Application of Spectroscopic Methods in Molecular Structure Determination

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Lecture - 13
Dynamic Processes by NMR Spectroscopy
Applications of variable temperature technique.

Hello everyone, welcome to module 13 of the course on Application of Spectroscopic Methods and Molecular Structure Determination. In this module, we will see some aspects of the variable temperature NMR technique, and how to study dynamic processes in molecule by NMR spectroscopy at various temperatures.

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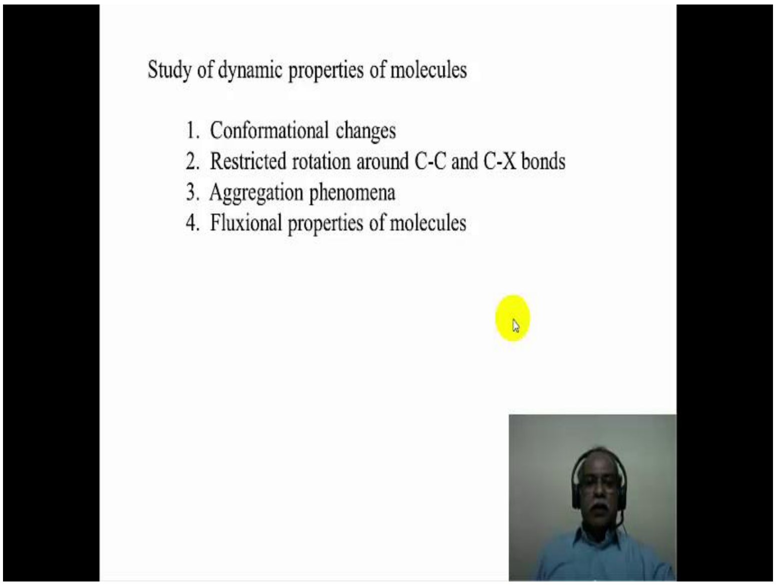

Study of dynamic properties of molecules

1. Conformational changes
2. Restricted rotation around C-C and C-X bonds
3. Aggregation phenomena
4. Fluxional properties of molecules

Now, NMR spectroscopy is a very powerful tool, and it can be used for a study of several different types of dynamic properties of the molecules. Some of the dynamic processes are listed here, which can be studied by NMR spectroscopy. Now conformational change a chair form of cyclohexane going to another chair form, for example can be studied by NMR spectroscopy. Bond rotations carbon-carbon bond or carbon-heteroatom bond rotating the restricted rotation of this kind of bonds can be studied by NMR spectroscopy. When molecules trend to aggregate in solution such an aggregation phenomenon can be studied by NMR spectroscopy. A typical would be pi stacking aggregation of aromatic systems in solutions. Finally, the fluxional properties of molecules can also be studied, a very classical example would be the fluxional property of bullvalene that has been studied by NMR spectroscopy.

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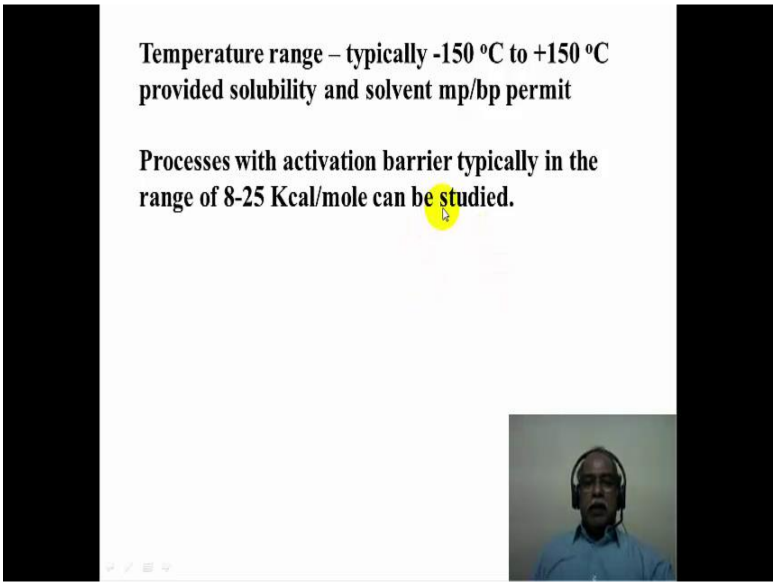

Temperature range – typically -150 °C to +150 °C provided solubility and solvent mp/bp permit

Processes with activation barrier typically in the range of 8-25 Kcal/mole can be studied.

Now, the sample tube in the NMR spectrometer can be either cooled up to minus 150 degree Celsius or it can be heated to plus 150 degree Celsius. This 300 degrees window is accessible provided the solubility and the solvent melting point boiling point permit such an operation. Now if the temperature of the sample can be cooled to such a wide range of temperatures then it is possible to study processes that has activation barrier typically in the range of about 8 to 25 kilocalories per mole can be studied using NMR spectroscopy.

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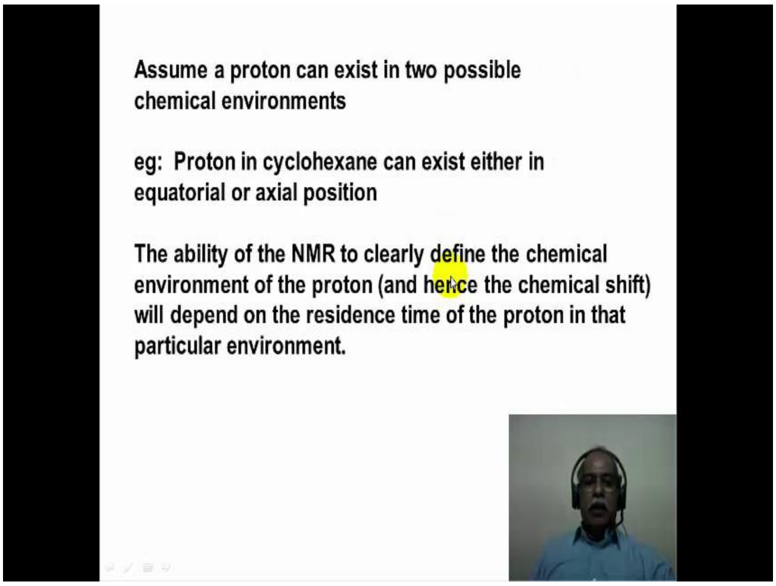

Assume a proton can exist in two possible chemical environments

eg: Proton in cyclohexane can exist either in equatorial or axial position

The ability of the NMR to clearly define the chemical environment of the proton (and hence the chemical shift) will depend on the residence time of the proton in that particular environment.

Now, let us look at the basic principle behind the study of variable temperature NMR spectroscopy for the dynamic processes of molecules. Now assume a proton can exist into 2 possible chemical environment. The example that I would like to site here is the proton in cyclohexane which can exist either in the equatorial position or in the axial position. The equatorial position and the axial positions are distinctly different chemical environment as we have seen earlier. So, if NMR can for example, distinguish whether a proton exist in the axial position or in the equatorial position that will be a very valuable information in terms of studying stereochemistry of cyclohexane kind of molecules. The ability of NMR to very clearly define the chemical shift environment of a proton and hence the chemical shift value of the proton will depend upon how long the proton is residing in that particular chemical environment.

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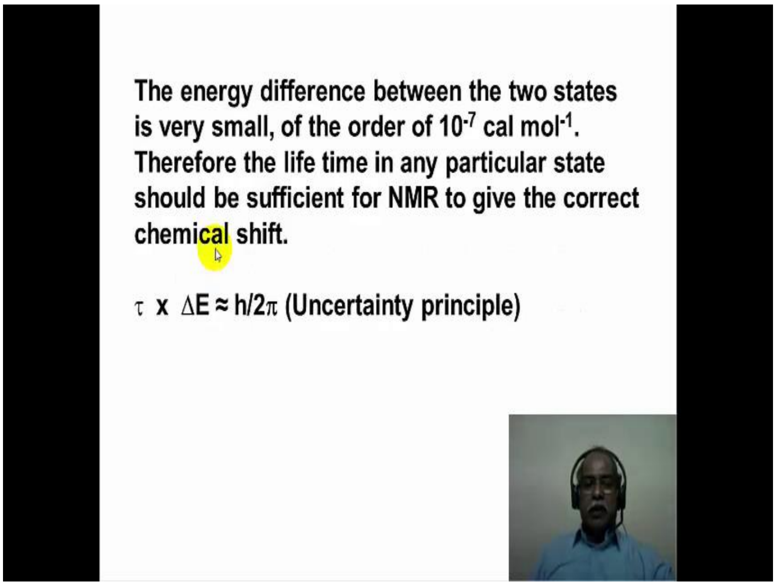

The energy difference between the two states is very small, of the order of 10^{-7} cal mol^{-1}. Therefore the life time in any particular state should be sufficient for NMR to give the correct chemical shift.

