Advanced NMR Techniques in Solution and Solid-State
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Module-54
MQ and Spin System Filtering
Lecture – 54

Welcome all of you. In the last couple of classes, we started discussing about multiple quantum NMR. We extensively discussed and we understood for multiple quantum, the transitions that are other than + or – 1, where the change in the magnetic quantum number delta M between any two energy states, is other than + or – 1 are called multiple quantum. They are forbidden transitions, you cannot directly detect them. That is what I said. But however, indirectly we can detect them. We saw that in one of the pulse sequences in the homonuclear multiple quantum NMR, how we can detect multiple quantum NMR spectrum. What is the basic requirement for multiple quantum to be detected? I said, the spin systems should be coupled. You can have two or three spins or four spins, number of spins coupled. One of the coupling may be 0, no problem. But they should be part of the couple spin system and the couplings should be reflected to the NMR spectrum. Only then we can see multiple quantum. That is what we observed. And also, we took the example of zero quantum and double quantum of two coupled spins. For the double quantum transition, the two spins will be simultaneously flipping. In the two spins case there is no passive spin to give rise to coupling. As a consequence, the local field is only the sum of the chemical shifts. So, in the double quantum NMR of two coupled spins, you get a single peak at the sum of the chemical shifts of two coupled spins and there is no splitting, get only a single peak. On the other hand, for the zero quantum of two couple spins, we get a peak at the difference of the chemical shifts. And again there is no passive spin. As a consequence, there is no splitting of that transition. So, you get single peak for double quantum and zero quantum or two couple spins. And the chemical shifts also we know at the sum or the difference of chemical shifts for DQ and ZQ. We also went through the multiple quantum of three coupled spins and more also. Just to understand the splitting pattern, we understood the coupling pattern of DQ and ZQ of two spins in three coupled spin systems.

Now, the third spin is a passive spin. If I take three spins, there are three possibilities of double quantum. Consider A, M and X there could be AM double quantum, AX double quantum and MX double quantum. All the three are there. And the passive spin is the third spin. So that gives rise to splitting of the double quantum line, double quantum transition because of the two spin states of the passive spin.

So, double quantum and zero quantum spectrum of three coupled spins are going to be doublets. And we understood, what is the frequency? What is sum? Where it comes? And the separation, what is separation etc. The separation of the double quantum in the three spin cases is the sum of the J coupling between active spins and passive spins. We extended similarly for ZQ. It is difference of the coupling between active spins and passive spin.

That also we understood and then we went to four spin, five spin, six spin examples. We understood how many transitions one can get in different spin systems, coupled spin system. How many multiple quantum spectrum transitions are there in different quantum. And in the four spin case, we also saw what happens if we go to DQ? Then two are passive spins and each passive spin will couple to two active spins gives a doublet with some separation. And another active spin coupled to the two passive will give rise to another doublet. Like that we get two sets of doublets, four lines will be there; and one larger separation correspond to one sum of the couplings and smaller separation correspond to another sum of the couplings. Like this we extended and understood everything; and then we understood the pulse sequence for the homonuclear multiple quantum detection.

And also, we understood how we can utilize this to understand the relative signs of the couplings in a weakly scalar coupled three spins case; A, M and X. We knew by using DQ and ZQ we can find out the relative signs of the couplings; that is fine. After that now, I will take one more simple application of the multiple quantum before we jump on to altogether a different topic today; that is called solid state NMR.

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Spin System Filtering

So, this is another application of multiple quantum NMR, called spin system filtering.

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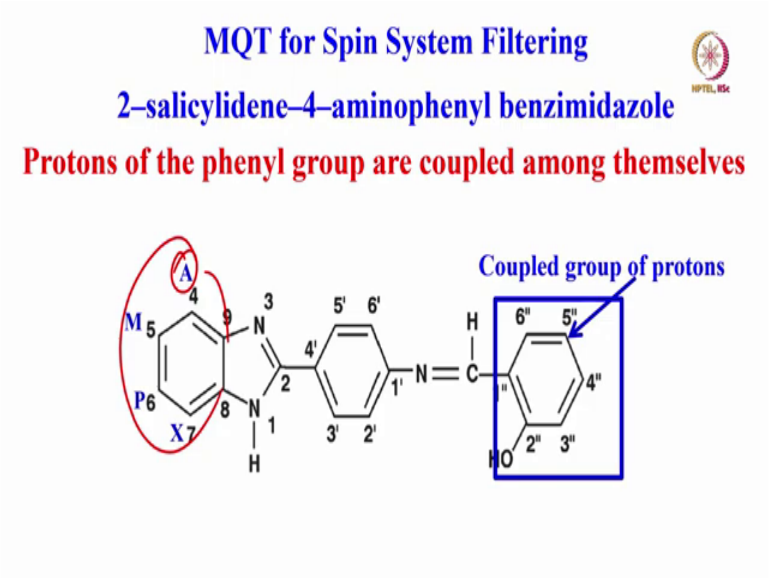
MQT for Spin System Filtering

2–salicylidene–4–aminophenyl benzimidazole

Protons of the phenyl group are coupled among themselves

Coupled group of protons

We will start like this, the multiple quantum how we can use for spin system filtering. It can be understood by a very simple example, on a big molecule like this. There are three phenyl groups for this molecule; and the protons of this phenyl group are coupled among themselves. For example, A, M, P and X here and four protons here and four protons here. Of course, forget about OH. All others are coupled among themselves.

They form couple group of spin systems. So, now, I want to tell you one thing, how we are going to get. How many transitions we are going to get. And how difficult it is to analyze the single quantum spectrum of such molecules. For regions of spectral complexity, if you consider the proton A, A can have a coupling with M give rise to JAM it can couple with the

P gives JAP; and then couple of X gives JAX. And similarly, JMX and JMP and also JPX; all couplings. In this phenyl group A spin give rise to three couplings, M will give two couplings and P gives to one coupling. So many couplings are there. And this one forms a coupled group of spin system. Similarly, this forms a coupled group, this also forms a couple group of spin system. There are three independent groups of coupled spin systems in this molecule.

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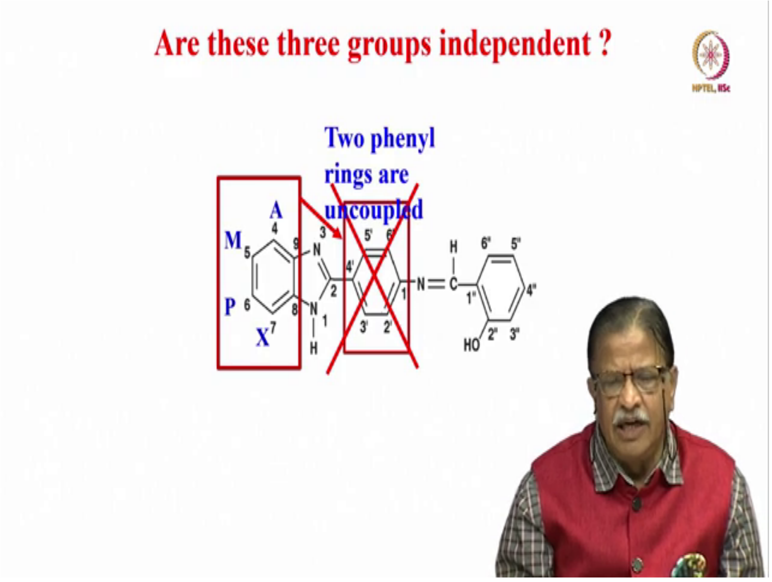

Are these three groups independent ?

