Advanced NMR Techniques in Solution and Solid-State

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Module-51
Introduction to Multiple Quantum NMR
Lecture – 51

Welcome all of you. In the last two or three classes, we discussed extensively about two dimensional NMR spectroscopy, where we discussed about correlation type experiments, especially homonuclear correlation, heteronuclear correlation, like COSY, TOCSY, HSQC and inadequate for correlation of the dilutes spins where it as an examples we took. And we also understood in some specific examples like COSY, what is the phase of diagonal peaks, How do they come? How do cross peaks come? What are their phases? And how we can overcome some of the problems by going to variants of the COSY type experiments. That is what we discussed. And later I discussed TOCSY in which I said COSY identifies immediate coupled neighbours and you have to go systematically by step by step ladder, whereas TOCSY identifies all the coupled spins of a spin system in a single experiment. There we also discussed it is similar to COSY but it uses a second pulse, we are applying what is called spin lock pulse, it is for isotropic mixing. Then what is going to happen is the spins lose their identity, there will not be any chemical shift evolution, only they will be coupled among themselves. And as a consequence, there will be transfer of magnetization to one another in the couple spin system. And this is what we understood.

And we went to heteronuclear correlation, took the example of carbon coupled to proton, especially the inverse experiment, HSQC. What happens in a coupled HSQC and a decoupled HSQC? How do you do the long range correlation, like in HMBC. In the case of HMBC experiment, long range correlations are retained, short range correlations, one bond C-H correlations, like what we see in HSQC are suppressed.

This is a fantastic experiment, where it helps you in identifying the connectivity among long range correlations of carbon and protons. Then, we went to INADEQUATE experiment, where we discussed about correlation of dilute spins like carbon 13, where I said, again, it is a very simple experiment, we have to adopt the double quantum, selection pathway, where we use a double quantum filter. And using the double quantum filter we will ensure that each carbon will give rise to correlation to its coupled neighbour. So, these two coupled carbons will give us a cross peek at sum of the chemicals in the F1 dimension. So, the easy way to identify in the INADEQUATE spectrum is go horizontally then vertically, you will find out from the cross peaks, and then again go horizontally. You find the next couple partner. Like that systematically and in a ladder wise, you can go step by step and identify all the carbons of the spin system, next to each other. So, with that, what we wanted to do is discuss something more, there are many interesting 2D experiments which can be utilize in the daily life, like NOESY, J-Resolved, ROESY, etc., because of shortage of time, I did not cover that. And I will see in case if the time is there at the end, in one class or two classes, if there is time, I will come back and discuss. Otherwise, pulse sequence everything you know how to understand, probably you can go through that. I if there is time we will come back. So, today I will switch over to a different topic which is called multiple quantum NMR. It is something different from conventional one-dimensional single quantum NMR, what you people have come across.

Like for example, any spectrum you are going to take routinely, day to day experiment you do in any NMR spectrometer laboratory. There, most of the time you get single quantum spectrum, whether it is 1 dimensional, 2 dimensional or 3 dimensional. Anything other than single quantum are forbidden transitions in NMR. That is what I said in the very first class.

And we will continue today and see how we can detect such transitions, something which are forbidden. Somehow intelligently if you can detect it. It has lot of advantages. So, in this class, what I am going to introduce to you is the multiple quantum NMR. That has several applications, we can utilize it in some way. So, we will start with that today and understand what is multiple quantum NMR.

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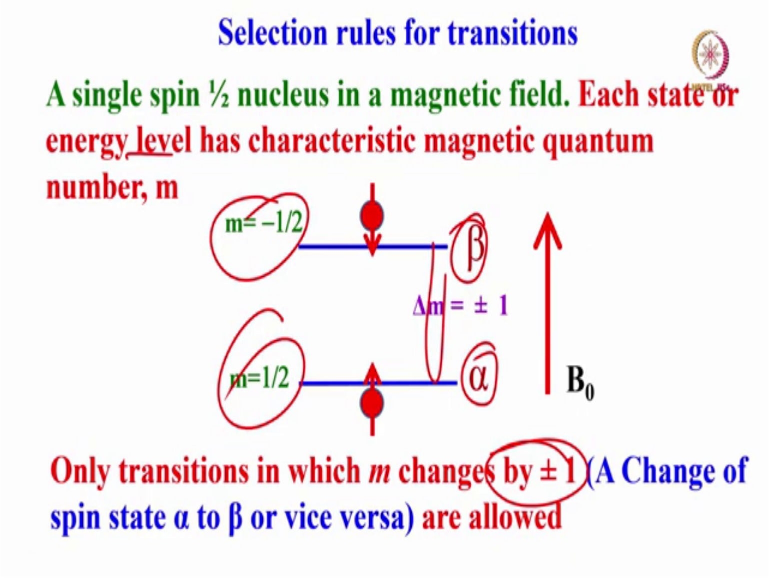

Selection rules for transitions

A single spin ½ nucleus in a magnetic field. Each state or energy level has characteristic magnetic quantum number, m

Only transitions in which *m* changes by ± 1 (A Change of spin state α to β or vice versa) are allowed

First of all, we will start with the selection rules for transitions. A single spin half nucleus, if you consider, we have beta state and alpha state; – 1/2 and +1/2. This in very first class in the first course, also in this course we discussed. And each state or the energy level has a characteristic magnetic quantum number, that is beta and alpha, correspond to m equal to –1/2 and +1/2. And the difference delta m is +1 or –1. And then I said in the very beginning, I repeat, when there is change in magnetic quantum number between two energy states is + 1 or – 1, then transitions are allowed; such transitions are allowed. All transitions with a change in the magnetic quantum number between two energy states is either +1 or –1 are allowed transitions in NMR, according to the selection rule. So, these are all allowed that is why they are called single quantum transitions, where delta m changes by +1 or – 1. For example, here I take an example of a single spin, you can take even more number of spins, not necessarily 1, it can be 2 3, etcetera, that is what we discussed earlier also. So, if you two have coupled spins, any one of them can switch its state from alpha to beta or vice versa, that is allowed, that is also a single quantum.