$\tau \times \Delta E \approx h/2\pi$ (Uncertainty principle)

If it is residing for example long enough then NMR will be able to tell the chemical environment to be either axial or equatorial. If it is too short, then also NMR probably will give an average value of the equatorial and the axial chemical environment positions. Typically the difference between the two states of residence is very small of the order of micro calories per mole. Therefore, the lifetime in any particular state should be sufficiently long enough in the NMR time scale to give the correct chemical shift value. The uncertainty principle is expressed here. Now this is the uncertainty principle expressed in terms of the residence time or the lifetime in a particular state and the difference energy between the two states. So, let us say for example, the axial and the equatorial states of particular hydrogen that has being present here. There can be a very large uncertainty in the energy state depending upon the lifetime of the molecule in that particular state.

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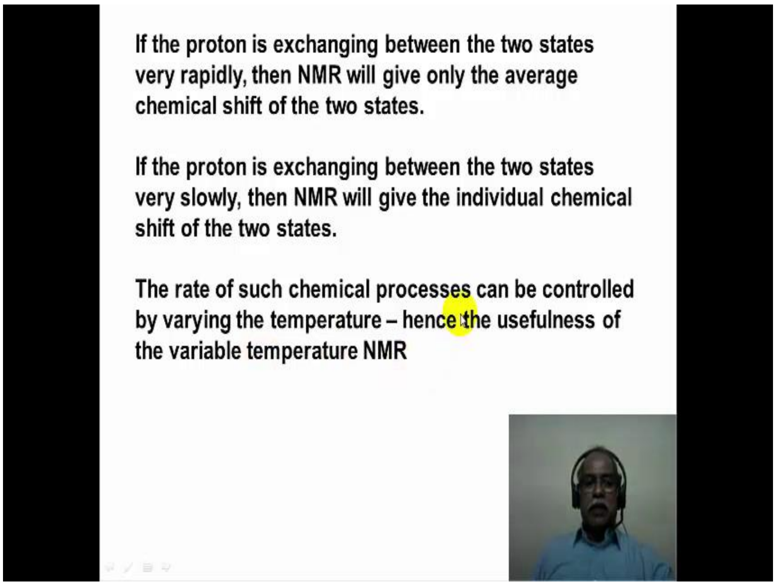

If the proton is exchanging between the two states very rapidly, then NMR will give only the average chemical shift of the two states.

If the proton is exchanging between the two states very slowly, then NMR will give the individual chemical shift of the two states.

The rate of such chemical processes can be controlled by varying the temperature – hence the usefulness of the variable temperature NMR

So, the NMR signal can be either very sharp or very broad depending upon 2 types of conditions that is met. What are the 2 types of conditions, if the protons is exchanging between the two states very rapidly, then NMR will only see an average chemical shift value of the two states the signal can still be will very sharp signal in this particular case nevertheless it will an average chemical shift of the 2 states. If the proton is exchanging between the two states very slowly in the NMR time scale, the NMR will give only the individual chemical shift values of the 2 states. In other words, NMR can distinguish the hydrogen to be either in the axial state or in the equatorial state in the case of cyclohexane. So, 2 signals will be obtained one corresponding to the axial and other one corresponding to the equatorial stage.

Now in between these two states neither too fast or nor too slow, the uncertainty will set in terms of the determination of the chemical environment of the particular proton. As a result of that in between states where the rate process is neither too high nor too slow, there will be a large uncertainty broadening up the signal is what one typically sees in the variable temperature NMR spectra. Now, what makes the variable temperature NMR a very special technique? Because chemical rate process can be controlled by temperature the rate of a reaction can be controlled by a temperature and hence the usefulness of the variable temperature NMR spectroscopy.

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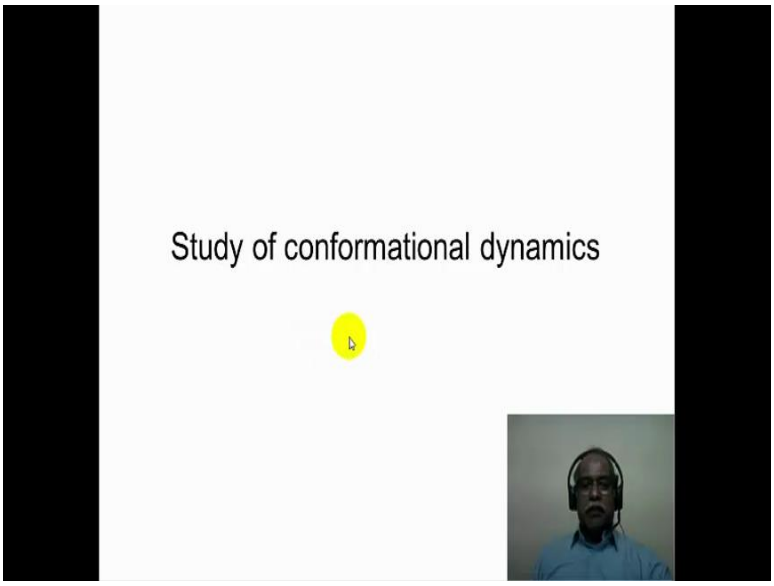

Study of conformational dynamics

Now, let us take the first example of the study of dynamic processes, which are based on conformational dynamics of molecules.

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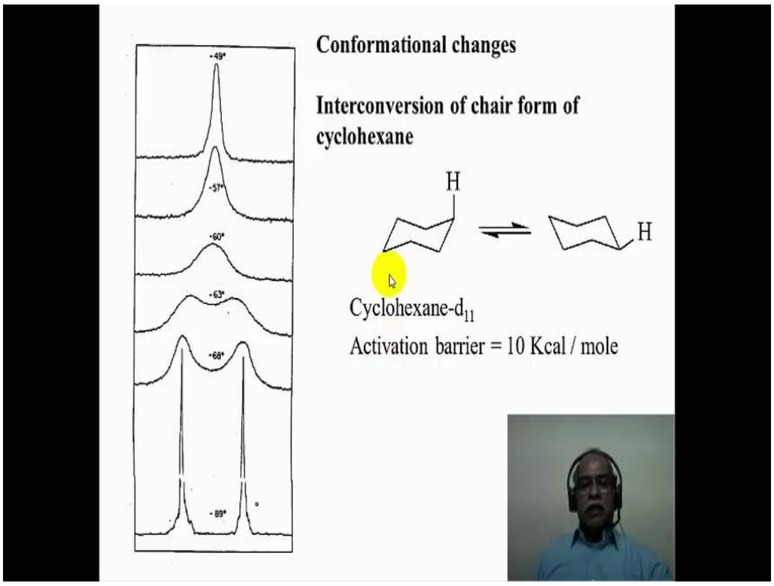

Conformational changes

Interconversion of chair form of cyclohexane

Cyclohexane-d_{11}

Activation barrier = 10 Kcal / mole

A very classical textbook example is the chair to chair interconversion of cyclohexane. This has been studied thoroughly by NMR spectroscopy. In order to study this process, the cyclohexane d 11 was taken. In other words there is only 1 proton that is present in the cyclohexane, all the other proton has been substituted with tutorium. So, depending upon the kind of chair conformation that cyclohexane has it either in the axial position or it is in the equatorial position. Now this study has been carried out by variable temperature NMR spectrum. The spectra are shown on the left hand side in this particular frame here. If we look at the NMR spectrum at minus 50 degree Celsius for example, which is already a low temperature process. NMR is unable to distinguish between the axial hydrogen and the equatorial hydrogen, what you see is only one signal corresponding to the average of the 2 states namely the axial state as well as in the equatorial state. In other words even at minus 50 degrees Celsius the rapid interconversion is taking place and in the NMR times scale NMR is enable to distinguish whether the hydrogen is residing in the axial state or in the equatorial state. What it gives is an average signal corresponding to neither of the states of the hydrogen being present in the either axial or in the equatorial position.

Now, let us go to the other extreme when that sample is cool to minus 89 degree Celsius for example. What happens is you see 2 signals corresponding, one corresponding to equatorial state of the hydrogen which is at the higher delta value, this is about 1.6 delta ppm in terms of the chemical shift value, and the other one which is coming at a lower delta value corresponds to the axial position hydrogen which is about 1.2 delta ppm or so. Now at this particular temperature, the interconversion of the 2 states is so slow that NMR is able to distinguish this particular conformer as the axial conformer, and this particular conformer as the equatorial hydrogen conformer corresponding to the 2 states.

Actually there is no energy difference between the 2 states the axial and the equatorial or essentially the same chair conformation. So, they should exist in equal population of one is to one ratio, and you can see from their height of the peak both the peaks are nearly equal in intensity. Therefore, the area under each of the peak is going to be approximately same. So, one is one mixture of the conformation where in the hydrogen is in the axial position, and another conformation where in the hydrogen is in the equatorial position corresponds to the 2 line that one sees in the spectrum. Anywhere in between the temperature, there is a large uncertainty as to whether the hydrogen is existing in the axial position or in the equatorial position, NMR is unable to distinguish between the 2 positions. And hence there is a large uncertainty associated with the measurement of the chemical shift which is reflected in terms of broadening of the signal.