Two phenyl rings are uncoupled

Now, how do we know they are independent because this group of protons will not couple to this phenyl ring at all; they are separated by several bonds. Do believe me there is no coupling of any of these protons with any of these protons, these two form two independent spin systems.

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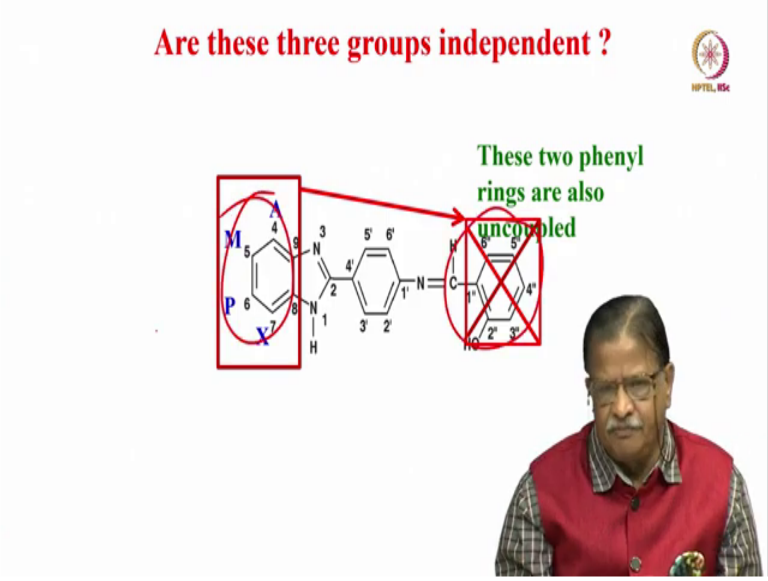

Are these three groups independent ?

These two phenyl rings are also uncoupled

Similarly, this and this form to independent spin systems, there is no coupling between these protons to these protons at all.

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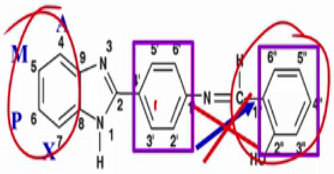
Are these three groups independent ?



These two phenyl rings are also uncoupled

There are 3 independent four coupled spin systems

And similarly, this phenyl ring and this phenyl ring are also uncoupled; there is no coupling between these protons to these protons at all. So, this forms three independent four coupled spin systems. Please remember, I said what is the maximum quantum you can detect in such systems. If you consider now the big molecule but three groups of coupled spin systems are there, with four spins each. So, you can have three four quantum spectra possible; three independent four quantum spectra can be detected from this.

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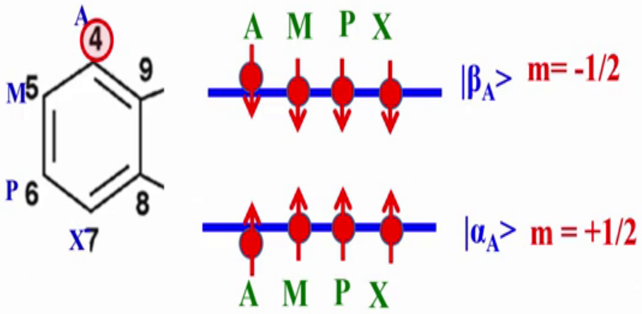
Number of transitions of each coupled Spin System

Flipping of a Single Spin



Spin A gives Multiplicity due to J_{AM}, J_{AP}, J_{AX}

The splitting pattern will be 8 lines (ddd)

For example, now, I look at this one. Before we go further how many transitions we get in single quantum. So, based on that we want to see can we do the spin system filtering, that we will understand. I will consider only phenyl portion of one of the rings. Now, I label these protons as A, M, P and X, here A, M, P and X. Now, I want to understand how many peaks we expect at the chemical shift of A spin. All are independent spins; chemically inequvalent.

Now, if I want to look at the chemical shift of A, A is an active spin. It is undergoing flipping like this. A will undergo flipping. Then what will happen? as I said it will couple with the passive spins, A can coupled with M, P and X; three different protons. Now, it can give rise to AM coupling, AP coupling and AX coupling. That means, A will split into doublet of a doublet of a doublet. So, it will give rise to eight lines. Just if you look at the chemical shift of A in this molecule, A spin should give rise to eight lines. Assuming they are all weakly coupled and these eight transitions are detectable; it will be doublet of doublet of doublet like pattern.

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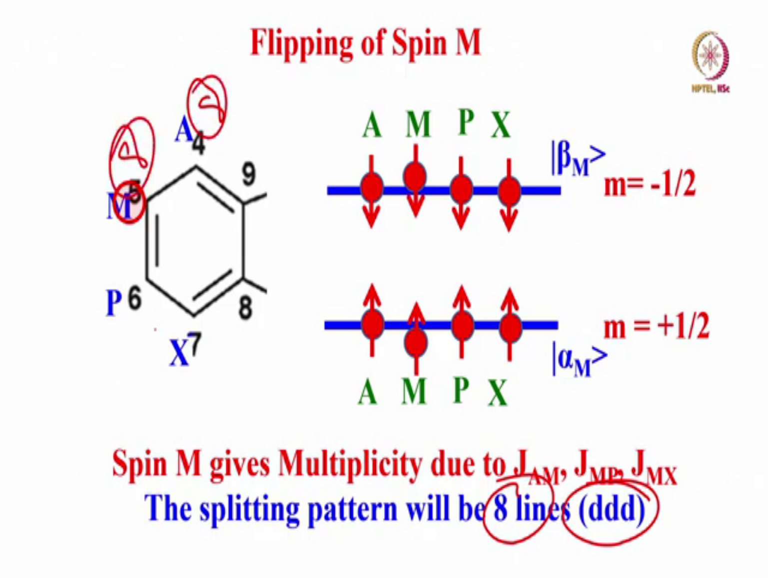

Flipping of Spin M

Spin M gives Multiplicity due to J_{AM}, J_{MP}, J_{MX}

The splitting pattern will be 8 lines (ddd)

Then what happens to M? if M is undergoing flipping M gives rise to again coupling with A, coupling with P and coupling with X. That also should give rise to eight lines, DDD will come; doublet of doublet of doublets. So, each of these spins will give eight lines. A will give eight lines, M will give eight. Similarly, P and X also give eight lines each.