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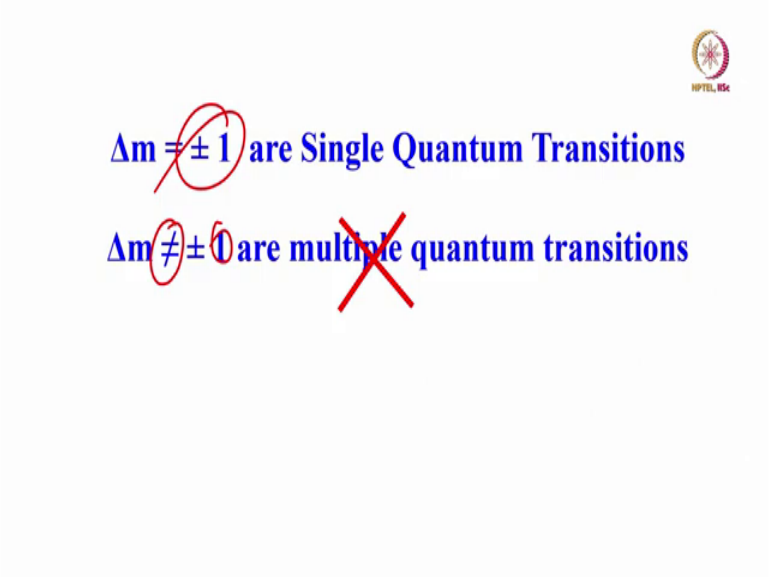

$\Delta m = \pm 1$ are Single Quantum Transitions

$\Delta m \neq \pm 1$ are multiple quantum transitions

So, this is what the conventionally we detect in NMR, routinely that is delta m equal to +1 or –1; they are called single quantum transitions. Remember the delta m equal to + or –1 is single quantum. Delta m not equal to + or –1, you may remember this one, that not equal to +1 or –1 are called multiple quantum transitions; anything other than that could be one 0 here; 0, 2, 3, 4 5 anything. They are called multiple quantum transitions and these are forbidden transitions in NMR, and you are not going to detect them.

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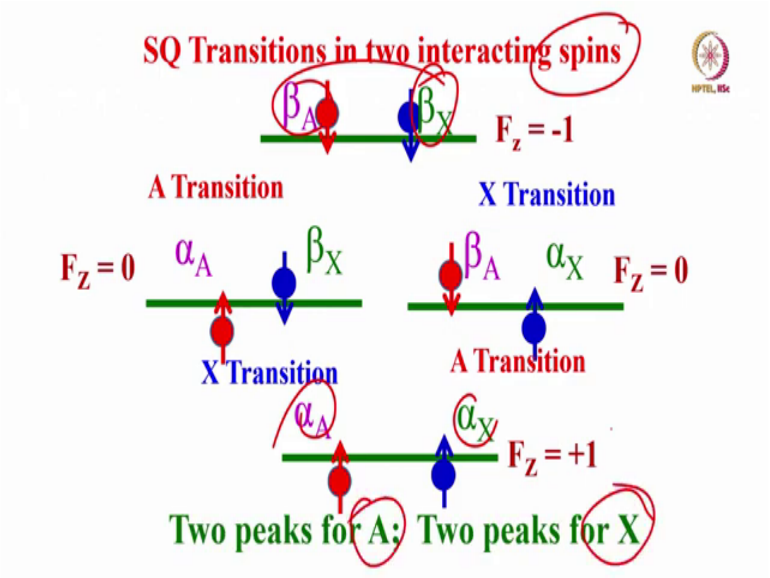

SQ Transitions in two interacting spins

Two peaks for A; Two peaks for X

So, let us see what are single quantum transitions and multiple quantum transitions. Of course, explicitly this single quantum transition by the energy level diagram of the two coupled system also, we discussed earlier. Again, let me repeat, now consider two coupled spin system A and X. Now, there are four possible orientations of the spins; product functions if you consider, the quantum mechanical analysis also we did for this.

Now, there are four energy states corresponding to beta beta, this is A beta, X is beta both the spins are down; this is alpha beta and beta alpha this is up this is down or this is down this is up; and both are up alpha alpha, alpha A and alpha X. And we know the total magnetic quantum number for each of these energy states is – 1, 0, 0 and + 1. Now, according to the selection rule, single quantum transitions are allowed. Delta m, the chang in the magnetic quantum number should be equal to either +1 or – 1. So that means, any one spin; at any given instant of time a single spin is going to change, or flip from alpha to beta or beta to alpha. For example, this one here A spin is changing from alpha to beta and beta to alpha, this is allowed transition. This corresponds to A transition. Similarly, here alpha A is changing to beta A and beta A is coming to alpha A, this also allowed transition, it is A transition.

Now, look at the other one here alpha X is changing to beta X and beta X is coming back to alpha X, again change in the delta m is equal to +1 or –1, allowed transition. This corresponds to X transition. What other transition is possible here, look at it this one. So, here alpha X is again changing the beta X and it is delta m equal to + or – 1. So, this also allowed transition. So, this is again the X transition, allowed.

So, in the single quantum transitions of two interacting spins, two coupled spins, you have only four possible transitions, you can look at it. No other transitions are allowed here. So, in a two spin system, we can get maximum of four transitions; this is what we observed. In the analysis of AX and AB we saw that there are four transitions, allowed when two spins are coupled. So, two peaks you get for A, and two peaks you get for X.