Now, between minus 63 and minus 60 you can see there is a coalescence that is taking place. There are 2 peaks here which coalesces to only one peak at this particular temperature. So, this particular temperature is known as the coalescence temperature. The coalescence temperature is important, because several kinetic parameters can be obtained from the coalescence temperature. And above the coalescence temperature of course, you see an average signal of only if you take the chemical shift value of this, this will exactly the arithmetic average of this 2 chemical shift values. In other words, you can see that it comes at midpoint corresponding to this particular chemical shift to chemical shift value, midpoint is corresponding to this particular chemical shift and that is a average value of the axial equatorial conformation equilibrium being very rapid.

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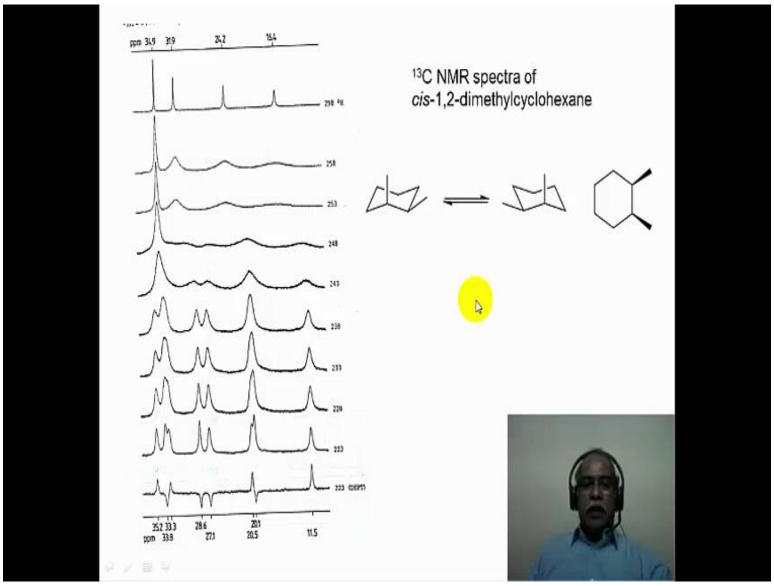
^{13}C NMR spectra of *cis*-1,2-dimethylcyclohexane

Now, let us take the example of the carbon 13 spectroscopy of 1, 2 dimethylcyclohexane particularly. The cis isomer of 1, 2 dimethylcyclohexane should have 1 axial methyl group and 1 equatorial methyl group. Both the axial and equatorial methyl group point in that same direction, and hence it is a cis isomer. If you want to refresh your memory about the dynamics of the cis isomer of the 1, 2 dimethylcyclohexane, please refer to (Refer Time: 09:49) book on stereochemistry of organic compounds. Now this particular molecule is a chiral molecule, and it does not have any kind of symmetry elements that is present here. Therefore, if this molecule where to exist in this particular form then all the carbons that are present in this molecule should be distinguish chemical shift wise and there should be 6 of the ring hydrogen so sorry ring carbons and 2 of the methyl carbons which are also chemically distinct, one is axial and the other one is equatorial.

So, one would see 8 signals in the carbon-13 NMR spectrum of such a molecule. Now what is a dynamic process that is taking place the dynamic processes is establishment of this equilibrium of one chair form going to another chair form. In the process, actually what happens is one of the enantiomer gets converted to the antipode of the enantiomer. In other words, this is a processes of resumization. Cyclohexane 1, 2 dimethyl cis isomer of 1, 2 dimethylcyclohexane is an example where it is a non resolvable chiral molecule, non-resolvable because it is rapidly undergoes a resumization by going from one chair form to another chair form which is a resumization processes itself. Now while going through this transformation it has to go through a transition state which look very similar to the plain or transition state. In other words, this chair form has to go to this particular chair form. At some point of time, in the transition state it as to sort of attain a planarity kind of a structure which is this particular structure and this structure has a plain of symmetry as you can see this molecule. So, this would be an a-chiral system where has this 2 conformation would be chiral in nature.

Now, let us look at the carbon-13 spectrum. This is the depth spectrum, in other words in this particular spectrum the CH 2 carbons will come as negative peaks and the CH and the CH 3 carbons will come has positive peaks in terms of the phase of the peak that is being seen you can have a negative phase or the positive phase. Depending upon whether it is a CH 2 in which case it is a negative phase or if it CH or CH 3 odd number of hydrogen being present then it would be a positive phase of the NMR signal. So, as I said if this molecule were to be existing in a frozen state without the conformational interconversion, there will be a one is to one mixture of these 2 isomers which are enantiomers. Enantiomers are indistinguishable by NMR spectroscopy, they are chemically equivalent. So, their chemical shift value of this axis equatorial carbon and the this equatorial carbon will be identical. So, one should see eight signal in the NMR spectroscopy of which four of them will be CH 2 type of carbon, 2 of them will be CH carbon, and two of them will be CH 3carbon.

So, if you see 4 signal which are in the negative phase one 2, 3, 4 these 4 signals correspond to the CH 2 and 2 of the CH and 2 of the CH 3 will have positive phase 1, 2 these are probably the CH carbons and these are the CH 3 carbons. So, there are 8 signals that are seen in the NMR spectrum carbon-13 spectrum of the cyclohexane. So, variable temperature is measured in the carbon-13 NMR spectrum of dimethylcyclohexane in this particular case. This is the normal carbon-13 spectrum whereas, this is the depth spectrum the depth spectrum is essentially recorded to distinguish between the CH 2, CH and CH 3 carbons. If you look at the normal carbon NMR spectrum also, you will see 8 signal 1, 2 another signal is merged with this 3, 4, 5, 6, 7th one is again merged it is not resolved so 7, 8. There are 8 signals that are very clearly seen in the NMR spectrum.

Now let us assume that this is sort of not frozen, it is undergoing a rapid interconversion between these 2 states. If it is going to rapidly inter convert between the 2 state the NMR is going to see the molecule as if this is a state that is being present, because this is very similar to a transition state structure between the 2 structures that are mentioned here. So, if NMR sees a signal corresponding to a structure of this kind where there is a planar symmetry, then you should see only half the number signals in the NMR spectrum that is 1 signal corresponding to the CH 3 here, which will be identical to this CH 3. One signal corresponding to this CH and this would be essentially identical to this CH, one signal corresponding to these CH twos and one signal corresponding to these CH twos. Indeed, when look at the spectrum at room temperature, where there is a rapid interconversion of one conformer and the other conformer. NMR is enable to distinguish the axial equatorial methyls. So, the methyls gives just only one peak in the NMR spectrum which is shown here for example.

So, the NMR spectrum should see 1, 2, 3, 4 only 4 signals should be seen. So, indeed only 4 signals are seen in the high temperature NMR spectrum. What do I mean by high temperature is at room temperature where the rapid interconversion is taking place. At low temperature or let us say for example, 223 kelvin or so, the interconversion is slot down considerable such that NMR is able to see the axial equatorial methyl separately and the conformation gives this is a chiral conformation, so eight different signals are seen in the NMR spectrum. So, the molecule is a beautiful example of essentially a chiral molecule existing in 2 enantiomeric forms. An enantiomeric being indistinguishable, you just to see as if there is only one type of molecule in the NMR spectrum of the cis dimethylcyclohexane 1, 2 dimethylcyclohexane at low temperature. Whereas, at room temperature close to room temperature essentially you see the average (Refer Time: 15:30) signal corresponding to 4 carbons in the NMR spectrum, because this would be the average of these 2 type of structures that you have in the NMR spectrum.

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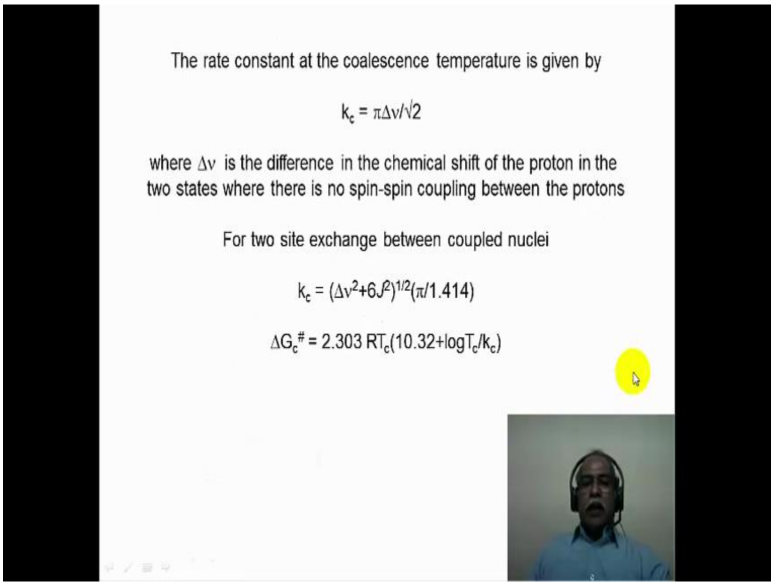

The rate constant at the coalescence temperature is given by

$$k_c = \pi\Delta\nu/\sqrt{2}$$

where $\Delta\nu$ is the difference in the chemical shift of the proton in the two states where there is no spin-spin coupling between the protons

For two site exchange between coupled nuclei

$$k_c = (\Delta\nu^2+6J^2)^{1/2}(\pi/1.414)$$

$$\Delta G_c^{\#} = 2.303\ RT_c(10.32+\log T_c/k_c)$$

Now, at the coalescence temperature, one can find out what is the rate constant of the (Refer Time: 15:47). The rate constant at coalescence temperature is given by this expression where k which is k c is the rate constant at the coalescence temperature which corresponds to pi delta nu. Delta nu is the difference between the chemical shift values of the 2 type of system, if it is a axial hydrogen and equatorial hydrogen delta nu corresponds to the difference between the chemical shift value of the axial hydrogen and the equatorial hydrogen divided by root 2. So, we can do a one point kinetics and get rate constant at the coalescence temperature using this expression provided there is no spin-spin coupling between the 2 protons. If there is a spin-spin coupling between the 2 side exchangeable proton then the coupling constant also gets into the expression. So, at this point of time, the k c would correspond to this particular expression that is given here. Now once you have k c at the coalescence temperature, one can also calculate the thermodynamic parameter in terms of the activation energy of that particular process using this expression, using the NMR technique, which would be a one point kinetic technique.

