One and Two Dimensional NMR Spectroscopy for Chemists

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Lecture No -1
NMR an historical perspective and NMR active nuclei

Welcome all of you to this course on one and two-dimensional NMR spectroscopy. I am Professor Suryaprakash from NMR Research centre of Indian Institute of Science, Bangalore. You go to any part of the world now or any good chemistry laboratory it is hard to find a person who does not use NMR spectroscopy or who is not familiar with NMR Spectroscopy. So, NMR spectroscopy is a very, very powerful technique.

It was discovered sometime in the middle of the last century. In a short span of nearly 60 and 70 years, now, it is one of the indispensable analytic technique.

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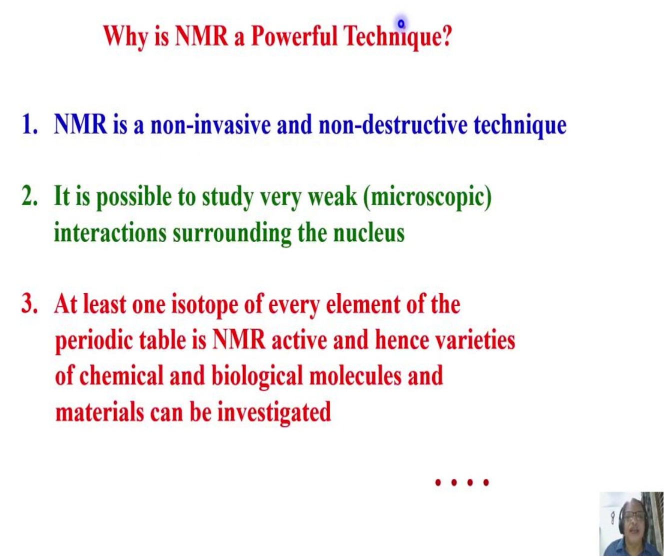

The question is what makes NMR spectroscopy a powerful technique. First thing, NMR is a Non invasive and non destructive technique. You can investigate your samples without destroying them and it is possible for us to study very very weak interactions surrounding the nucleus. Any microscopy perturbation because of the electronic charge distribution at the site of the nucleus can easily be investigated. Now if we go to the periodic table there are more than 110 elements you can find. But at least one element or one isotope of an element in the entire periodic table is NMR active. That means every element of the periodic table or at least one of its isotopes is NMR active. It means we can study varieties of chemical and biological molecules and even materials. Every molecule or every material, whether it is chemical or biological, can be investigated.

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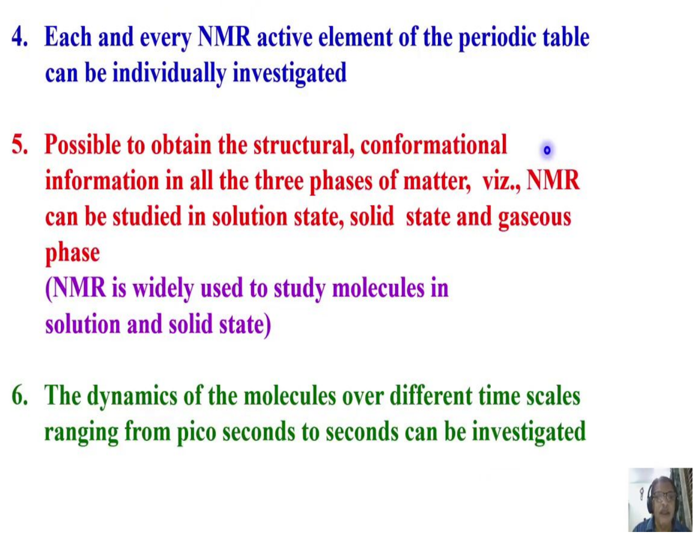