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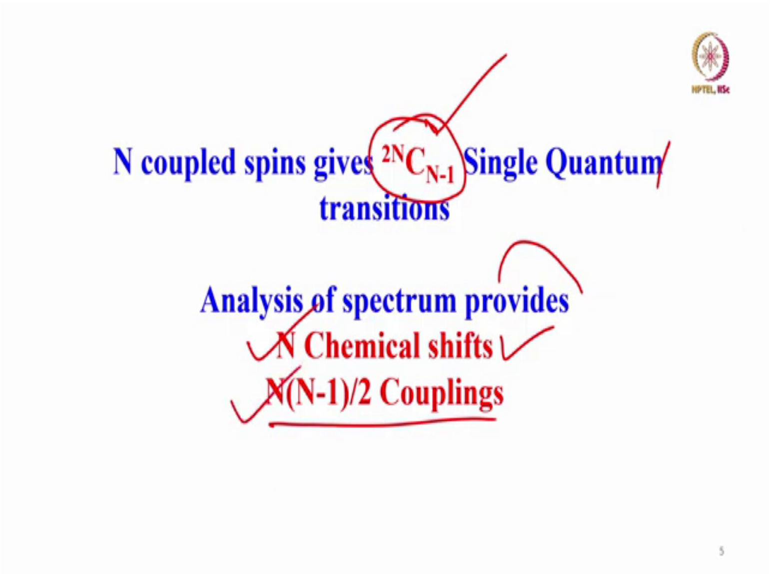

N coupled spins gives ${}^{2N}C_{N-1}$ Single Quantum transitions

Analysis of spectrum provides
N Chemical shifts
N(N-1)/2 Couplings

Fine so, In N coupled spins systems then how many single quantum transitions we can get? It is given by 2N CN –1, where N is the number of coupled spin, and analysis of such spectrum gives N chemical shifts and N into N –1 by 2 couplings. So, this is very important. If I have N coupled spin system this many number of transitions are allowed, detected and analysis of such spectra gives me only N chemical shifts and N into N –1 by two couplings.

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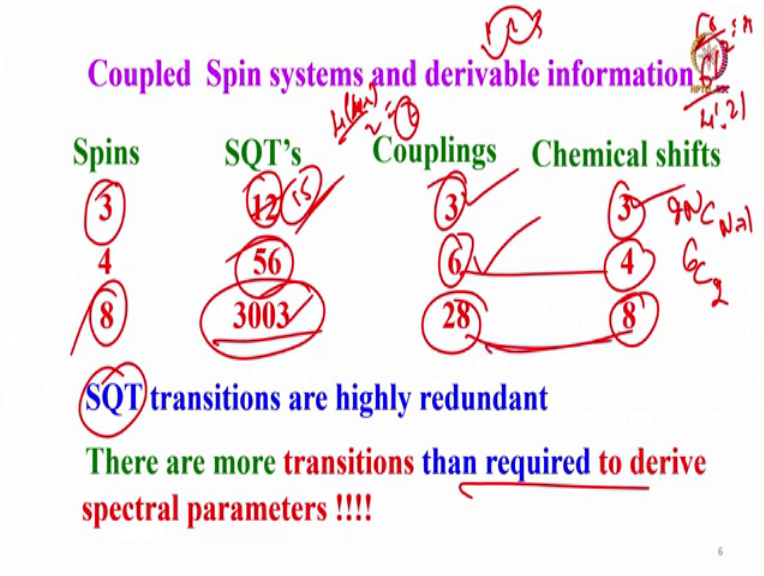

Coupled Spin systems and derivable information

Spins	SQT's	Couplings	Chemical shifts
3	12 15	3	3 $^{2N}C_{N-1}$
4	56	6	4 $^6C_2$
8	3003	28	8

SQT transitions are highly redundant

There are more transitions than required to derive spectral parameters !!!!

Now, if I have a coupled spin system, I know the derivable information and the number of allowed transitions for different spin systems, let us see, for different sizes of the spin system coupled spin system. Let us see how it happens. Now, let us say we have 3 spins coupled; what is the maximum number of single quantum transitions that are allowed. Of course, it is strictly speaking 2 N C N–1 if you put, it should be 15. 2NCN–1 if you see it, is equal to 2 into 3 is 6CN –1 is 2, 6 C 2; factorial 6 over the factorial 4 into factorial 2. This will become 6 into 5 divided by 2; it is 15. So, it has to be 15. Of course, in a weakly coupled case I have written as 12, 3 combination transitions will not be seen. In practice, in real reality theoretically, you should get 15 transitions for 3 spins. And number of couplings, you have to derive is how many, 3 spins are coupled. Let us say, 1 2 and 3, you get 1 2 coupling, 2 3 coupling and 1, 3 coupling; only 3 couplings you have to derive. And how many chemical shifts you have to find out from these. 3 spins, 3 chemical shifts; the 3 are chemically inequivalent. So, there are 3. So, you have to get 6 parameters from 15 transitions. Not bad, reasonably okay not a complex spectrum.

Just go by one more spin, let us consider four coupled spin system. It gives rise to 56 transitions, 56.

And how many parameters you have to determine? you have determine, 4 into 4 –1 by 2 which is equal to 6. You have get only 6 couplings and 4 chemical shifts. So, you have to determine 10 parameters; but there are 56 transitions. That is also tolerable. Go to the next one. For the 8 coupled spin system if you go, you will get 3003 transitions. You determine only 28 couplings, and 8 chemicals shifts that is all. For just to determine 36 parameters, you have 3003 transitions in the 1D spectrum. What does it mean? Single quantum transitions are highly redundant. There are more transitions than what is required to derive the spectral information. That many are not needed for us. Why would you require 3003 transitions to determine only 36 parameters. That is why single quantum transitions are highly redundant, when you want to analyze and derive the spectral information.