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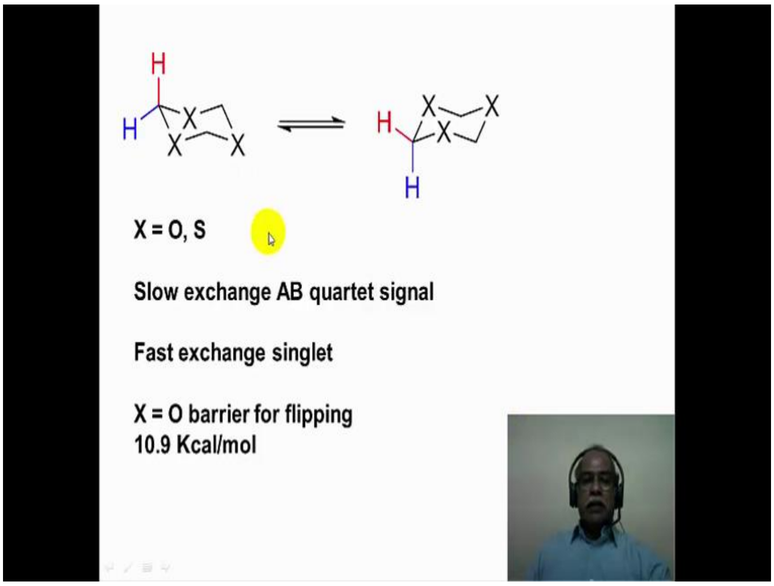

X = O, S

Slow exchange AB quartet signal

Fast exchange singlet

X = O barrier for flipping
10.9 Kcal/mol

Let us take another example of a chair-to-chair interconversion. It is not only cyclohexane that undergoes chair-to-chair interconversion. This kind of heterocyclic system where you have X is equals to oxygen or sulphur. In other words it is 1, 3, 5 trioxyn or 1, 3, 5 trithyne kind of molecules also undergo rapid interconversion from one chair form to another chair form. In the chair form interconversion is denoted by the axial hydrogen being red here, which becomes equatorial upon chair-to-chair interconversion. And the equatorial hydrogen being blue here which gets converted into the axial hydrogen during the chair-to-chair interconversion. Now, under the conditions are very slow exchange between these 2 molecules the NMR spectrum is going to be seen as a single spectrum of this particular molecule. The axial and the equatorial hydrogen are attached to germinal to this particular carbon, so they are going to be diastereomers topic in nature, so they would couple with each other. So, this coupling correspond to AB quartet kind of a signal in the NMR spectrum of such molecule.

In fact, this axial hydrogen is same as the axial hydrogen over here and the axial hydrogen over here the molecule as C 3 axis of symmetry. So, it does not matter which one of the methylene in groups that you take for analysis. Essentially you will get an AB pattern at low temperature. At room temperature, when it is rapidly inter converting between the 2 states of course, one cannot distinguish between the axial and the equatorial hydrogen, so essentially one gets only a singlet kind of an NMR spectrum at the room temperature or at a higher temperature where the rapid interconversion is taking place. Now, based on the variable temperature NMR study in case of 1, 3, 5 trioxane molecule the barrier for the flipping of one chair conformation going to the another chair conformation is very similar to the one that you for cyclohexane namely 10.9 kilo calories per mole. In fact, in the cyclohexane case the 10 kilo calories per mole activation barrier is probably the most precise value that is ever determined using a spectroscopy technique for such a conformation dynamic processes.

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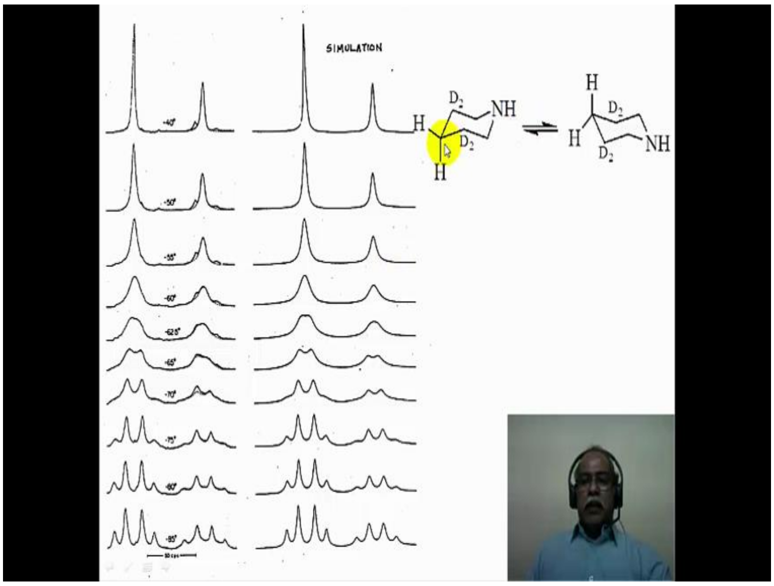

Now, let us take the example of piperidine as a molecule. In the case of piperidine, the 3 position and the 5 position are neutered. In other words substituted by deuterium, so that one can avoid the complication of coupling between these hydrogen and these hydrogen here in the NMR spectrum. So, what is present here is methylene group in the 2, 6 positions and another methylene group in the 4 position that is present in the molecule. Now this is the methylene region of the NMR spectrum of piperidine molecule. And you can see here at a very low temperature of minus 85 degree Celsius or so, there are 2 AB quartet seen here, 1 AB quartet has nearly twice the intensity of the other AB quartet. In fact, if you look at the hydrogen which are in the 4 position this would appear as an AB quartet at low temperature when there is not a rapid interconversion between the 2 states. Similarly, when you look at the hydrogens in the 2, 6 positions of this molecule also, you would see only a AB quartet corresponding to 4 hydrogen intensity that is the reason one of the AB quartet is twice as big as the AB quartet. So, this AB quartet which is in the 4 position which is away from the nitrogen has a lower chemical shift value. Whereas, the one that is adjacent to the nitrogen has a higher chemical shift value which is this particular AB quartet.

So, you see a 2 AB quartets corresponding to the diastereotopic methylene kind of a proton; in a frozen state where there is no rapid interconversion between the chair-to-chair interconversion between the 2 states. Now what happens if we heat the sample up to about minus 40 degree where the rapid interconversion start to take place the 2 AB quartet essentially collapse, because you can no longer distinguished the axial and equatorial position when it is rapidly undergoing interconversion from one chair form to the other chair form. So, this AB quartet collapse is to a singlet, this AB quartet also collapse us to a singlet. This corresponds to the 4 hydrogen in the 2 and 6 position, this corresponds to the 2 hydrogen in the 4 position which are these 2 hydrogen in this molecule.

Now such a dynamic process can also be simulated using computer simulation by putting in appropriate red constants for the processes. And essentially one can simulate not only the low temperature and high temperature spectrum, the line broadening at the intermediate levels can also be precisely simulated in the NMR spectrum and these are simulated NMR spectra and this corresponds to the experimental NMR spectra at various temperatures. Now, we can go from here for example, at low temperature, as you increase the temperature at one particular point, there is a coalescence temperature which is close to about minus 62.5 degree Celsius or so in this particular case and that coalescence temperature the AB quartet essentially coalescence to a single peak. It is somewhere between minus 60 and minus 62.5 degree Celsius or so, in this particular instance.