And another thing is interestingly each and every NMR active element of the periodic table can be individually investigated, that is important can be individually investigated, and what can I get out of it, you can get structural conformational information in all the three phases of matter. Now, we can study molecules by NMR spectroscopy in the solution state, in the solid state and also in the gaseous state. Ofcourse there is another wing where NMR spectroscopy is also studied in the intermediate state between liquids and solids, called liquid crystalline phase, where you can dope to your molecule or partially align your molecule in anisotropic environment by doping them in medium like liquid crystal and we can investigate. That means it is possible to investigate your molecules in solids liquids and gaseous and also liquid crystalline phase. Nevertheless, presently I can tell you NMR is widely used to study molecules in solution and solid state. Of course, there is lot of investigations are going on, lot of studies are going on by aligning the molecule to get what are called residual dipolar couplings. This is similar to investigations, in what I said liquid crystal medium. That is also going on.

Another interesting information that you can get as far as your molecules are concerned is the dynamics. If the dynamics are going on in your molecule, you can get it and investigate over different time scales. The molecular dynamics can vary from picoseconds to seconds. It can also be investigated. That is also an important point.

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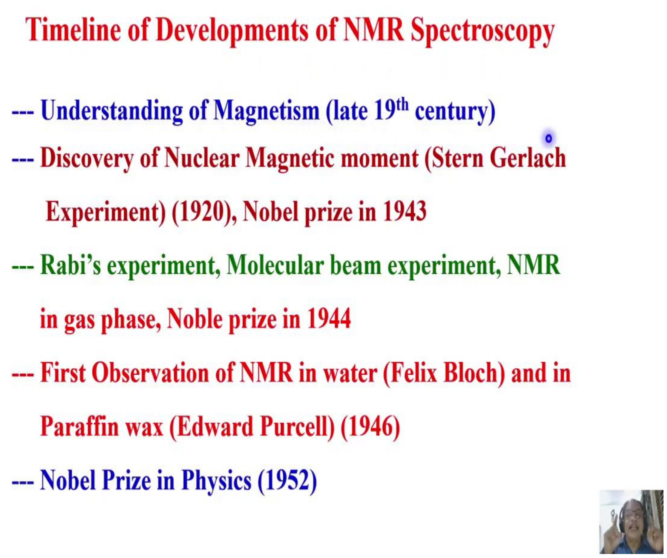

So that is why NMR is now a very, very powerful technique. Let us see how NMR developed in the last 6 or 7 decades. Though it started in 1945, it became very powerful in late 70s and 80s onwards. But let us see historically how it developed. So I am going to give you some historical perspective as far as the timeline of development of NMR Spectroscopy concerned. It is good to have some ideas about how things evolve in science when a powerful technique like this has to become so powerful and developed to this level.

First let us understand the magnetism. It is one of the concepts, you should know magnetism in NMR spectroscopy. If you want to understand NMR you should have some idea about magnetism. This concept and understanding of this was known sometime in the late 19th century. Second, the discovery of what is called nuclear magnetic moment, it is the famous Stern Gerlach experiment, which took place in the year 1920 and for which he was awarded Nobel Prize in the year 1943.

Remember this is the beginning when the nuclear moment was discovered. Then the real discovery of NMR I can say, started in year 1940 by Rabi's experiment. I would not say 1944, because he was given noble price in 1944, but he observed NMR by what is called molecular beam experiment in the gas phase. That is the famous Rabi's experiment. He observed NMR by what is called molecular beam experiment in gas phase, for which he was awarded the Nobel Prize in the year 1944. And the first observation of NMR in water and in paraffin wax was done by Felix Bloch and Edward Purcell in 1946. Both of them observed NMR signal, simultaneously and independently, and both of them were jointly awarded Nobel Prize in physics in the year 1952.