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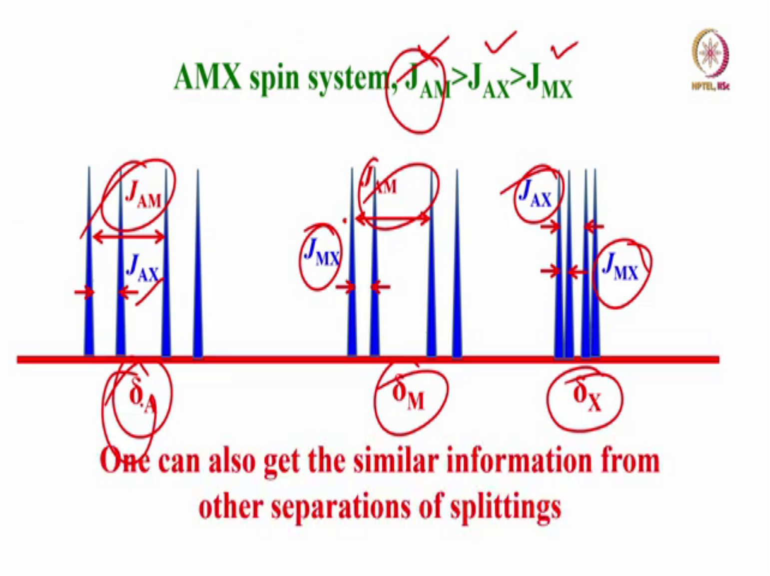

AMX spin system, $J_{AM}>J_{AX}>J_{MX}$

One can also get the similar information from other separations of splittings

Let us understand how it is, look at the simple 3 spin case, I take the example of AMX, the 3 coupled spin system. I consider a situation JAM is greater than JAX greater than JMX. And this is the chemical shift of A, chemical shift of M and chemical shift X. As I said three spins should give you 15 lines. I=In a weakly coupled case we are getting 12 lines, fine. Even these 12 lines we can have two solutions to determine chemical shift and coupling constants.

Look at this one. This separation gives me JAM and this separation gives me JAX. I am looking at A and the M and X or the passive spins, I get JAM, JAX; and look at M, I get JAM here and here JMX. And if you come to X spin this is JMX and this is JAX. So, we are going to get two couplings at each chemical site, at the chemical shift of A you get two couplings, M you get two couplings, at the chemicals shift of X we get two couplings, fine.

All six couplings and all three chemical shifts you can derive, fine; that is understandable. I will get three couplings and three chemical shifts. Now, look at it here itself, AX you can get from here, you get from here, MX you get from here, you get from here, AM we will get from this one, and also from this one. Already, there is redundancy of information; you can get already in the two places when you analyze this. That is one possible solution.

You can get JAM at two places. JMX at two places, two separations. JAX you get from two separations, at the chemical shifts of A M and X. So, these multiplicities will give coupling information but there is a redundancy of the information content. Now, what happens? can I get this information by some other way?

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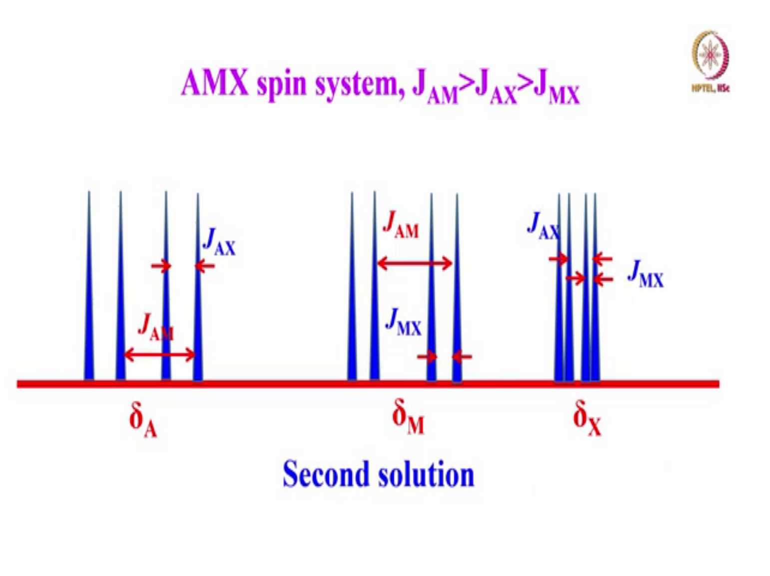

AMX spin system, $J_{AM}>J_{AX}>J_{MX}$

Second solution

Again, this is also possible, this gives me JAM and this also gives me JAX. Again this will give me JAM, this will give me JMX and this is JAX this will give me JMX. So that means, again, in the second solution, you can get this coupling from other splittings, or separations also. But again, there is redundancy of information. What I am trying to say is in a simple single quantum NMR spectrum, there are so many transitions even for 3 spins, that there is redundancy of the information; transitions are highly redundant. We do not require that many to derive the required information.

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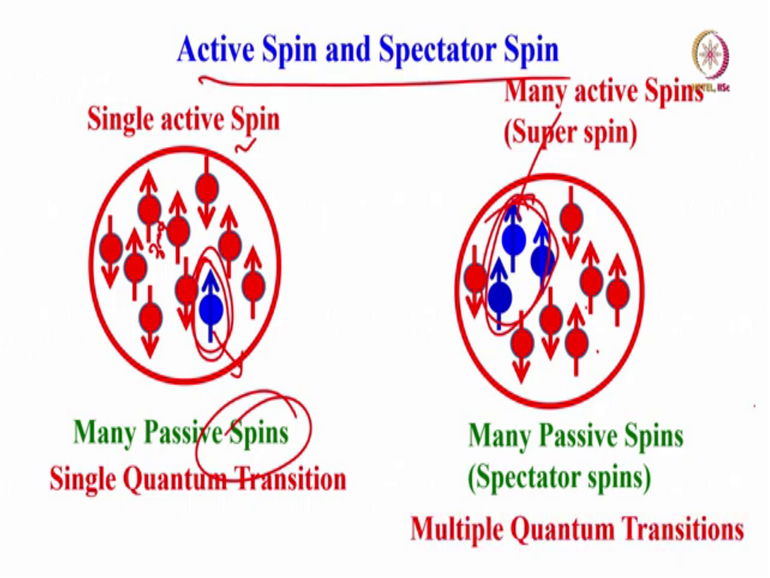

So, with this, now, I will introduce what is called the active spin and also a spectator spin, which is nothing but a passive spin. As far as multiple quantum is concerned, we know we introduce active spin and passive spin earlier, we discussed that active spin is the one which is under going the flipping at any given instant of time. And passive spins are not involved in the flipping but it will give rise to coupling with the active spin.