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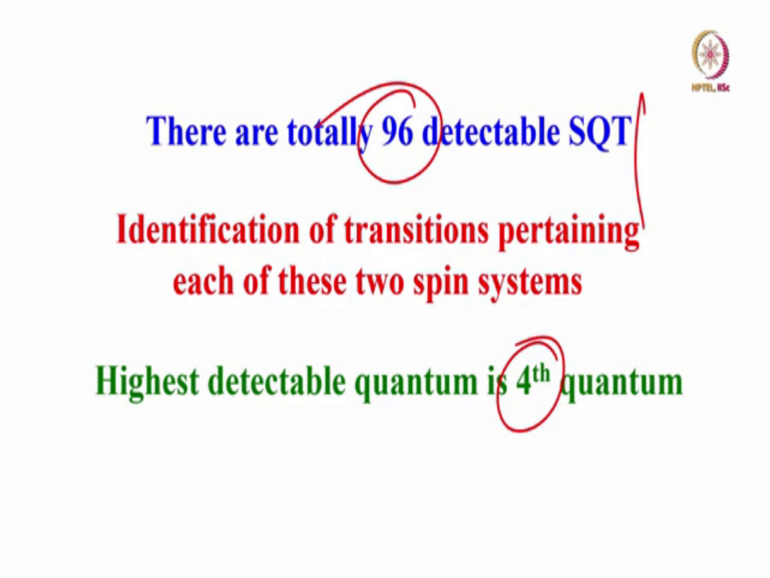

There are totally 96 detectable SQT

Identification of transitions pertaining
each of these two spin systems

Highest detectable quantum is 4^{th} quantum

So, how many peaks you get, eight for each proton, 8, 8, 8 and 8. That is 8 into 4, totally 32 peaks. There are three such phenyl rings. So that means there are 96 transitions possible that can be detected in this molecule with three phenyl rings which are well isolated. Now, remember generally in the proton NMR spectrum, the peaks of the phenyl groups come somewhere around 7 PPM. So, all these peaks will overlap. That is what I showed you in one of the earlier examples, all these peaks will overlap. Now, to identify this is not an easy job. So, what we have to do? we have 96 transitions, the analysis is going to be complex, it is going to be really a tough task, challenging. How do you overcome this? The simplest solution is, detect the highest quantum NMR of such molecules. Now, as I said, there are three groups of phenyl rings, each of them containing four coupled spins. So, highest quantum detectable is 4th quantum. So, if you do non-selective detection of fourth quantum, you are going to get three peaks in the 4th quantum dimension. You can separate out the peaks pertaining to each phenyl ring, in the 4th quantum dimension.

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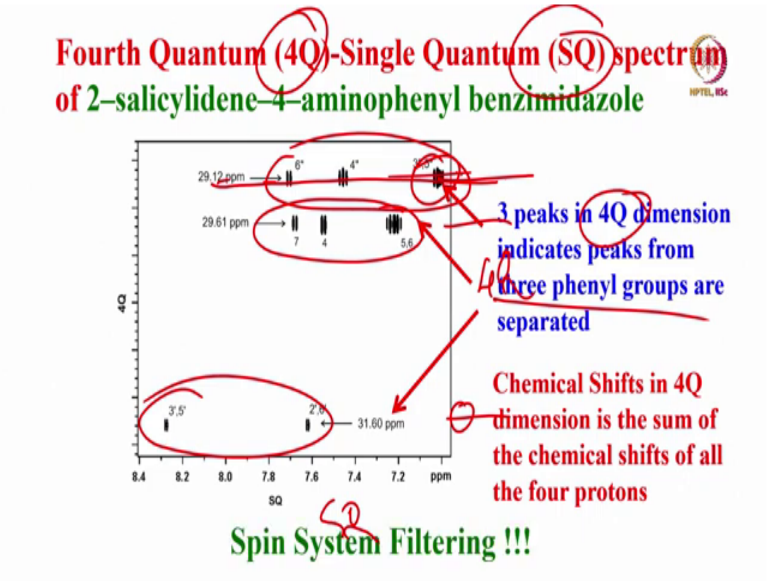

Fourth Quantum (4Q)-Single Quantum (SQ) spectrum of 2–salicylidene–4–aminophenyl benzimidazole

3 peaks in 4Q dimension indicates peaks from three phenyl groups are separated

Chemical Shifts in 4Q dimension is the sum of the chemical shifts of all the four protons

Spin System Filtering !!!

So that is what you can do. So, the 4th quantum single quantum correlation experiment if you do, using the pulse sequence which I showed earlier, in the previous class, which is a homonucler multiple quantum coherence spectrum. Then you are going to get three cross sections here; in the 4th quantum dimension. This is the 4Q dimension. This is SQ dimension, this is called 4Q-SQ correlation spectrum.

Now, take the cross section of this. It identifies four protons of one phenyl ring; this identifies four protons of one phenyl ring. This will identify four protons of one phenyl ring. That means if you take a projection of these, you would get one dimensional spectrum in the SQ dimension. That will be a complex spectrum. What did we do by doing this? By doing non selective excitation of 4th quantum what did we do? We separated out the peaks corresponding to each phenyl ring. That is what we did. So, it will significantly simplify my analysis, my analysis becomes fairly simple. that is what happens. Now, three peaks in the 4Q dimension indicate that peaks from three phenyl rings are separated out. That is what it is. And where do these come? We already discussed, all the peaks correspond to this phenyl rings come at the sum of the chemical shifts of the four protons of that phenyl ring.

Similarly, for example, this comes at the sum of the chemical shifts of the four protons pertaining to that phenyl ring. This is what happens. So, based on the sum of the chemical shapes of individual protons, in each of these phenyl rings, we are able to separate out the 4th quantum spectrum; or using 4th quantum all the phenyl rings. This is called spin system filtering which enables easy analysis of the complex spectrum, when there is severe overlap.

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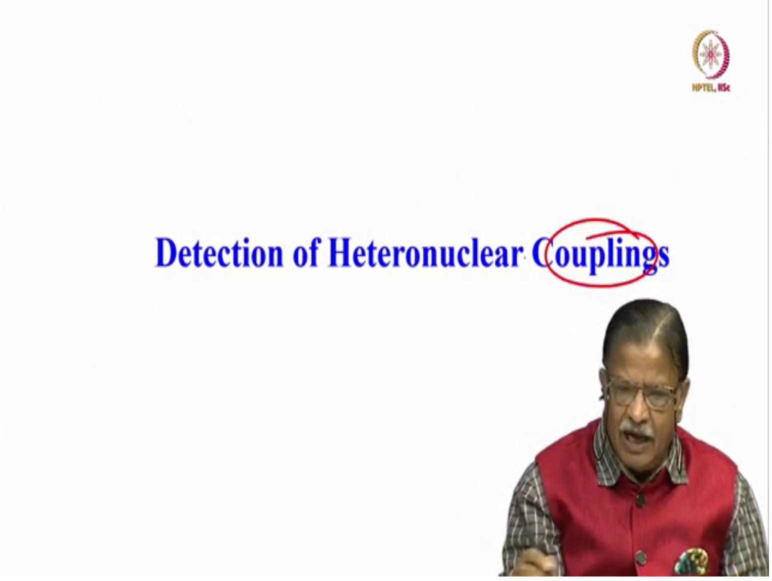

Detection of Heteronuclear Couplings

Now, we can also use this to detect heteronuclear couplings. That is also possible. And I will take this example.

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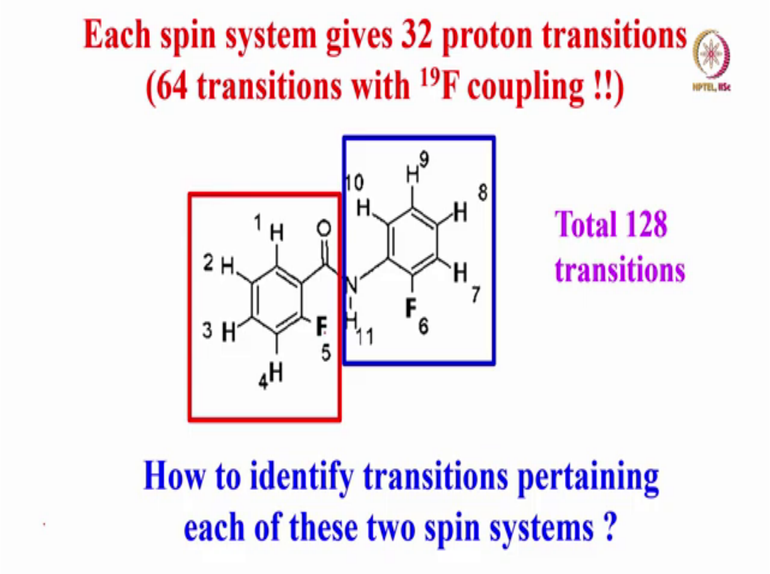

Each spin system gives 32 proton transitions (64 transitions with ^{19}F coupling !!)