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--- Discovery of Chemical Shift (1949)

--- Availability of First Commercial Spectrometer (1953)

--- MAS for solids in late 50's

--- J Coupling, NOE, Hahn Echo, Decoupling, CP, FT NMR (60's and 70's)

--- 2D NMR in 70's

Now of course the exploration in NMR spectroscopy started going further, and in the year 1949 the chemical shift was discovered that was really transform the way NMR Spectroscopy is what it is today. The discovery of chemical shift is the most important thing in NMR. Without the discovery of chemical shift NMR would not have been what it is today. That is very important discovery. And so in the 1950's, in the year 1953 first commercial spectrometer was made available. And late 1950 onwards 50's onwards magic angle spinning was introduced for the study of solids, where you can study NMR spectroscopy in the solid state. Ofcourse many, many interesting parameters and important concepts where developed in the late 60s and 70s, like J Coupling, Nuclear Overhauser Effect, Hahn Echo, Decoupling, Cross Polarization and most importantly the introduction of a mathematical tool called Fourier transformation in NMR. These are marvelous discoveries which found enormous utility. And in 1970's another dimension was added to NMR spectroscopy where NMR rebirth started, rebirth happened that is called two-dimensional NMR. Another dimension was introduced, and two dimensional NMR was started in 1970.

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--- 80's onwards

→Numerous Pulse Sequences for Diverse Experiments

→Multi Dimensional NMR

→MRI and Functional Imaging

→ Structures of proteins

And from 80's onwards the number of pulse sequence were designed, both two dimensional and three dimensional, for diverse experiments to extract spectral information in an orchestrated manner. It literally took off in 80's. So, multidimensional NMR, MRI and functional imaging started emerging and people were able to get structures of proteins, 3 dimensional structures of proteins.

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1991: Nobel prize for Chemistry, Development of high resolution Methods, Richard Ernst

2002: Nobel prize in Chemistry, for three dimensional structure of biomolecules, Kurt Wuthrich

2003: Noble prize in Medicine, for discoveries concerning MRI, Paul Pauterbur and Peter Mansfield

2020: > 1GHz Commercial Spectrometers

And remember for all these things in the year 1991, the Nobel Prize was conferred on Professor Richard Ernst for chemistry for the development of high resolution NMR methods. In the year 2002 Kurt Wuthrich was given Nobel Prize in Chemistry for three dimensional structures of biomolecules and in 2003 Nobel Prize was awarded to jointly for Paul Lauterbur and Peter Mansfield for the discoveries concerning MRI. In the year 2020 onwards more than one gigahertz spectrometer is commercially available for routine utility.

See how NMR has evolved in just 60 or 70 years. Most interesting thing you must notice is, first NMR was discovered by physicist. The Nobel prize was given jointly for Felix Bloch and Purcell for Physics in 1952. Then it was taken over by chemist. Till then it was in the realm of physics, taken over by chemists and afterwards it was taken over by biologists. See you are able to get three dimensional bio molecular structures. Then it moved on to medicine. See it started with physics, chemistry, biology and medicine. It is covering various branches of science. That is how NMR Spectroscopy evolved.

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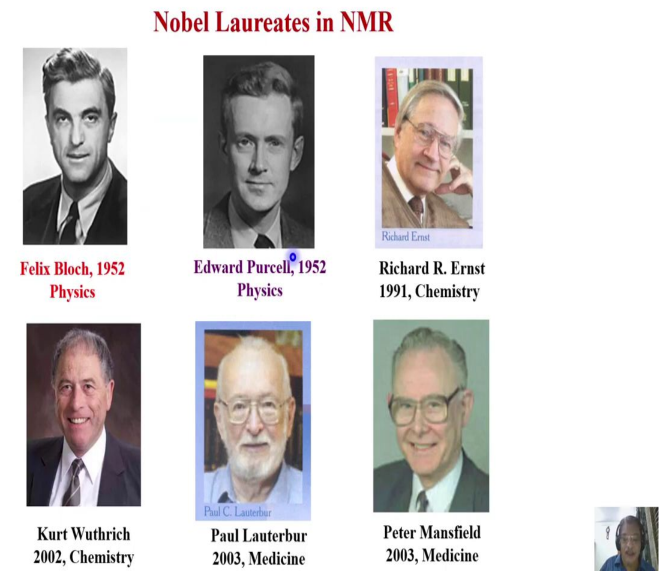