That is what I said. When I consider the spin system, at any given instant of time, you can flip one of the spins and it will couple with the remaining passive spins, which are just watching it. And that gives rise the coupling. So, these spins will undergo flipping when they undergo flipping at the chemical shift positions of that, and it gives rise to the coupling with the passive spins. This is what important information which would discussed active spins and passive spins long ago. And in the first course and even in this course also we discussed active and passive spin. Now, that was for the single quantum transition. Let us say what are active spins and passive spins when it comes to multiple quantum? Now, let us say I have a group of coupled spin systems, like this. So many spins are coupled, I am going to flip only one of them, which is colored in blue, from alpha to beta. Now, as far as I am concerned, this is an active spin, all the remaining spins are passive. But the they all form a coupled spin system, they are all coupled among themselves. One of the coupling may be 0, does not matter, this could be 0. But overall, they form a coupled spin system. So, it is the only single active spin here and there are many passive spins here. This is a nothing but a single quantum. That is what you see in single quantum NMR.

Now, look at this one. Supposing if I am able to flip all the 3 spins here, at a given time, all at a time simultaneously, then there is a coherence transition. All the 3 will simultaneously undergo transition; then what will happen? Now, these are the active spins, 3 are active spins, many active spins are there, together when they are flipping, I will call it a super spin. No problem, I will give my own definition, it is a super spin. And there are many passive spins again. Here many passive spins are less compared to single quantum, because more spins are flipping at a time; and these are called spectators spins or passive spins. So, remember, in the single quantum, at any given instant of time, only one spin is flipping from alpha to beta or beta to alpha. Whereas in the multiple quantum many spins are flipping at a time and there will be less passive spins; this is multiple quantum transition.

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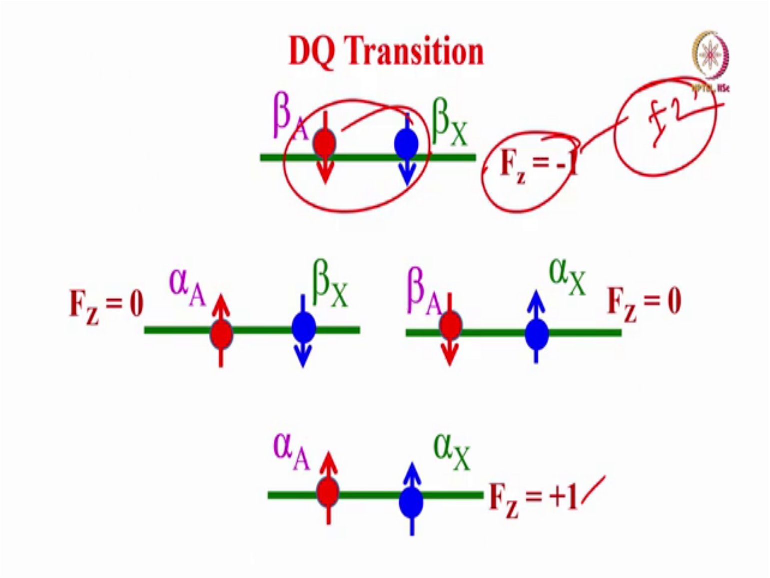

Now, transitions other than delta m = +1 or – 1. Let us see how we can detect, what are they? not how to detect whatever they? Again, let us consider the example of two spins, two coupled spins. Now, 4 possible spin states and the total quantum number, the magnetic quantum number for all of them. For example, this is –1, +1, 0, 0. Now, as I said simultaneously beta beta to alpha alpha states the spins can undergo transition, is that allowed or not allowed? You se,\e, look at this one, it is not allowed. But still let us say if this transition is allowed; what is the change in magnetic quantum number between these two states? +1 or –1. So, it is +2 or –2, it is a forbidden transition, at a time two spins are flipping, it is called double quantum. Double quantum transition is the one where simultaneously two spins should be flipping from beta beta to alpha alpha; or alpha alpha to beta beta; and the change in the magnetic quantum number is either + 2 or – 2.

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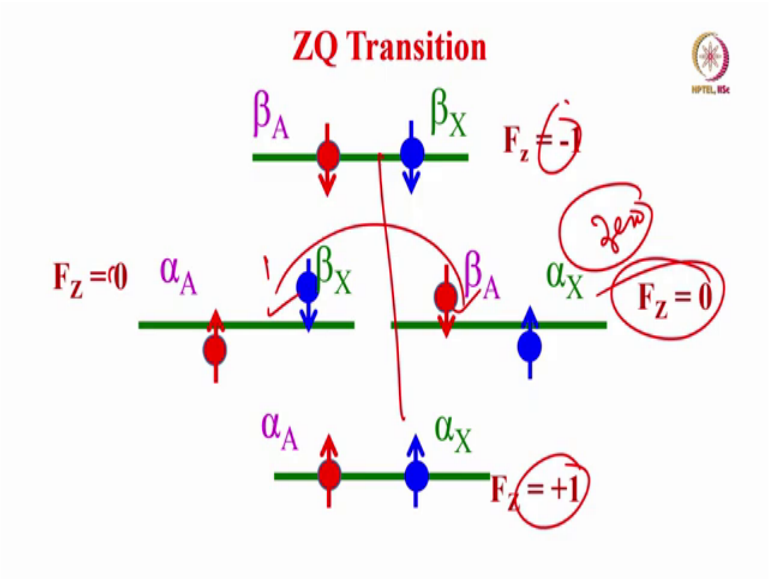

ZQ Transition

Now, zero quantum, let us see. This we saw, this is – 1, 0, 0 and +1. Now, I can think of a situation, is it possible to make this undergo transition simultaneously? alpha beta to beta alpha, like this? Alpha alpha here can go to beta alpha, is it allowed? No, it is not allowed, because change in the magnetic quantum number is 0; 0 to 0 that transition is forbidden. But somehow, if I detect that, then it is called zero quantum.