Total 128 transitions

How to identify transitions pertaining each of these two spin systems ?

For example, a molecule like this, each phenyl ring gives rise to 32 transitions, each proton, each spin, gives rise to 32 transitions. Here is one spin system of four protons, I am talking about only four protons. Right now, I am not talking about this fluorine and then this fluorine, this phenyl ring gives rise to 32 peaks. This gives rise to 32 peaks. But if it couples with fluorine, 32 will become 64, due to fluorine coupling, will be seen in the proton spectrum.

And the spins which are coupled to fluorine, this fluorine splitting you will see only the fluorine in NMR spectrum; that is what we have been discussing. So, we should get in principle 32 into 2, 64 peaks. Totally 64 here + 64, you should get 128 lines for this molecule, simple molecule. So, totally 128 transitions you can think of, easily you will get it if you take one dimension NMR spectrum of it, this is what you are going to get.

So, how to identify the transmissions pertaining to each of these two spin systems? Just now we discussed. Simple homonuclear 4th quantum experiment you do; that is what you do.

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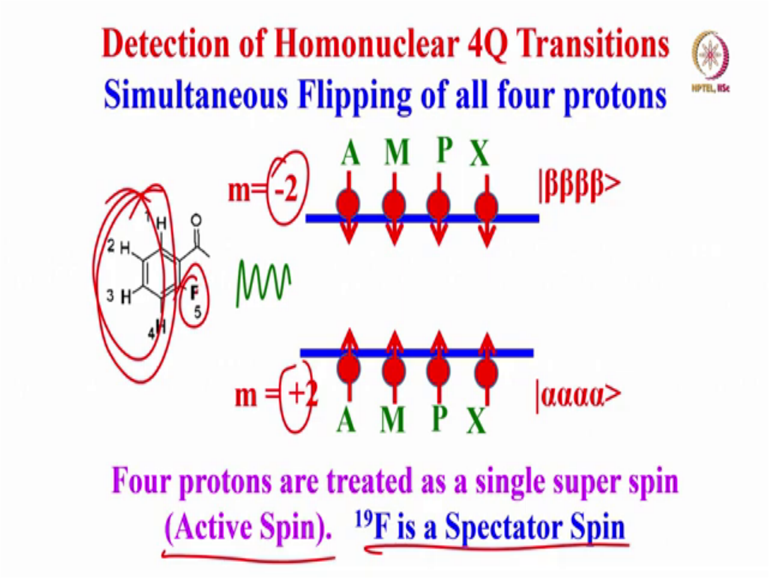

Detection of Homonuclear 4Q Transitions

Simultaneous Flipping of all four protons

Four protons are treated as a single super spin (Active Spin). ^{19}F is a Spectator Spin

Simultaneously flip all these four protons from alpha alpha alpha alpha to beta beta beta beta and vice versa, all of them from +2 to – 2 and vice versa. Then all the four protons are treated as a single super spin called an active spin; 19F is a spectator spin. So, fourth quantum gives you a single peak, because all four protons are simultaneously flipping. But remember fluorine is also a spin half nucleus and the passive spin. It has spin states, alpha and beta.

So, it will couple to these four protons that mean the 4 quantum the single line will become a doublet because of coupling with fluorine; that is exactly what is going to happen.

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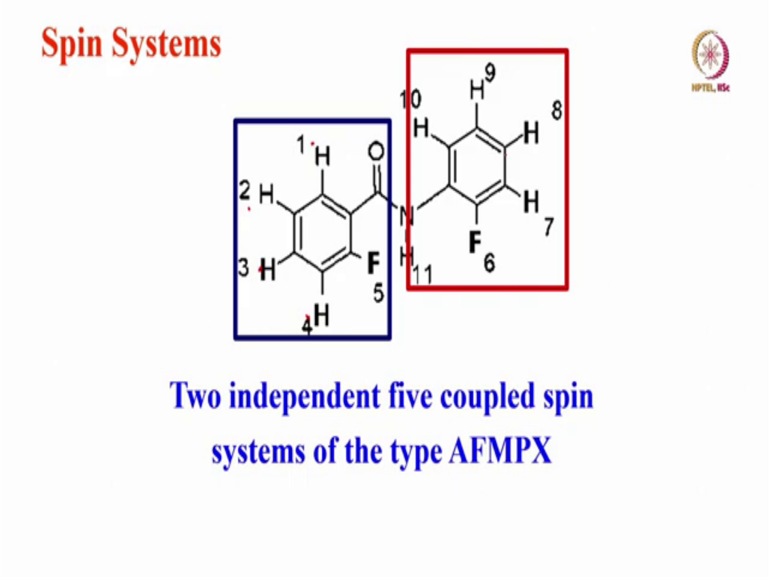

Spin Systems

Two independent five coupled spin systems of the type AFMPX

So, now again, these two are independent five spin systems. In NMR jargon, we call them as AFMPX, whatever that spin system you can call, it is five spin system, this is also five spin system. So, four homonuclear, one heteronuclear spin is there, in each ring.

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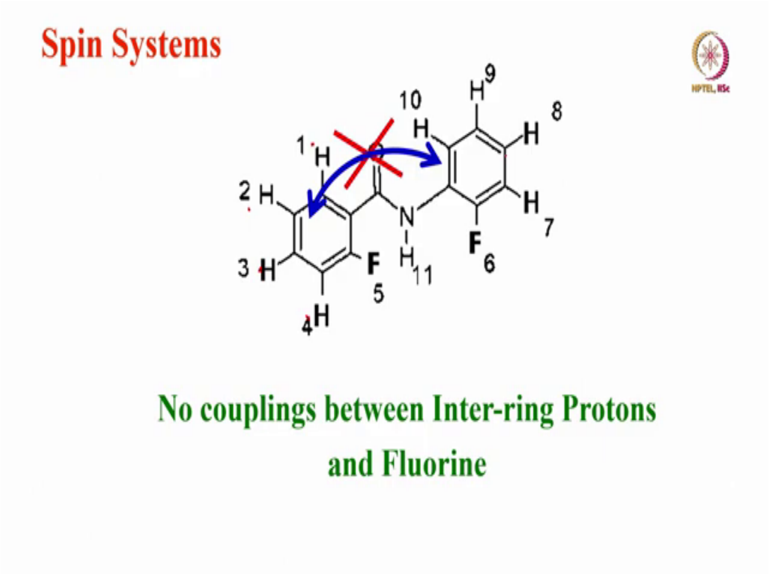

Spin Systems

No couplings between Inter-ring Protons and Fluorine

What we will do is, again since there is no coupling between inter phenyl rings, we consider them as two independent spin systems.