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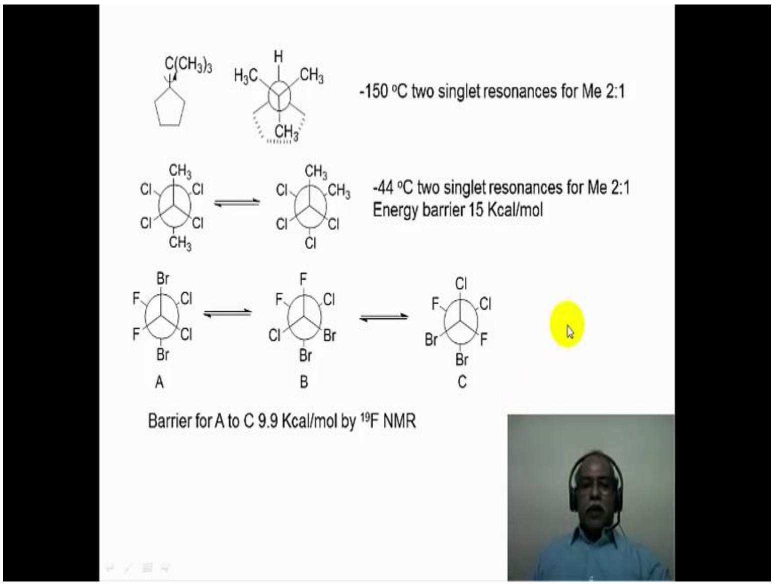

-150 °C two singlet resonances for Me 2:1

-44 °C two singlet resonances for Me 2:1
Energy barrier 15 Kcal/mol

Barrier for A to C 9.9 Kcal/mol by ^{19}F NMR

These are examples of simple carbon-carbon rotation or restricted carbon-carbon rotations which can be studied at low temperatures. Now normal temperature if we look at the tertiary butyl cyclopentane, there will be a rapid rotation between this carbon and this carbon. So, one will not able to distinguish the 3 methyl groups of the tertiary butyl group at ordinary temperatures. However, if the sample is cool to minus 150 degree Celsius, it is possible to freeze the molecule a form from undergoing rapid interconversion of conformation. This is a Newman projection formula of this 3 carbons that are seen here. In other words, this carbon is in the front and this carbon is in the back side of the Newman projection and the hydrogens are clearly shown of the cyclopentane ring and the hydrogen that is attached to this particular carbon is coming here.

Now if you look at this particular picture, this is actually the gauche conformation or the staggered conformation of this carbon-carbon bond rotation. Now if the carbon-carbon bond rotation is frozen, this is likely to be the most stable conformation because the bulky groups are far away from each other in terms of the position of the bulky groups. If that were to be the case these 2 methyl group should have a chemically identical environment and this chemical this particular methyl group should have a different chemical environment in comparison to the other 2 methyl groups. So, a sample measured at a very low temperature of minus 150 degree Celsius has 2 singlet in the ratio of two is to one, one corresponding to this particular methyl groups, which are these 2 methyl group with a intensity of two, and this particular methyl group come separately with the intensity of one because this has 6 hydrogens, these 2 methyl group and methyl group has 3 hydrogen that is why the intensity ratio two is to one

Now, let us take the example of 2-2 to 3-3 tetrachloro butane n butane for example. Here the chlorine groups are fairly bulky groups. So, one can freeze the rotation of this particular molecule, the carbon 2, carbon 3 bond rotation can be frozen. Under these conditions, if you look at very low temperature NMR spectrum, these are probably the 2 confirmations which are going to be the most populated conformation in the among the various conformations that are possible, because these are the 2 conformers which are staggered conformation. Now if we look at this conformation alone, the 2 methyl groups are chemically identical environment, they are not distinguishable because they are flanked by 2 chlorines in each case. So, if you measure the spectrum of this molecule alone then there will be only one signal for the 2 methyl group.

Similarly, if you measure the NMR spectrum of this conformational alone, there is a C 2 axis of symmetry bisecting this molecule in this particular way. So, this 2 methyl groups are changeable by C 2 operation. Therefore, they are chemically identical in their environment, but the chemical environment around of this 2 methyl groups are very different from the 2 methyl groups here. Here the methyl groups are flanked by 2 chlorines, whereas here one is flanked by a chlorine the other one is flanked by a methyl group. So, chemical shift wise, although these 2 are identical, these 2 are different from the other 2 which is in the other confirmation. In other words the methyl group in this conformation have a different chemical shift environment compared to the methyl group in this particular conformation. If this 2 conformations are the most populated conformation at very low temperature, then this should be even more favorable because the 2 methyl groups are anti where this 2 methyl groups are gauche with respect to each other.

So, at low temperature of minus 44 degrees Celsius 2 singlet resonances are seen in this particular spectrum corresponding to two is to one ratio. In other words, this conformer population is twice as much as the conformer population which is correspond to this one. The activation barrier for the carbon-carbon bond rotation in this molecule is calculated to be about 15 kilocalories per mole. One can use various nuclei for the variable temperature NMR spectrum we have already seen one example of the carbon nuclei being used in the variable temperature NMR spectrum of the cis 1, 2 dimethylcyclohexane. Here fluorine nucleus is used for the conformational study of this difluoro dibromo dichloroethane derivative.

Now if you look at this various conformations, the one where the 2 bromines which are the bulky groups in this particular system which are the farthest away from each other in this particular conformation. In other words conformation A is going to be the most stable conformation, conformation B and C are going to be the least stable conformation of which for example, C is going to be the least stable because the 2 bulky groups which are bromine and that 2 chlorine groups which are also bulky with in comparison to the 2 fluorine for example, this will be the least preferred conformation and this will the most preferred conformation.

The barrier to go from A to C has been calculated using the fluorine NMR spectroscopy. The fluorine NMR spectrum, if you measure the spectroscopy at very low temperature, you can see one signal corresponding to these 2 fluorine, one signal corresponding to these 2 fluorine, and one signal corresponding 2 these fluorine here which are chemically distinguishable from one to another in terms of A, B, C being chemically distinguishable. The activation barrier to go from A to C has been calculated by the variable temperature NMR to be about 9.9 kilo calories per mole.

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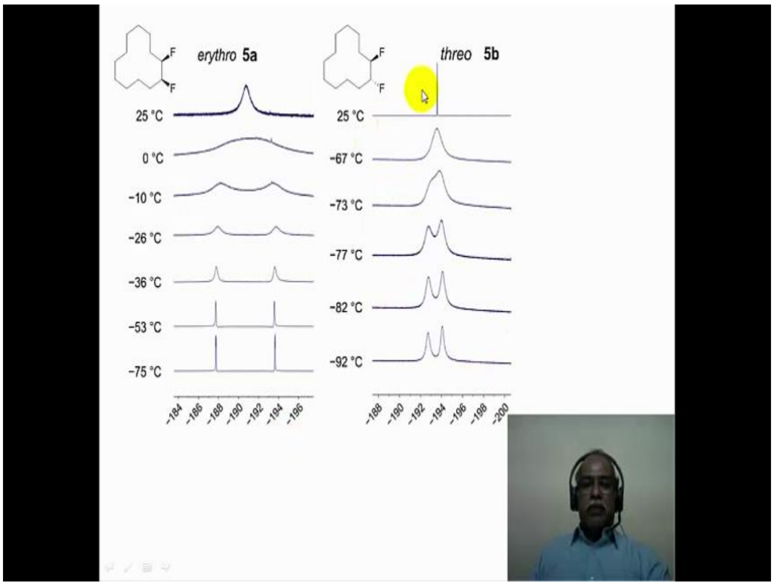

These are some exotic examples of fluorine NMR being used for the fluorine 19 has an isotope which is a spin half isotope. So, it is just like a proton spectroscopy that we are talking about. Spin half nucleus is what we are talking about. There are 2 isomers possible for this 1, 2 disubstituted derivative or this time this is a large macrocyclic rings, so it should undergo a rapid conformational change because of the size of the ring is fairly large. And these 2 fluorines are in the erythro isomer and this 2 fluorines and in the threo isomer as it is in the erythro and threo the 2 fluorines are not distinguishable they are nearly identical chemical environment with respect to each other.

So, at room temperature when you measure the spectrum where this undergoes a rapid interconversion with among the various confirmation NMR would be able to distinguish between this 2 fluorines being either axial or equatorial in this particular macrocyclic system. So, it essentially gives only one signal for the threo and one signal for the erythro for the 2 fluorine atoms, and this is essentially seen at room temperature. When you cool it to very low temperatures of minus 75 in the case of the erythro and minus 92 in the case of threo the signal splits into 2 singlet, 2 singlet because these 2 fluorines are now distinguishable with respect each other. So, one can see 2 fluorine separately one probably corresponds to an axial kind of a position, the other one corresponds to an equatorial kind of a position. Similarly in this molecules also the 2 fluorines becomes distinguishable and that is the reason you see 2 signals here.

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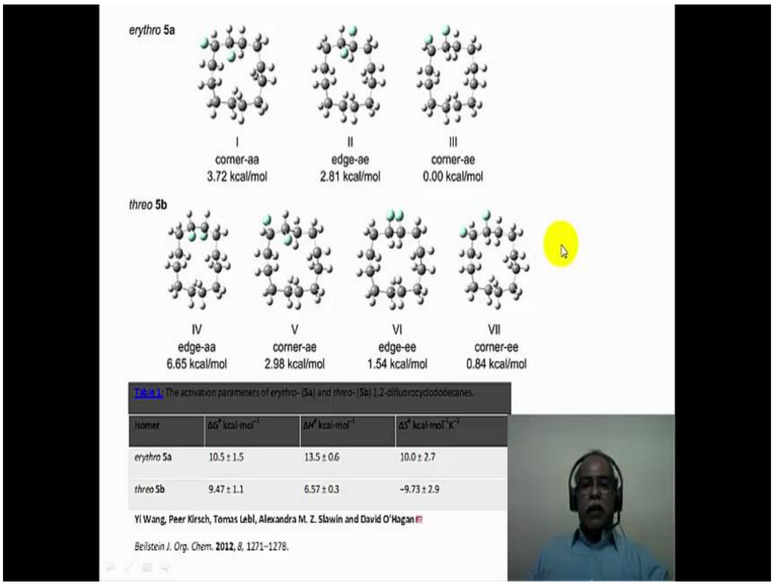

Table 1: The activation parameters of *erythro*- (5a) and *threo*- (5b) 1,2-difluorocyclododecanes.