Because change in the magnetic quantum number is 0. So, in the two coupled spin case we have the possibility of detection of one double quantum and one zero quantum. In addition to four single quantum transitions, that is possible.

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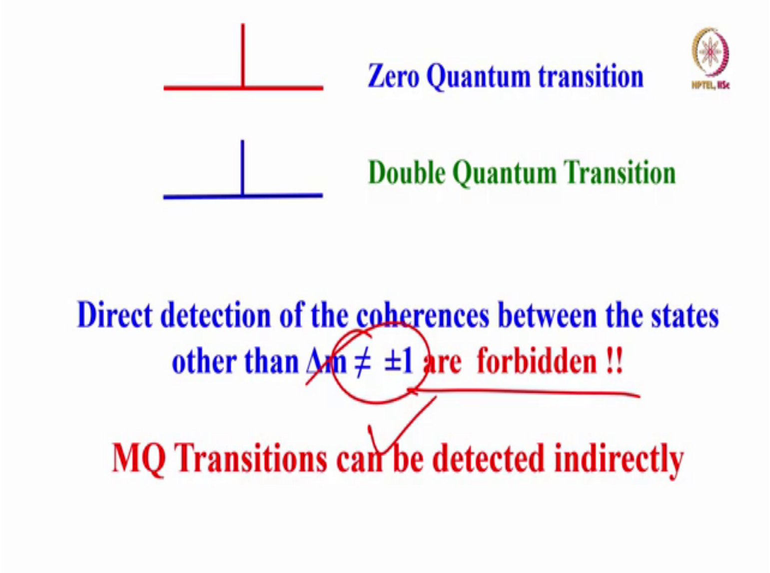

Zero Quantum transition

Double Quantum Transition

Direct detection of the coherences between the states other than $\Delta m \neq \pm 1$ are forbidden !!

MQ Transitions can be detected indirectly

This is what is called the zero quantum transition; and this is the double quantum transition. Both of them, in two coupled spin case, gives single transition only; at single frequency we get a peak. So, the direct detection of the coherences between the states other than delta m equal to + or –1 are forbidden. And MQ transitions you have to detect only indirectly. There is no direct detection of MQ transitions, indirectly we can detect, that is possible.

And if you detect that indirectly, it has numerous applications. And we will touch upon, we will discuss more about multiple quantum and then touch upon one or two applications, in this course.

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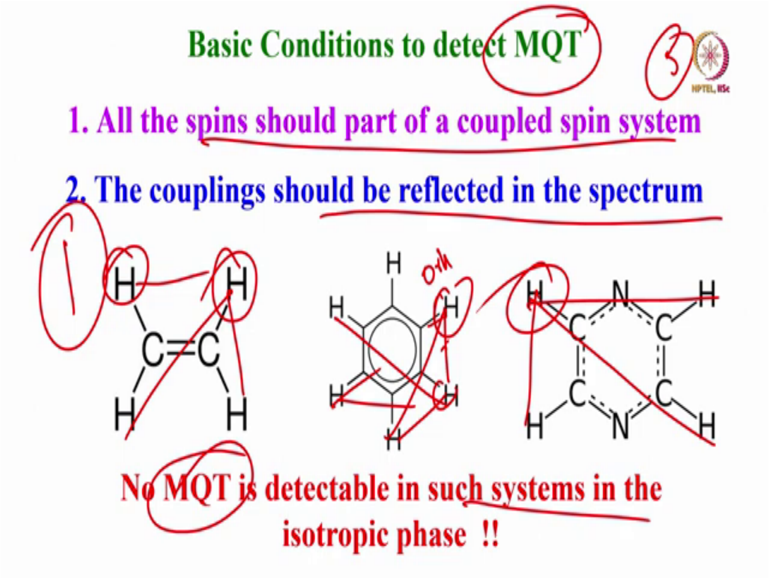

Basic Conditions to detect MQT

1. All the spins should part of a coupled spin system

2. The couplings should be reflected in the spectrum

No MQT is detectable in such systems in the isotropic phase !!

So, now, you might ask me a question, can I detect the MQT in every molecule? is it possible? That question can come; But remember there are basic conditions; First, all the spins should part of a coupled spin system. I told you, I have let us say 5 spins, all of them should be coupled among themselves 1, 2s 3 4, 5. 1 is coupled to 2 3 4 5, 2 is coupled to 1 4 5. One of the couplings may be weak or zero, it does not matter, but they should form a part of the coupled spin system; then we can detect MQT; that is one of the condition. Secondly that couplings should be reflected in the spectrum. For example, if I go to the magnetically equivalent spins or chemically equivalent spins, you may have a J-coupling but you do not see that in the spectrum. An example like this, look at this, this is ethylene molecule. As far as you are concerned, if you look at the isotropic NMR spectrum for this molecule, you are going to get a single peak, because all the four protons are chemically equivalent here. But if you look at the molecule, each proton experiences three couplings. This can be coupled to this proton, it can coupled to this proton and it will coupled to this proton. Similarly, if you go to this one, this can couple to the this, this can couple with this, this can couple to this.

Each proton experiences couplings with the remaining protons. There are three couplings for each proton and all of them are identical. The three couplings are different, but each proton experiences identical three different couplings. Look at the benzene molecule again. Here one proton can experience an ortho coupling like this, one a meta coupling like this and a para coupling like this. Go to this one; same. It again this proton experience, the ortho, meta and para; come to this one ortho, meta and para; each proton experiences three different couplings. All the six protons experiences three different couplings of similar strengths. All of them will experience same ortho coupling, same meta coupling and same para coupling. And look at this simple molecule pyrazine here. This is one coupling, this is one coupling and this is one coupling. Each proton again experiences three different couplings. They are all chemically equivalent. What you take if you take the isotropic NMR spectrum of any of these three molecules, how many peaks you get? Only one pick, one peak for this, one peak for this, one peak for this. So, such type of molecules will not give rise to MQT.