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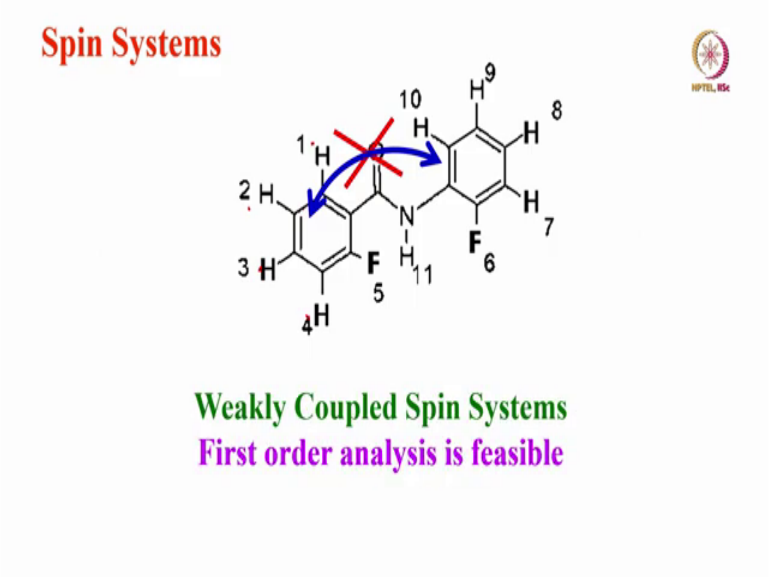

Spin Systems

Weakly Coupled Spin Systems

First order analysis is feasible

So, they are weakly coupled spin systems and first order analysis is easy to do, we can do that.

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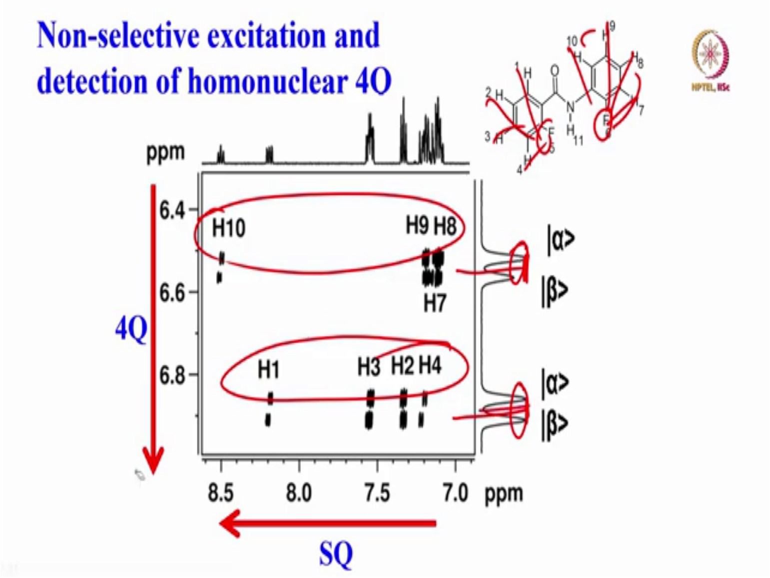

Non-selective excitation and detection of homonuclear 4Q

So, we do the 4th quantum NMR to separate out the peaks pertaining to each spin system. Very interestingly, peaks separated out here, this correspond to one region; corresponds to the peaks of one phenyl ring; for example, 7, 8, 9 and 10. These correspond to phenyl protons 1, 2, 3 and 4. All of them have been separated out. But here interestingly, you may notice one more thing; what is that you are noticing here, each line is a doublet. This is a doublet, this is a doublet, what is a doublet separation corresponds to? These doublets separations correspond to coupling of Fluorine with each of these protons. So, it is a sum of couplings between protons, 67, 68, 69 and 610; that gives the separation. Similarly, this separation correspond to sum of 15, 25, 35, 45 J couplings. That is why in the 4th quantum each peak is a doublet.

Now, where does this peak come at the center of each of these doublet corresponds to sum of the chemical shifts of all these four protons here; and these four protons here. So that you are going to get four protons here and four protons here and then chemical shifts are here. What more you are going to get in this spectrum, apart from spin systems separation, very interesting thing is? You can see this[this corresponds to this ring.

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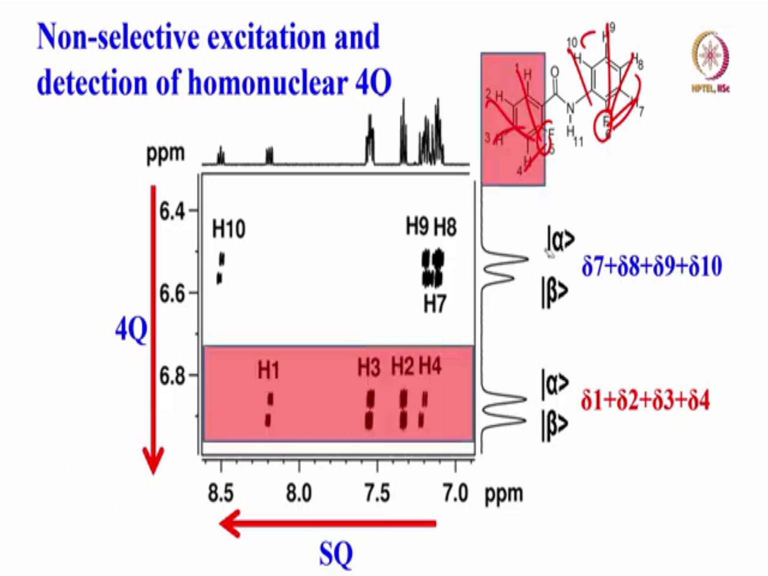

Non-selective excitation and detection of homonuclear 4Q

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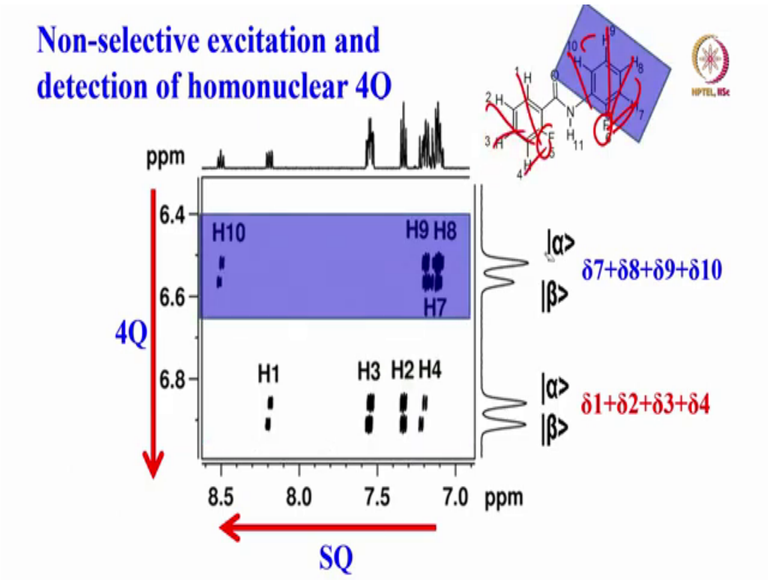

Non-selective excitation and detection of homonuclear 4Q

This correspond to this ring.