Isomer	$\Delta G^{\ne}$ kcal·mol^{-1}	$\Delta H^{\ne}$ kcal·mol^{-1}	$\Delta S^{\ne}$ kcal·mol^{-1}K^{-1}
erythro 5a	10.5 ± 1.5	13.5 ± 0.6	10.0 ± 2.7
threo 5b	9.47 ± 1.1	6.57 ± 0.3	-9.73 ± 2.9

Yi Wang, Peer Kirsch, Tomas Lebl, Alexandra M. Z. Slawin and David O'Hagan

Beilstein J. Org. Chem. **2012**, *8*, 1271–1278.

This has been theoretical calculated as the number of various conformations that are present in this molecule. If you look at this particular conformation, where the 2 fluorines are given the the sayan color the 2 fluorines are indicated by the sayan color. In this conformation, the 2 fluorines have chemically different environment and this is a most stable in terms of the relative energy being zero kilocalories per mole. This is 2.81 kilo calories higher energy compare to this 3 conformation one is about 3.7 2 kilo calories higher energy compare to conformation three. So, in conformation three, the 2 fluorines are different and that is why a at low temperature one sees this 2 fluorine separate signals. At room temperature, there is rapid interconversion among the various conformation. So, the 2 fluorines become indistinguishable at the higher temperature. Same is the case with the kind of the threo isomer also; the 2 fluorines have distinctly different chemical environment at low temperature. This is a lowest conformation energy compared to the other conformers this would be highly populated at low temperature. So, the 2 fluorines are different in chemical environment. So, 2 signals at low temperature at high temperature or at room temperature there is rapid interconversion of this various conformers. So, the 2 fluorines become indistinguishable. As a result there is only one signal that is present in the high temperature NMR spectra.

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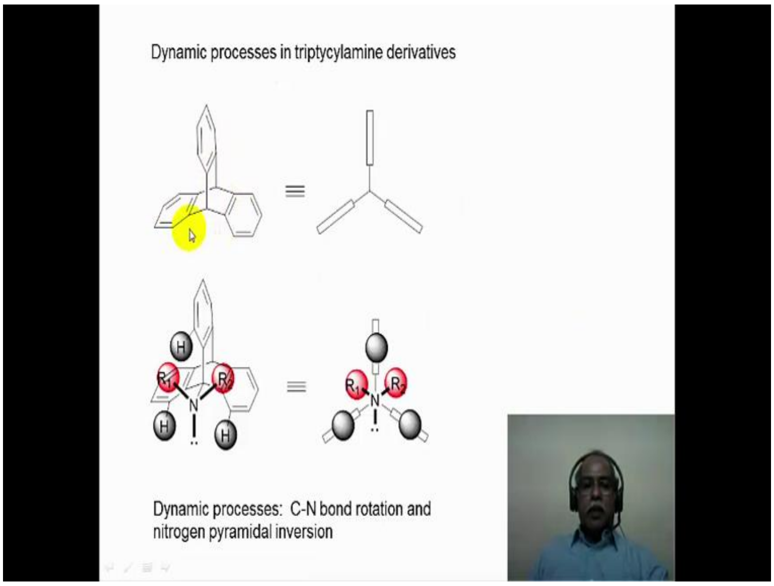

Dynamic processes in triptycylamine derivatives

Dynamic processes: C-N bond rotation and nitrogen pyramidal inversion

Now, this is a propeller shaped molecule, this is called a tryptophan sorry triptycene not tryptophan this molecule is call triptycene, and this is a propeller shaped molecule for example. In this molecule, when you put a substituent here that substituent is hindered from rotating freely by this 3 hydrogens which are indicated. In other words cartoon representation of this molecule is shown here. This is a conformation of the molecule you can see very clearly that in the nitrogen substituent that is present in this cavity the free rotation of the nitrogen is going to be hindered by the bulky groups that are being present in the nitrogen interacting with this 3 hydrogen which occupy this positions. So, the rapid rotation of the carbon nitrogen bond is not possible in this molecule that is one process. The second process is the nitrogen can also undergo inversion pyramidal inversion, the lone pair is down here the lone pair can also become up by the pyramidal inversion. So, this is essentially a propeller shaped molecule where the carbon-nitrogen bond as restricted rotation in this molecule.

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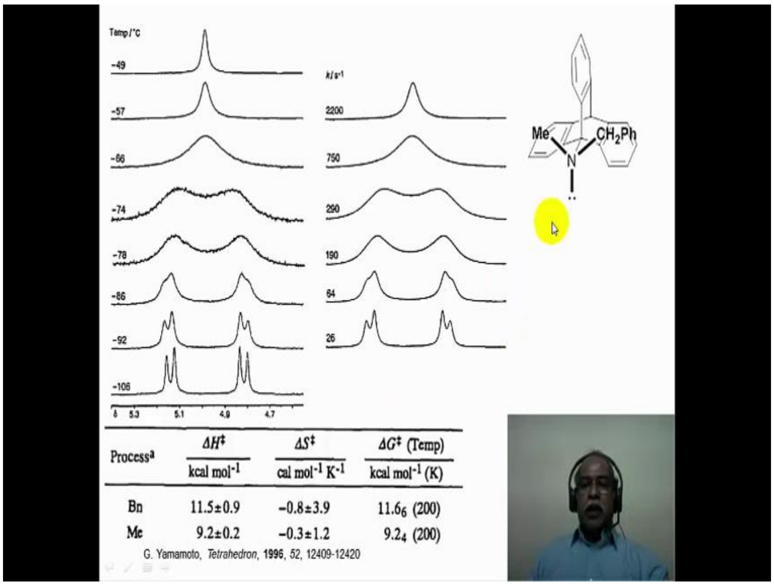

Process[a]	$\Delta H^\ddagger$ kcal mol^{-1}	$\Delta S^\ddagger$ cal mol^{-1} K^{-1}	$\Delta G^\ddagger$ (Temp) kcal mol^{-1} (K)
Bn	11.5±0.9	−0.8±3.9	11.6_6 (200)
Me	9.2±0.2	−0.3±1.2	9.2_4 (200)

G. Yamamoto, *Tetrahedron*, **1996**, 52, 12409-12420

This has been studied by NMR spectroscopy. Now if you look at this molecule this would be a chiral molecule, if this is conformationally frozen in this particular state, the reason being there is no planar symmetry or there is no s n symmetry present in this molecule. So, as it is the molecule is chiral in the frozen conformation like this, when there is no rapid carbon nitrogen bond rotation. So, this 2 CH 2 hydrogens, these 2 hydrogens on the CH 2 become diastereotopic in nature. So, we are looking at this CH 2 hydrogen of this molecule; at low temperature when there is no rapid rotation of the carbon hydrogen bond because of the chiral environment that is present in this molecule. The CH 2 appears as an AB quartet because CH 2 is a diastereotopic hydrogen in this particular system.

When this becomes rapidly inter converting in terms of the carbon nitrogen bond rotation being very high at a higher temperature; in other words at minus 49 degree Celsius or so that carbon-nitrogen bond becomes rotatable easily. At those temperatures, the CH 2 is no longer distinguishable and is suggest to see a singlet for the CH 2 hydrogen in this particular molecule. And this is simulated spectrum putting in this rate constants corresponding to various temperatures. One could easily simulate the spectra that is shown in the experimental side which is this side and this is a simulated spectra. Based on the variable temperature NMR spectrum the activation barrier for this particular process has been given in this table as 11.6 kilo calories per mole for the n benzyl derivative and for the n methyl derivative is about 9.24 slightly smaller when that is a n methyl group in this system.