So, no MQT is detectable in such systems in the isotropic phase, I am stressing this point, in the isotropic phase, because if a dope this molecule in the partially ordered system, you bring in another parameter of NMR, called dipolar couplings. If there are dipolar couplings, interestingly we can see couplings among all of them; and it will be reflected in the spectrum, the dipolar couplings. Then you could detect MQT, no problem. But in the isotropic phase, no MQT is detectable in these type of systems, which are chemically equivalent are magnetically equivalent and the couplings are not reflected in the spectrum. Please understand this.

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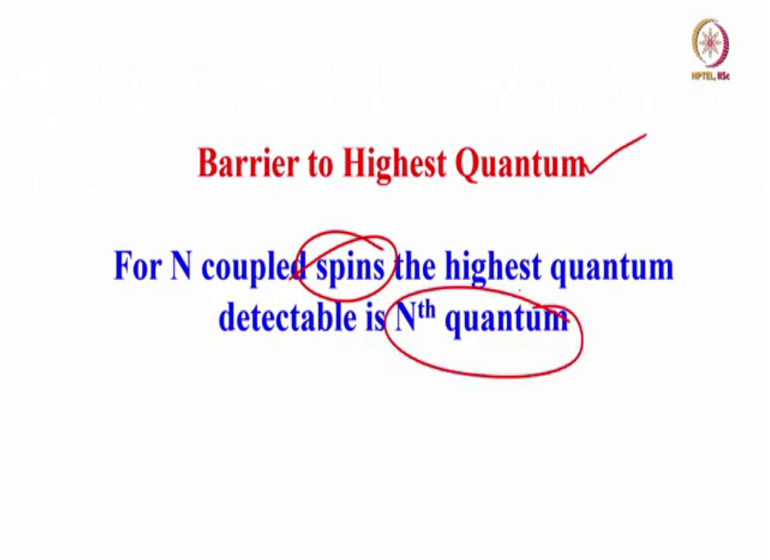

Barrier to Highest Quantum

For N coupled spins the highest quantum detectable is Nth quantum

Now, we will go to the barrier to the highest quantum. What is the barrier to the highest quantum? For N coupled spins the highest quantum detectable is Nth quantum, For N coupled spin system maximum you can get is Nth quantum, you cannot get beyond that.

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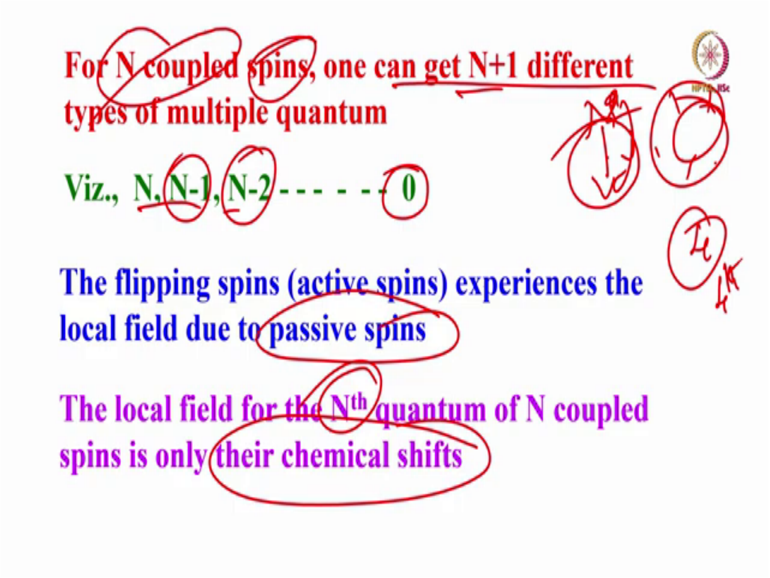

For N coupled spins, one can get N+1 different types of multiple quantum

Viz., N, N-1, N-2 - - - - - - 0

The flipping spins (active spins) experiences the local field due to passive spins

The local field for the N^{th} quantum of N coupled spins is only their chemical shifts

That is the barrier to the highest quantum. So, how many such quanta you can detect if I have N coupled spin system? For N coupled spins, one can get N +1 different types of multiple quantum. The highest is N. We have for N coupled spin system the highest quantum is N; then where do we get N +1? Remember N, N –1 etcetera, but 0 is also included; zero quantum also you can detect. So, as a consequence, if there are a N coupled spins, you can get N +1 different types of multiple quantum. What do you mean by different types? as we go further I will discuss this with you and I will tell you. Even in the double quantum or N –1 quantum, N–2 quantum there could be varieties, different types of N – 1, N – 2, N – 3. Different spins will be undergoing flipping.

The flipping of the spins, the active spins always experience the local field due to the passive spins. This is true even in the single quantum. If one spin is undergoing flipping from beta to alpha. Then it will experience coupling with the other spin, which passive spin sitting next to it, or J-coupled to it. These passive spins create a local field the site of this spin. The local passive spins will create a local field at the site the active spin. So, it experiences that, means this active spin is coupled to passive spins. That is important, please understand. The active spins are always coupled to passive spin, because it creates a local field at the site of the active spin. So, local field for the Nth quantum is what then? There is no local field at all; because there is no passive spin. All spins are active spins.

If I have four spins coupled among themselves, if you go to fourth quantum, there is no passive spin. That means there is no J-coupling. Then we will do all these things come in the spectrum? All four of them are flipping at a time. Coherently all the four will undergo flipping. Then, where do this peak come? It comes only at the sum of the chemical shifts, because the local field is only due to the chemical shift and not the J-coupling. All of them are flipping at a time at this local field, which is sum of their chemical shifts, sum of all the four. So that is what happens.