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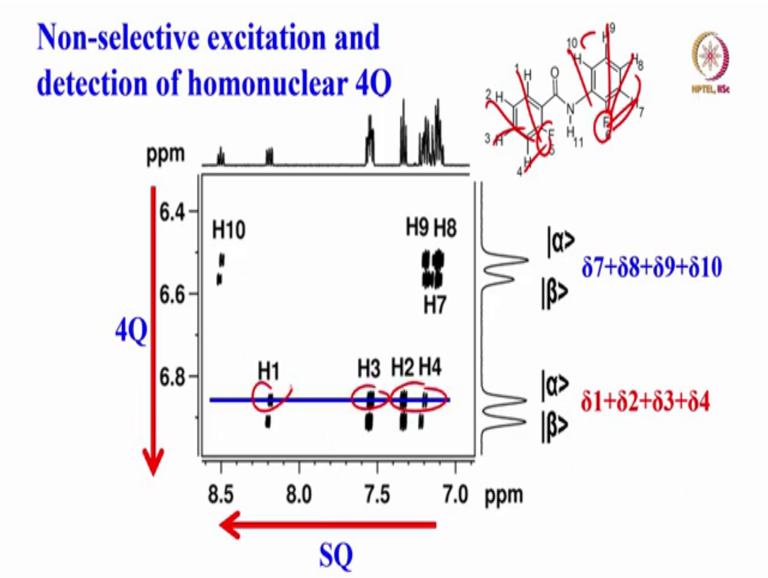

Non-selective excitation and detection of homonuclear 4Q

If you take a cross section along this you will get a one dimensional spectrum. Where chemical shift individual protons, in addition to that, the proton proton couplings can be studied here. Hope you understood. You can get proton proton chemical shifts, if you take the cross section of any of these things.

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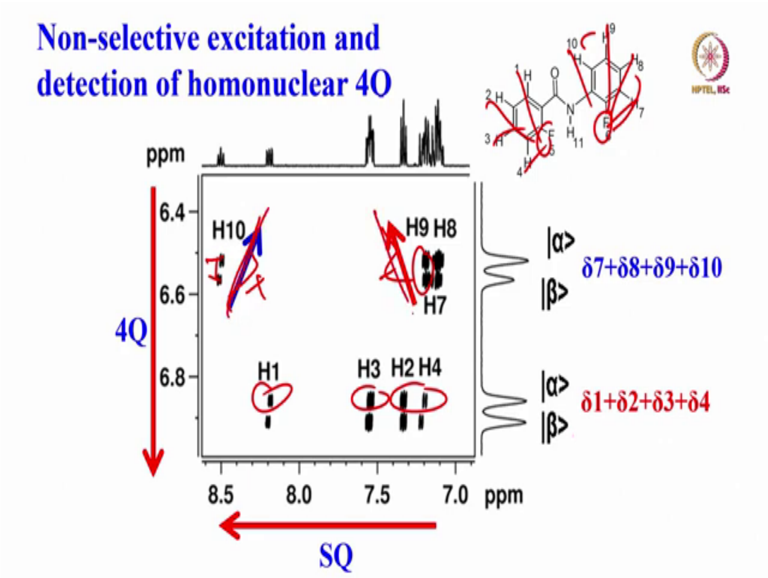

Non-selective excitation and detection of homonuclear 4Q

Another interesting if you notice, here, this is tilted in this direction. the cross sections here this cross section of one of them is tilted in this direction. What that is it going to tell you? It tells you that the sign of the coupling between this and this are completely opposite, they are opposite in signs; the relative signs of this coupling and one of these proton couplings are opposite. If this is positive, this is negative or vice versa.

So, it gives you the information about the relative signs of the coupling. Of course, this displacement of the cross sections also gives the heteronuclear couplings, you can get lot of information from this 4Q-SQ spectrum. It simplifies the spectrum, you can get HH coupling by taking the cross section, direction of the displacement of the cross sections gives the relative signs of the couplings also, at the same time, you can measure heteronuclear couplings.

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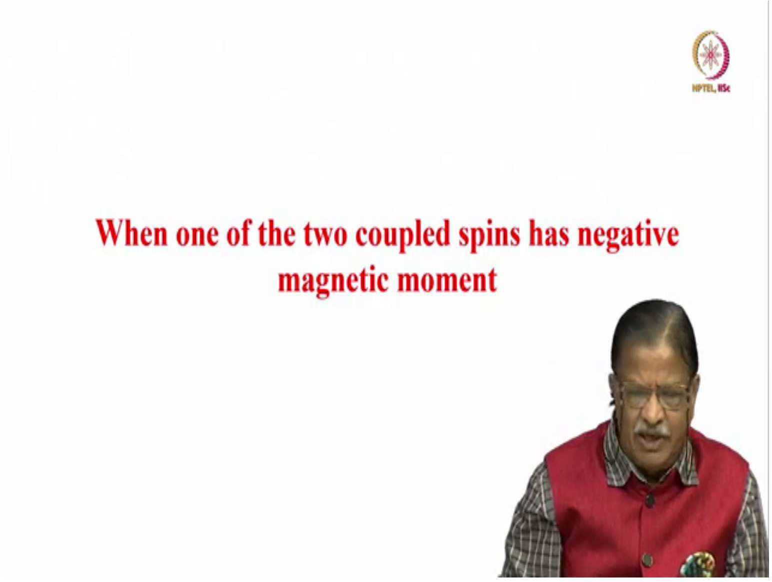

When one of the two coupled spins has negative magnetic moment

Simple non selective excitation of one of the 4th quantum spectra of this molecule. when one of the spins, the fluorine is a passive spin, gives a lot of information for us. You understood how we can utilize the multiple quantum technique for spectral simplification and getting the relative signs of the heteronuclear couplings and also simplify the spectral analysis.

Now, this is with that I will give you one last example. What happens when one of the two coupled spins has a negative magnetic moment? That we did not discuss? Remember, I said when I was talking to you in the very first class, if you put up the nucleus with a positive gamma in the magnetic field, its sense of precession is in one direction, you can put a nuclear with a negative gamma in the magnetic field, its sense of up precession is in the opposite direction. This what we understood.

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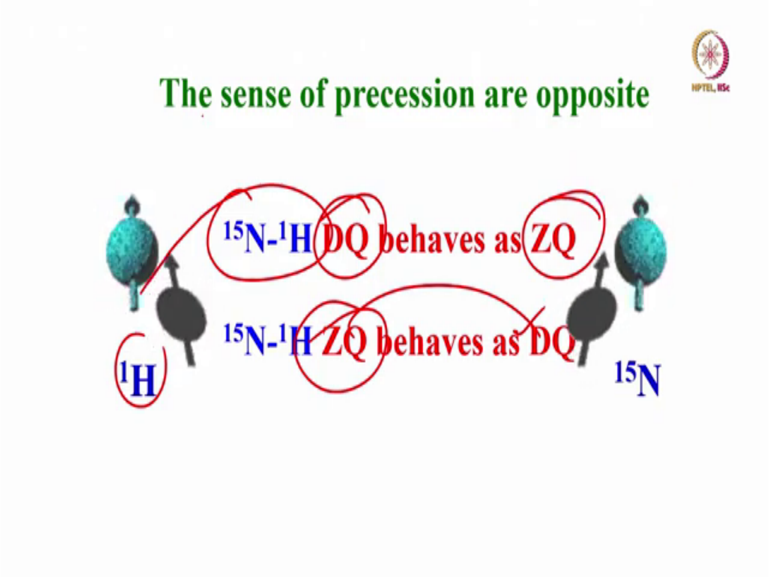

The sense of precession are opposite

^{15}N-^{1}H DQ behaves as ZQ

^{15}N-^{1}H ZQ behaves as DQ

Now, if you want to use this thing to find out what happens if I have one of the spins, with a negative magnetic moment? Consider for example, nitrogen 15 and proton, nitrogen 15 has a negative magnetic moment, proton has a positive magnetic moment. These two have opposite gyro magnetic ratios. As a consequence, they start precessing in the opposite directions. Now, this understanding tells me that double quantum in such situations behave like zero quantum, because they are already have opposite gyro magnetic ratios, they will be spinning in the opposite directions. So, in the double quantum, instead of adding they will subtract. If you want to measure the chemical shift in the double quantum, we said it comes at the sum of chemical shifts, this is the frequency at which it comes. Instead, this now comes at the difference of the chemical shifts. It tells me DQ behaves like ZQ when one of the spins is having a negative magnetic moment.