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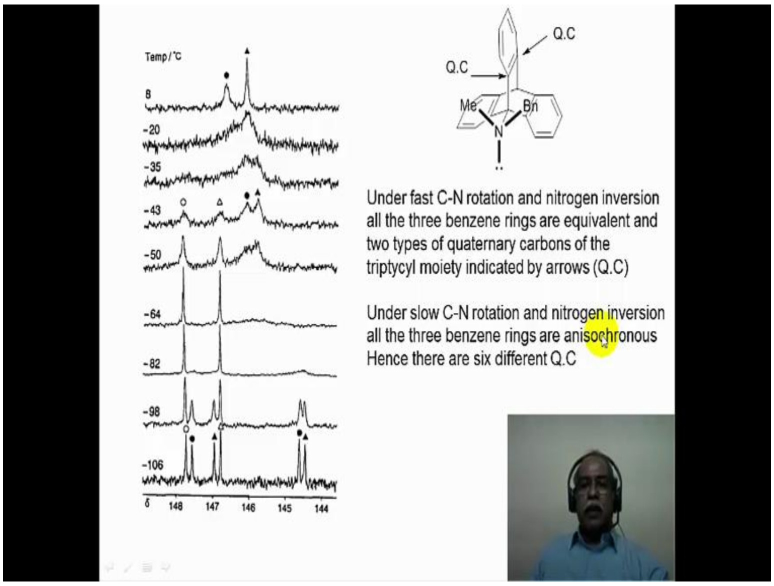

Under fast C-N rotation and nitrogen inversion all the three benzene rings are equivalent and two types of quaternary carbons of the triptycyl moiety indicated by arrows (Q.C)

Under slow C-N rotation and nitrogen inversion all the three benzene rings are anisochronous Hence there are six different Q.C

One can also look at it from the carbon-13 NMR spectroscopy point of view, these are the quaternary carbons labeled as QC there are 3 quaternary carbons in the front one, 2 and 3 these are the quaternary carbons. The back side also there are 3 quaternary carbons, which are aromatic carbons one, 2 and 3 if this molecule is truly chiral at low temperature one should be able to see this 3 carbon separately, and the backside 3 quaternary carbons also one should be able to see it separately. So, this is what happens at low temperature when the spectrum is shared at minus 168 degree Celsius. There are 6 carbons that are seen corresponding to carbon number one, carbon number two, carbon number 3 which is in the front; carbon number four, carbon number five, carbon number 6 in the back side which essentially constitute the 6 lines that you see in the carbon-13 spectrum of this particular compound. If the molecule is undergoing a rapid rotation and the chirality is lost as a result of that then all the 6 3 carbons in the front and the 3 carbons in the back should come as single signal. So, essentially, you see 2 signals, one corresponding to the carbons in the front the other one corresponding to the carbons in the back side of the molecule which are these 3 carbons which are present.

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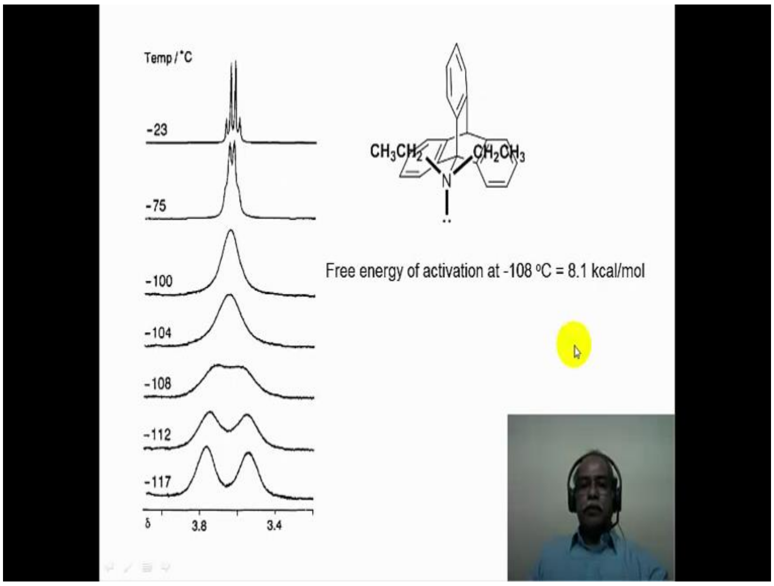

Free energy of activation at -108 ºC = 8.1 kcal/mol

When the chirality is removed by putting 2 identical groups on the nitrogen. This is a n diethyl group where as the previous examples is n-methyl n-benzyl group and that is what make this molecule chiral a chirality is removed now. So, essentially what you see is the 2 methyl groups sorry the 2 hydrogens on the methyl group essentially appearing as a simple cortex in this particular case. And when these molecule is in frozen state, there are 2 conformations possible; the methylene group can be either in this position or it can be in position also. So, 2 different environment is what do seen for the methylene which is seen by the 2 hums that are seen, it is not at fully this temperature is not low enough for example, to completely freeze out the molecule. So, that is why you see broadening up the line.

If it is possible to measure the spectrum even at low temperature perhaps one would see 2 cortex kind of a system is what one would see in this particular case. So, the 2 methylenes become indistinguishable and become a single signal at high temperature; at low temperature these 2 methylenes are possible to distinguish from one another because of the pyramidal inversion that is taking place. So, activation barrier for this process is about 8.1 kilocalories per mole for the rotation of the carbon nitrogen bond in this molecule.

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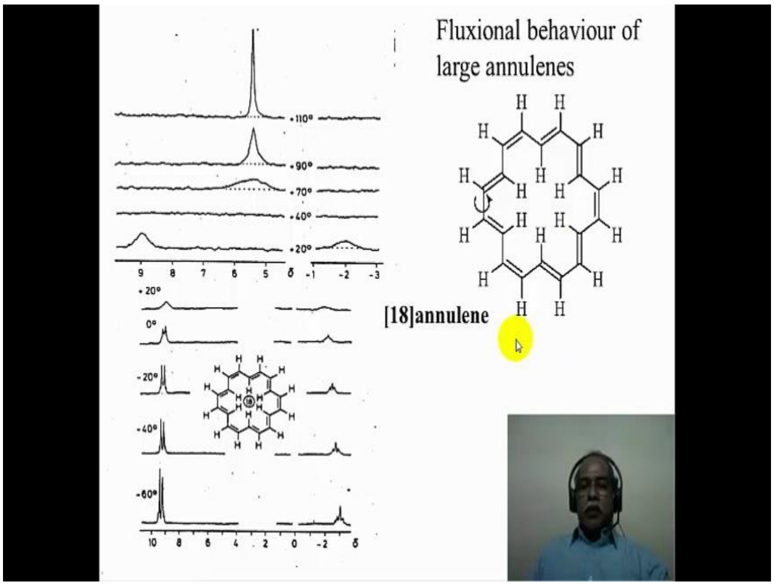

Fluxional behaviour of large annulenes

[18]annulene

Here is another very interesting example of an 18 annulene molecule. Please recall the isotropic effect of aromatic ring current effect. This is an aromatic molecule because it is an 18 annulene molecule corresponding to 4 n plus 2 electrons system. Now, there are 6 hydrogens in the cavity of the molecule and there are twelve hydrogens on the periphery of the molecule. So, if this is truly aromatic and planar in nature this 6 hydrogen should be highly shielded because they come in the shielding zone where as these twelve hydrogen should be highly deshielded because they come in the deshileding zone of the ring current effect of an isotropic this particular molecule. However, the molecule is big enough to undergo conformational change. In other words, if you rotate this carbon-carbon single bond this hydrogen can be brought in and this hydrogen can be taken out. So, the hydrogens which are originally inside can go out, and the hydrogen which are originally in the outside peripheric can also come inside 6 at a time. So, there is possibility of a rapid interconversion between the inside hydrogens and the outside hydrogen.

So, if such a process is taking place very rapidly, the NMR would not be able to distinguish between the hydrogens which are inside and the hydrogens which are outside. In fact, when the spectrum is measured at plus 110 degree Celsius, a sharp singlet is what is seen in the molecule for all the 18 hydrogen, there are no other hydrogens which are distinguishable in this molecule. The inside outside process, in and out process is what is taking place rapidly by carbon-carbon bond rotation. So, as a result ones see all the eighteen carbon as a singlet in this particular system.

Now see what happens at low temperature when the spectrum is measured at minus 60 degrees Celsius, but minus 60 the molecule is frozen and it is probably in the planar most stable conformation because it is a aromatic system. If it is non planar of course, it will not be aromatic. In fact, it a probably goes through a non planar transition state when it is undergoing a rapid interconversion of the inside hydrogens going out and the outside hydrogens coming in. Now at the very low temperature, when the molecular conformation is frozen in this particular fashion, the inside hydrogens can be very clearly seen at minus 3 delta ppm which is this signal here as a multiplet, and the outside hydrogen which are the 12 hydrogen can also be seen around 9.5 ppm or so delta. So, this is a highly deshielded hydrogen aromatic hydrogen; this is a highly shielded hydrogen which is also aromatic, but it is in the core of the aromatic unit in this particular case.

Now, there are 12 hydrogens in this particular multiplets and the 6 hydrogen in this particular multiplets. So, one has to take arithmetical average of the the statistical average of this 2 not the arithmetical average, the statistical average of this 2 chemical shift values attain the chemical shift value of the average doubt signal which is this particular signal. In between, we can see there is a large uncertainty associated with the determination of the chemical shift value; particularly, if you look at plus 40 degree Celsius the uncertainty so much that you do not see any signal also. You just see a flat line NMR for this particular spectrum for this particular compound and uncertainty so much so that you do not see any signal at plus 40 degree. This is a scenario which is an interesting scenario that you measure in NMR spectrum and you do not see a signal insight of the fact there is a sample that is present because of the uncertainty principle essentially wipes out the signal to be a flat line in this particular case.