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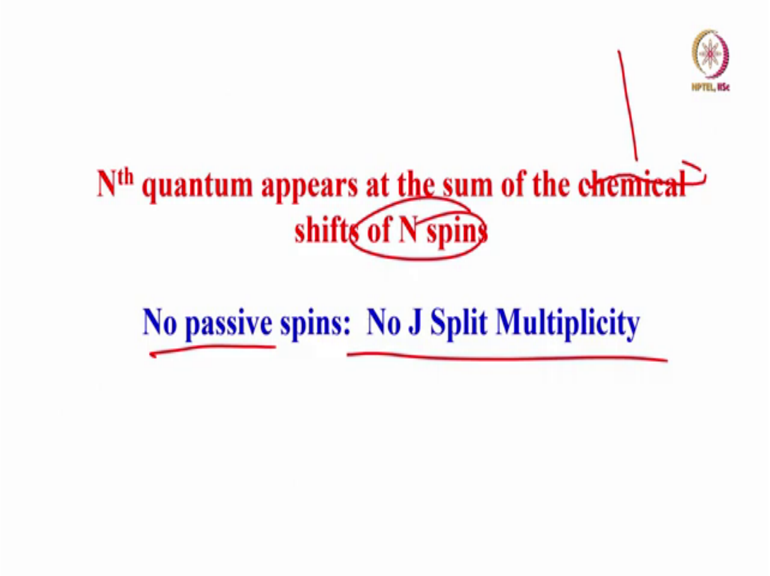

N^{th} quantum appears at the sum of the chemical shifts of N spins

No passive spins: No J Split Multiplicity

So, Nth quantum appears at the sum of the chemical shifts of N coupled spins. And in the Nth quantum there are no passive spins and no J split multiplicity. That means how many peaks we get? simple logic; Nth quantum, because all N coupled spins are simultaneously, changing from alpha alpha alpha to beta beta beta and vice versa. Since there is no other passive spin you get only a single peak. So, Nth quantum always gives a single peak at the sum of the chemical shift of the N coupled spins. Please remember this.

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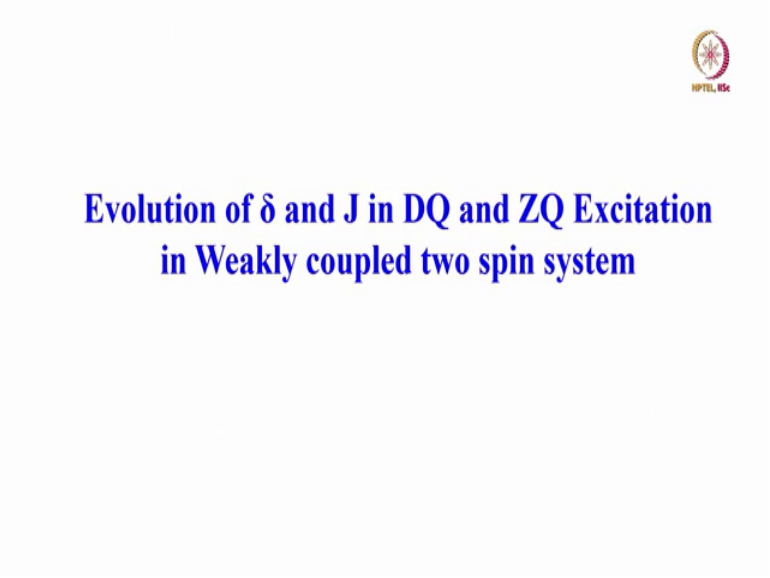

Evolution of δ and J in DQ and ZQ Excitation in Weakly coupled two spin system

So, we will now understand the evolution of chemical shift and J-coupling in double quantum and zero quantum excitation in a weakly coupled spin system. How it works? What will happen if we want to see double quantum and zero quantum in two spin case? How chemical shift evolve? How J-coupling will evolve? And then we will take the example of a three spin. Since time is getting over, I will take up this in the next class. Right now, what I want to tell you is today I started introducing the multiple quantum NMR. Basic point I wanted to tell you is the basic condition to see and multiple quantum is all the spins should be coupled among themselves; they should form part of a coupled spin system. And the coupling should be reflected in the NMR spectrum.

The multiple quantum transitions are the ones where the change in the magnetic quantum number between the different energy states is other than + or –1. It is not +1 or –1 other than that; it could be + or – 2, + or – 3 etcetera, or even 0. They are called multiple quantum transitions. In the conventional NMR what you detect is a single quantum NMR and these multiple quantum transitions are forbidden. As a consequence, you cannot detect them. So, what we detect in the conventional day to day NMR experiment that we do, is the single quantum NMR, they are single quantum transitions. And also as I pointed out single quantum transitions are highly redundant, there are more transitions in a coupled spin system than required to get the spectral information. For example, if I want to analyze, let us say eight couple spin system. How much I have to get? I have to get how many information? I must get 56 couplings and then eight chemical shifts. Whatever it is, they are the small numbers. But how many transitions are allowed? Which is given by 2NCN –1 formula, it is 3003 transitions. Why do we require 3003 transitions to get only small, 8 chemical shifts and only 56 J-couplings. It means single quantum transitions are highly redundant.

So, if you go to higher and higher quantum you will have less transitions. Simple we took the example of a two spin case; two spin J-coupled, how many double quantum are there? Only one. How many zero quantum are there? Only one. But how many single quantum are there? Four. As a consequence, you must understand as we go to higher and higher quantum; the number of transitions what you can detect drastically comes down.

We will we will see that later. And then barrier to the highest quantum of the N-coupled system is Nth Quantum. And in the Nth quantum there are no local fields. So, all these fields are simultaneously flipping from alpha alpha to beta beta beta, states and vice versa. As a consequence, the local field is only the chemical shifts. So, the Nth quantum spectrum of N-coupled spins will give you a single peak at the sum of the chemical shifts of all the coupled spins.

So, now we can understand what will happen, how the double quantum excitation occurs, zero quantum excitation occurs, for two spin case, three spin case, etc. And then how we can utilize them to understand some of the important problems in chemistry; how can we use this method to derive some information. We will come to that later. I will stop here today. And we will come back and continue with this in the next class. Thank you.