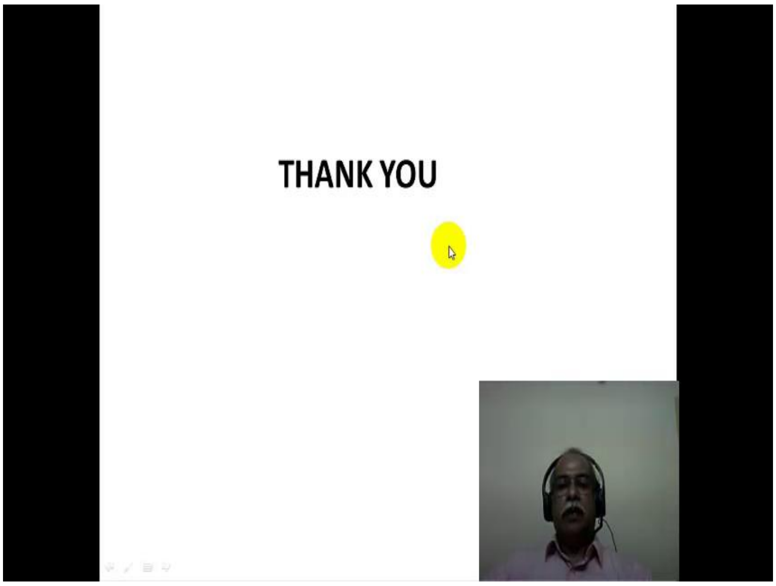

THANK YOU

So, what we have seen in this particular module is simplification of second order spectra by 3 different techniques. First; using a high resolution, high frequency NMR spectrometer. Which essentially increases delta, delta to j ratio to much higher values as the spectrometer frequency increases. Then we looked at the effect of decoupling experiment. Selecting decoupling leads to simplification NMR spectra. Thirdly, we saw the effect of shift reagents in terms of induced shift being very high, again the delta delta to the j ratio becomes more than 10 and results in the first order spectrum. Simplification of spectrum is what is taking place.

Thank you very much.