Similarly, if you go to ZQ, ZQ behaves like DQ. Instead of subtraction, it gets added up in the double quantum dimension. This is what happens. The sense of precessions are opposite. If this is proton is precessing like this, the nitrogen is precessing in the opposite direction.

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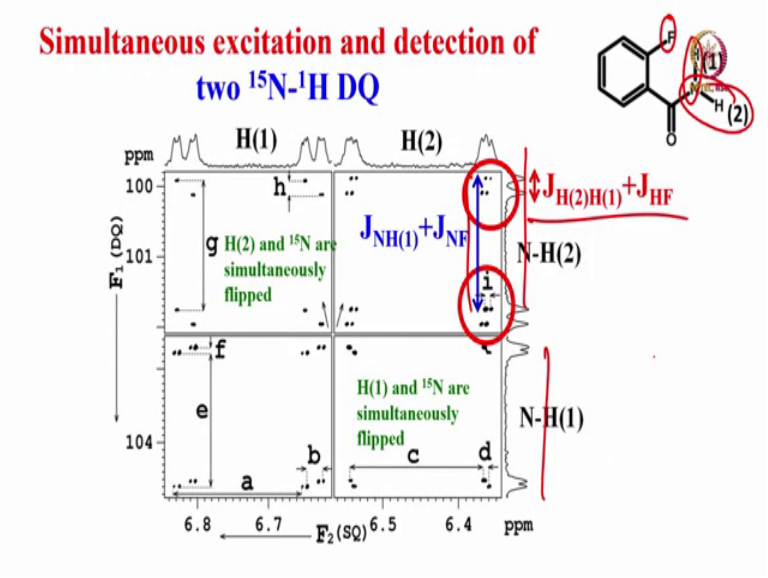

Simultaneous excitation and detection of two ^{15}N-^{1}H DQ

So, do an experiment with a molecule like this. It is a double quantum experiment taking nitrogen 15 into account in its natural abundance. Now, nitrogen 15 proton double quantum you can do. Now, this is coupled to this, this is coupled to this. Now it is a four coupled spin system. Now, there are two possible double quantum here, this nitrogen and this proton can give rise a double quantum; and this nitrogen and this proton can give us a double quantum. Each time fluorine and another leftover proton are the passive spins. With that knowledge, if you do a double quantum, non selective excitation here, you get two double quantum spectra which are plotted here. And one of the separations gives as you the coupling of H2 proton and fluorine and then other one gives you another coupling. This is what, and you can see this separation here; you can measure. And that will give rise to coupling; sum of the two couplings which we have been discussing. So, this is what we can do.

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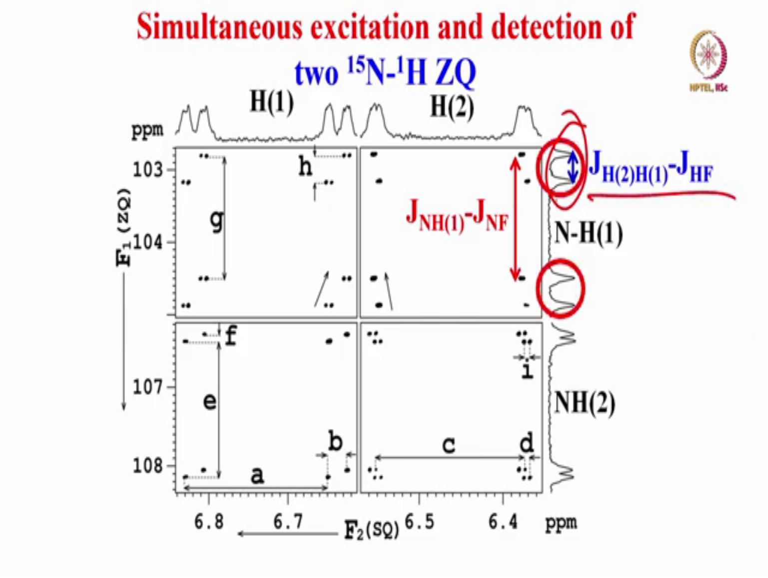

Simultaneous excitation and detection of two ^{15}N-^{1}H ZQ

The same thing if you do zero quantum, as you can see, here the separation is larger than this one. See, this is DQ. So that means, in this case ZQ instead of subtracting, it is getting added up; that is the advantage. You remember, when you have one of the spins, which has a negative magnetic moment, in the zero quantum spectrum the separation becomes larger, because the coupling between active spins and passive spins is not getting subtracted, but getting added up. So, this is what it is. And with this you can get the signs of the coupling, if you look at the tilt of the displacement, you can get all the information.

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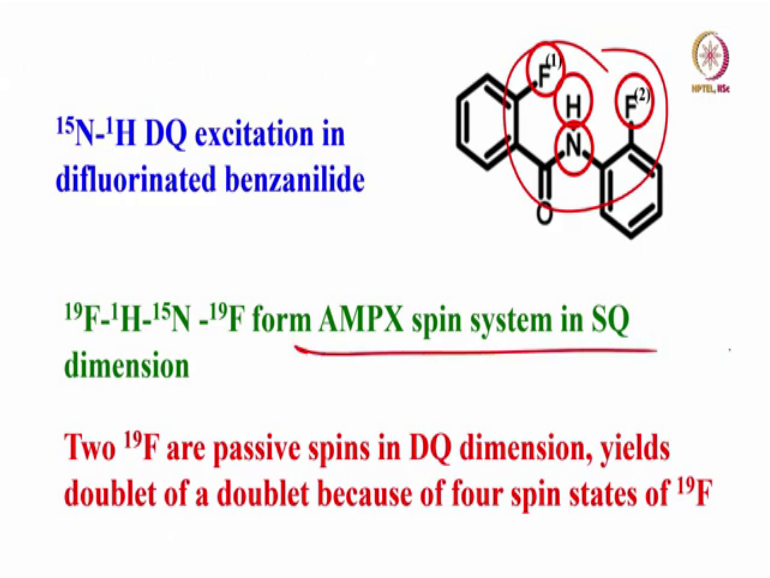

^{15}N-^{1}H DQ excitation in difluorinated benzanilide

^{19}F-^{1}H-^{15}N -^{19}F form AMPX spin system in SQ dimension

Two ^{19}F are passive spins in DQ dimension, yields doublet of a doublet because of four spin states of ^{19}F

So, like this, you can have this type of molecules, simultaneously you can NH double quantum. You can have two fluorines simultaneously as the passive spins, you can get coupling from the double quantum dimensions.