And today it is an ubiquitous technique. And just of course if anybody is offering a course on NMR spectroscopy they cannot avoid showing the Nobel laureates who are pioneers of this field. That is Felix Bloch, Edward Purcell who were awarded Nobel Prize for Physics for the discovery of NMR. Richard Ernst, Nobel Laureate in chemistry 1991. Kurt Wuthrich Nobel Laureate, in 2002 in chemistry and Paul Lauterbur and Peter Mansfield were given the Nobel Prizes in medicine in the year 2003 for their work concerning MRI.

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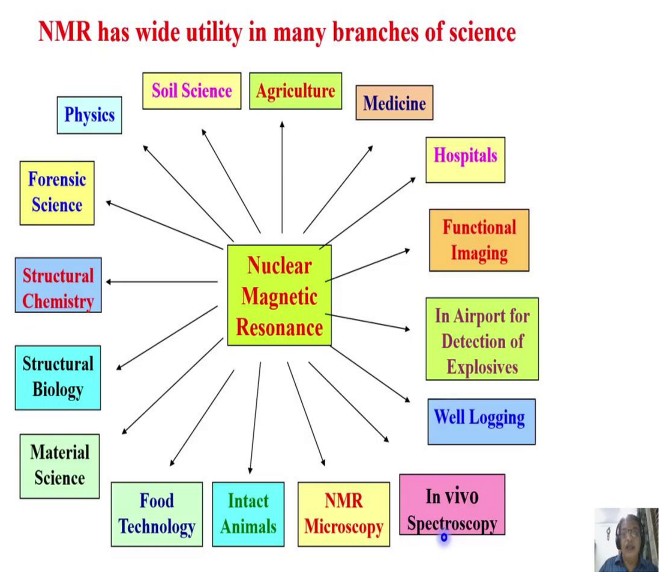

Now with this let us see utility of NMR in various branches of science. As I said NMR is ubiquitous technique. It is a technique which is very powerful and used in various branches of science. Here I am going to show you or I am showing you only the bird's eye view of different science at different branches in science where NMR is utilized. But there are many, many apart from this. This is not the end, it is not the only thing. There are many, many other things which I am not able to put in this slide.

NMR is exploited in agricultural field, medicine, in hospitals where MRI is a very powerful technique now, with functional imaging you can study what is happening in the brain. In airport for the detection of explosives and unconventional application like this, in well logging, in vivo spectroscopy, NMR microscopy, you can also study intact animal. This is exploited more in food technology, in material science, which is another branch where enormous work is going on. Of course in structural chemistry and structural Biology, right from the discovery of chemical shifts, it is very well utilized, and lot work is going on in this area. It is used in forensic science, physics, soil science. These are all only the tip of an iceberg and today it such a powerful technique and ubiquitous technique; not only in science, but also used in every branch of engineering. In many branches of Engineering people are using NMR.

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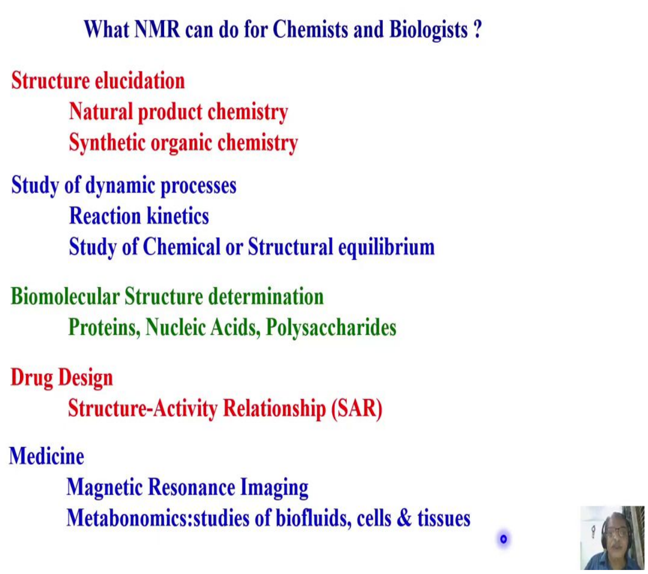