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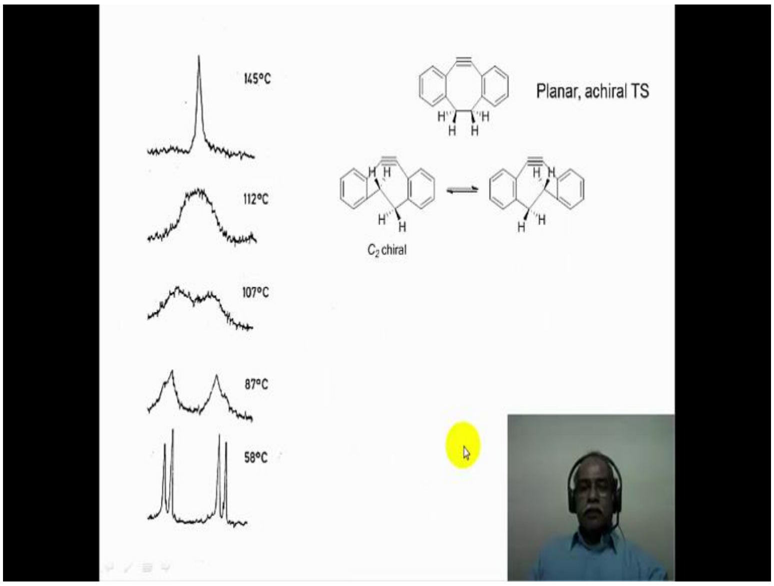

Another example, a very similar example to the cyclohexane system that we talked about. This is a this is a cycloalkane is a strained system. The molecule is not planar as it shown. The molecular conformation is a C 2 symmetry conformation which is the chiral conformation. The molecule can undergo C 2-C2 kind of a this is also C 2 symmetry and this is also C 2 symmetry and they are mirror images of each other they can undergo rapid interconversion by this carbon coming down, and this carbon going up which is the conformational change that we are talking about in this case. And such a conformational change would make the molecule look like this one in the transition state. If it were to this conformation, this as a planarity associated plane of symmetry associated with the molecule. So, this is a chiral transition state. So, at 145 degree Celsius for example, this molecule sort of NMR point of view looks like this and all the methylene hydrogen are equivalent, so you essentially get a singlet at high temperature.

At low temperature, if it has to be a chiral conformation like this, these 2 hydrogen will be diastereotopic because this is a chiral molecule, so diastereotopic hydrogen. These are enantiomers which are indistinguishable nevertheless within the enantiomer one of the enantiomer, this CH 2 will be a diastereotopic hydrogen which is identical to this CH 2 because of the C 2 symmetry. So, such a diastereotopic hydrogen gives AB quartet which is nicely seen at 58 degree Celsius or so. So at room temperature, when you measure the spectrum this is what you are going to see essentially AB quartet for this molecule because it is a chiral conformation that we are dealing with in this particular case.

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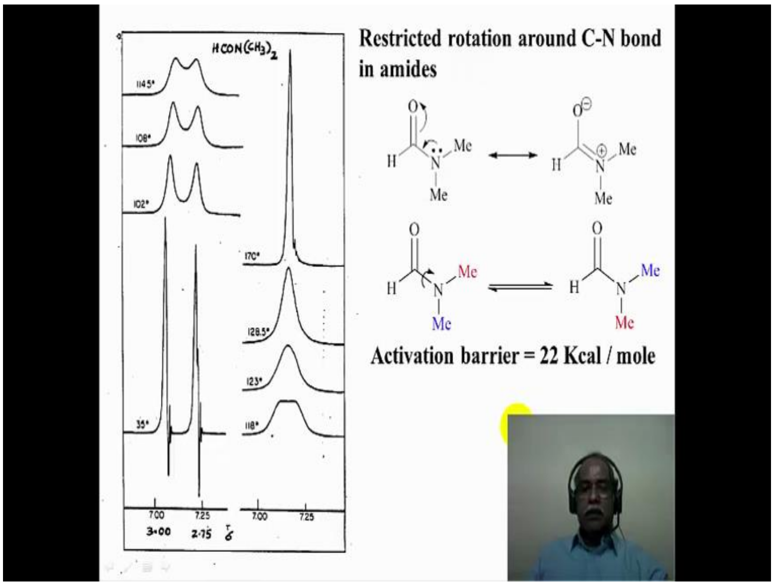

Restricted rotation around C-N bond in amides

Activation barrier = 22 Kcal / mole

This is another standard textbook example of a restricted carbon-nitrogen bond rotation in amides n m dimethyl form amide is discussed here. Now because of the participation of the nitrogen lone pair o delocalization onto the oxygen, the molecule attains a sort of a double bond character between the carbon-nitrogen bond because it has a double bond character, it activation barrier for free rotation is fairly high. So, this molecule does not undergo free rotation at room temperature. Activation barrier calculated from the variable temperature NMR spectrum is about 22 kilo calories per mole. So, at room temperature, this molecule can be giving 2 signals corresponding to the red methyl and the blue methyl; the red methyl is cis to the oxygen, the blue methyl is trans to the oxygen; chemical shift environment wise this will be different from this particular methyl group. So, as a result of that this molecule essentially under the conditions of room temperature will give 2 signals for the 2 methyl groups and you see 2 signals at room temperature around 35 degrees you see 2 signal. One that is next to the oxygen cis to the oxygen probably this particular signal; one that is trans to the oxygen is probably this particular signal here.

And if it is undergo rapid interconversion, this 2 methyl groups will interchange it is place the blue now has become the cis to the oxygen, and the red has become the trans to the oxygen. If such a rapid interconversion wise to take place the coalescence will take place and the 2 methyl will essentially appear as a singlet. In fact, at 170 degree Celsius the molecule shows a singlet for the two-methyl groups. So, because of the restricted rotation having this kind of a barrier you have to heat up this sample to high temperature before coalescence can take place. So, coalescence temperature is roughly 123 or so, because you can still see 2 peaks in this region here at 180 degree eighteen degrees. So, the coalescence takes place around 120 or so, which is corresponding to the coalescence temperature. Above the coalescence temperature, you have a sharp singlet; and below the coalescence temperature, you have 2 signals corresponding to the 2 methyls which are indicated by color coding.

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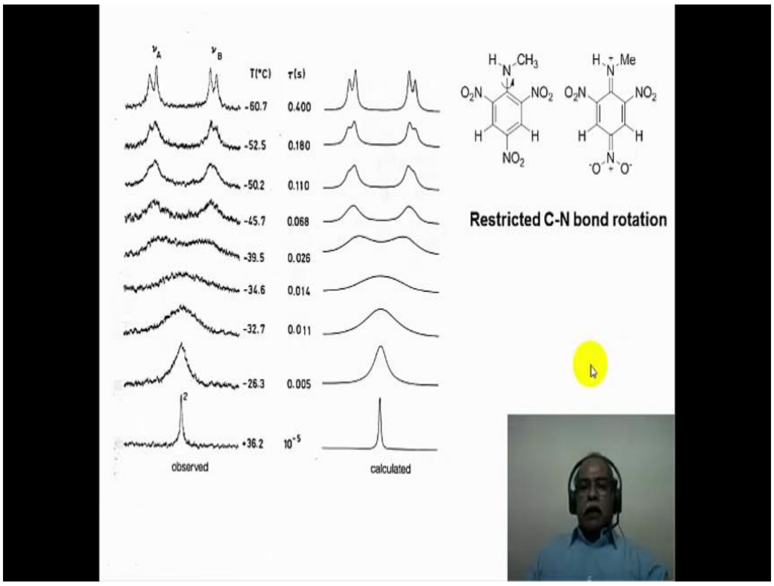
Restricted C-N bond rotation

Here is the last example of this particular lecture. We are talking about again a restricted rotation of the carbon-nitrogen bond. This is a trinitro n methyl aniline is the molecule; trinitro n methyl aniline they are 2 hydrogens in the aromatic unit. Suppose, if there is a restricted rotation around the carbon-hydrogen bond, if the molecule can be represented like this then this 2 hydrogen are no longer in the same chemical environment, it should be possible to distinguish them. And if there is a coupling between these 2 nitrogen which is a meta coupling. So, this these should doublet and this also should be doublet due to the meta coupling in this particular molecule. However, if there is a rapid rotation of the carbon nitrogen-bond, these 2 hydrogen chemical environment will average out it will give only a singlet. Indeed at room temperature, you do see only a singlet that at very low temperature when there is a restriction of the carbon-nitrogen bond rotation this methyl group in this nitrogen makes this hydrogen and this hydrogen distinguishable chemically.

So, what you see is an AB quartet corresponding to the meta coupling between the AB system which is this coupling that we are talking about. This is a simulated spectrum based on the computer simulation, using this kind of a time lifetime of this molecule for the various rotational rate constant is what is the inverse of this will be the rotational rate constant of the process that we are talking about. So, we are not done with the dynamic processes of NMR. In the next module also, we will continue with the dynamic process of frictional molecule and certain organic, organometallics examples of the molecular dynamics by variable temperature NMR. So, see you in module-14 and continue with this lecture in that particular module.

Thank you very much.