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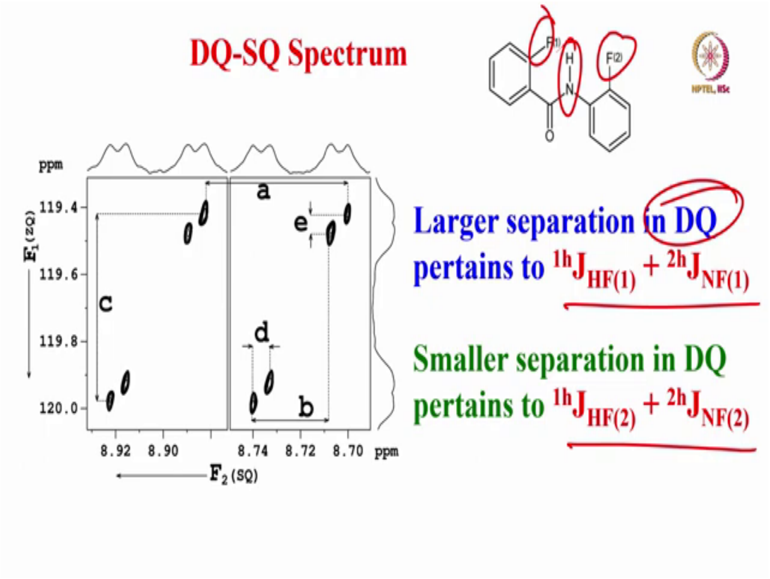

DQ-SQ Spectrum

Larger separation in DQ pertains to $^{1h}J_{HF(1)} + {}^{2h}J_{NF(1)}$

Smaller separation in DQ pertains to $^{1h}J_{HF(2)} + {}^{2h}J_{NF(2)}$

So, this is exactly an example for this in the double quantum dimension. If you do double quantum of nitrogen proton, these two are passive spins, and you can measure the separations and get HF couplings, NF couplings everything, including the relative signs of the couplings based on the displacement vectors.

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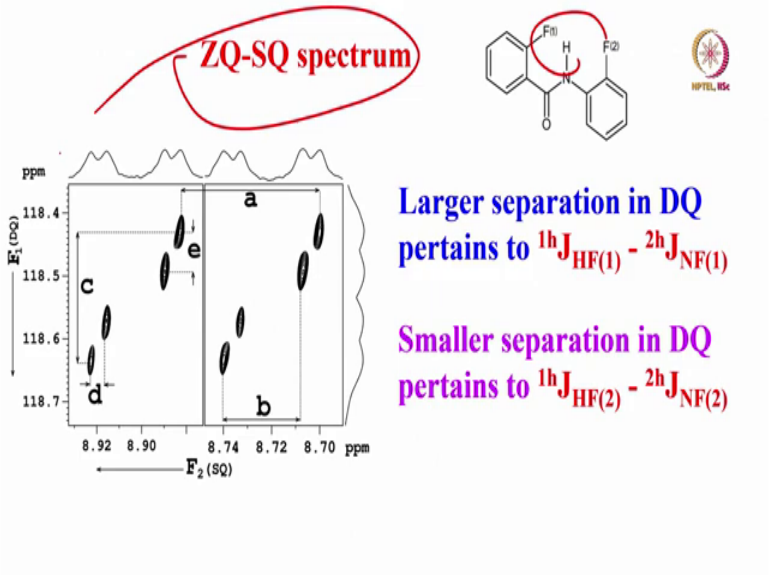

ZQ-SQ spectrum

Larger separation in DQ pertains to $^{1h}J_{HF(1)}$ - $^{2h}J_{NF(1)}$

Smaller separation in DQ pertains to $^{1h}J_{HF(2)}$ - $^{2h}J_{NF(2)}$

So, this is what I was I wanted to discuss about the multiple quantum. This is an example; same thing for the ZQ-SQ correlation of this molecule. So, what I want to tell you as of today before completion of the multiple quantum is, in the multiple quantum NMR we discussed a lot about how we can get multiple quantum? And what are the conditions required to observe the multiple quantum? How the passive spin splits the highest the quantum spectrum in case if there is a passive spin, how do we get the relative signs of the coupling in the homonuclear spins case and the heteronuclear spins case? All those things we discussed. This was very very interesting application of multiple quantum. Mind you it is not directly detectable, they are forbidden transitions.

All transitions other than change in the magnetic quantum number between two energy states which is either + 1 or – 1 are considered as multiple quantum, including zero quantum. They are called multiple quantum transitions. We have to detect indirectly in a two dimensional way, it is called DQ-SQ correlation or ZQ-SQ correlation, 4Q-SQ like that, it is the correlated spectrum.

So, using the correlated multiple quantum spectrum, we have several applications related to the signs of the coupling, spectral simplification and spin system filtering, everything we understood by taking lot of examples. And also we understood what happens if one of these spins has a negative magnetic moment. We took the example of one of the molecules where nitrogen 15 is present. When want to see nitrogen 15 and proton double quantum, then other protons and fluorine were passive spins. And that gives rise to splitting. But one important thing is they rotate or precess in the opposite directions. It means double quantum behaves like a zero quantum, and the zero quantum behaves like a double quantum. It means addition of couplings in the DQ dimension is a subtraction in DQ. And subtraction of the couplings in the ZQ dimension is the addition of the couplings. Similarly, chemical shifts come at the difference here, and it comes with the sum here. So, like this, we discussed and understood a lot. You can utilize this multiple quantum NMR at appropriate places to find the utility of these things. It is widely used, and of course, it could be homonuclear and heteronuclear multiple quantum. I have been discussing all along only about homonuclear multiple quantum, even though a heteronuclear spin is present in the molecule.

You can also have heteronuclear multiple quantum. One of the examples we saw is that nitrogen 15 proton MQ. It is heteronuclear multiple quantum and we discussed homonuclear multiple quantum also. So, everything is possible, the pulse sequence for heteronuclear multiple quantum is slightly different, I did not show that. And zero quantum detection is also done in a slightly different way. For example, how do we select the particular quantum? We can use gradients, in the homonuclear case. Even in heteronuclear case also you can do. If you want to select a particular quantum you have to calculate what is the gradients ratio. If you want to select first quantum, or fourth quantum, etc. accordingly you have to apply the gradients. So that you are going to select the particular quantum spectrum in a N couple spin system.

But how do you select the zero quantum; that is a trick, I did not discuss that because of lack of time. But to please understand, this cannot be done by applying gradients. This can be done by applying what is called phase cycling. Remember, we discussed about the phase cycling we discussed about the application of the gradients for the selection of coherent transfer pathway.

Exactly here, you can adapt the phase cycling and select the zero quantum detection; The zero quantum only and I analyze that. Although I showed spectra, of double quantum, zero quantum etc. I showed the pulse sequence also for the same; but the selection of particular quantum like double quantum or any multiple quantum can be done by gradients. Whereas in the case of zero quantum, you have to do it only by phase cycling.

So, I think I have given you enough of information about multiple quantum. You can start applying it. What are the advantages? How you can analyze the spectrum? Everything we have discussed, a lot in the last two or three classes. I would I stop here. Now the time is also getting over.

So, what we will do in next class, we will start discussing about completely different topic called solid-state NMR, where I will be introducing a new type of experiments. How do you get the spectrum, high resolution spectrum in the solid state, by adopting certain experimental techniques. So, we will come back and continue with the solid state NMR in the next class. I will remind you that all these information is important. The spins do not know whether they are in the solution state or the solid state. Only the interaction parameters, the types of interactions are different.

So, we understand what are the types of interaction that are present in solids; which are different from liquids. We can design new experiments to get high resolution. So, we will come back and discuss that in the next class. I will stop here. Thank you very much