With these let me ask you a question or we can ask ourselves what NMR can do for chemists and biologists? Of course, the structure elucidation, that is natural product chemistry and synthetic organic chemistry. What do chemists do? they extract products they get natural products or synthesize the molecules in laboratory and they want to get their structures. They want to elucidate the structures. NMR can give that.

If you want to study dynamic processes, like reaction kinetics, if you want to study chemical structural equilibrium that is possible to study, and of course biomolecular structure determination of proteins, nucleic acids and polysaccharides is routinely practiced now. For drug design, we can study structure-activity relationship and of course in MRI as I said medicine MRI metabolomics, very we can study biofluids, cells and tissues. Variety of such things can be done and NMR is very, very useful now a days for chemists and also for biologists.

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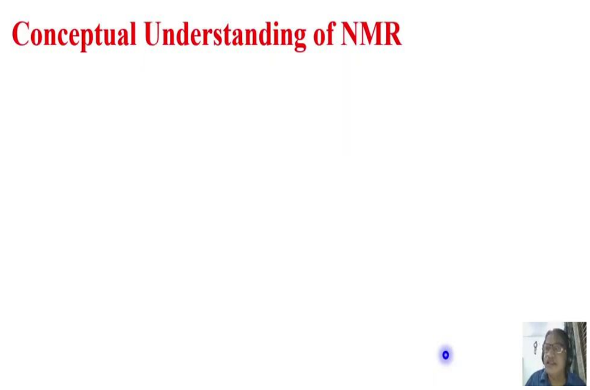

So with this it is good to understand something about the concepts of NMR Spectroscopy before we take a deep plunge into the techniques of one and two dimensional NMR.

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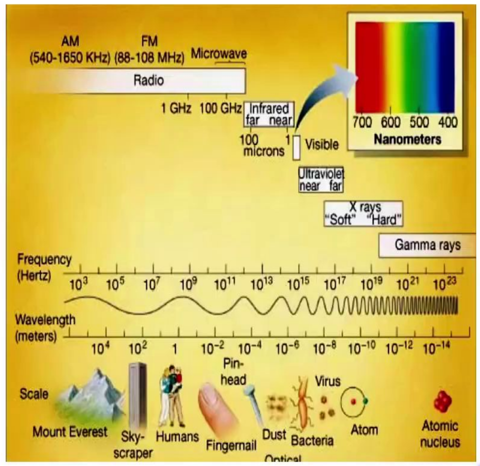
Electromagnetic Spectrum



Conceptual understanding: First let us see, this is an electromagnetic spectrum. You can see various frequency ranges are given here; for example gamma rays, X-rays both soft and hard, ultraviolet, visible range, infrared, of course UV is also here. Infrared, Microwave and this is radio frequency. This is the radio frequency range and of course you can see it is given both in the frequency scale and also in wave length.

As you go from left to right, you see low frequency region. The radio frequency is a low frequency region and as you go towards Gamma Rays the frequency is increasing, it is the high frequency region. If you come back from right to left of course it is the wavelength and see here wavelength is lower because frequency is higher when you come to radio frequency region; the wavelength is larger, it is given in meters. The wavelength is in meters. You can see in this picture what are the things we can study in different branches of spectroscopy.

You can study varieties of phenomena happening in the molecules, such as, rotations, vibrations, electronic transitions, varieties of things can be studied. by using X-rays you can get crystal structure, etc. Now the question is where NMR comes in the electromagnetic spectrum. In this electromagnetic spectrum. NMR appears in radio frequency region. Remember NMR appears in radio frequency region of the electromagnetic spectrum.

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Spin Angular Momentum
and
Magnetic Moment

With this will now try to understand something about spin angular momentum and magnetic moment. These are the two terms which very often extensively we will be using NMR. If anybody is talking about NMR, they cannot avoid using the terms like spin angular momentum and magnetic moment. So, let us understand what they are.

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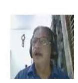
Angular momentum

A rotating object possesses angular momentum

Different types of angular momentum

1. **Rotational angular momentum of atom or molecule**
2. **Orbital angular momentum of electron**
3. **Spin angular momentum of electron**
4. **Spin angular momentum of nucleus**



Of course when we have to discuss about angular momentum, most of you would be knowing, if we have a rotating object, the rotating object processes angular momentum. What type of angular momentum? You can have varieties of angular momentum, for example you can see the rotation angular momentum of an atom or molecule, you can also find orbital angular momentum of electrons. We have spin angular momentum of electron. We have spin angular momentum of nucleus. Just I am giving you one or two examples. This is not the exhaustive thing I am listing.

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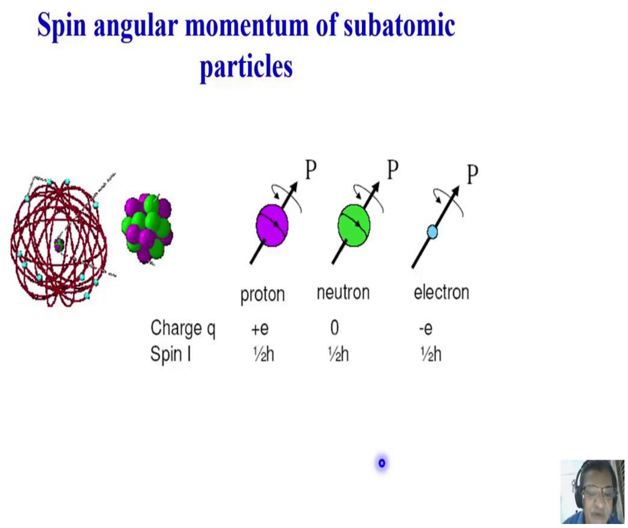

I said the angular momentum of the nucleus, that is what we have to understand. Before we go into the nucleus let us see the spin angular momentum of subatomic particles like proton, neutron and electron. They have properties like this which are listed here. Proton has a positive charge. Its spin angular momentum is half. Neutron charge is zero. It has a spin angular momentum of half Electron has a negative charge with a spin angular momentum half. of course these are all expressed in the unit of Planck's constant half h, half h, half h, that is the unit of expressing spin.

This is of course, you know the size of a Proton and electron. The sizes also depicts what it is each one, what is a proton size, neutron size, and electron relatively to each other. So these are the properties of subatomic particles.

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Spin is a quantum mechanical concept. There is no good classical analogy

It is not, produced by rotation of the particle. It is an intrinsic property of the particle (is always there, even at 0 K)

Then why it is called spin ?

It is described by equations treating angular momentum (P) and it is a vector

Now the question is what is the spin? How do we understand spin, classically? Spin, remember spin is a quantum mechanical concept and there is no good classical analogy; there is no analogy classical analogy at all. It is generally known, that we all study or we would have been taught in our early days of school that spin is described by the rotation of the particles. That is rotation about its own axis, clockwise anticlockwise. Varieties of theories were given to make us understand. It is ok those days to get some ideas about spin.

But literally it is not produced by the rotation of the particle. It is an intrinsic property of the particle. It is always there even at 0K. Even at zero degree Kelvin it is there. It is an intrinsic property. If I say proton has spin half, it is there that is all. It is the natures property, nature has given to us. We cannot question why? It is an intrinsic property. Then questioning if we say it is not produced by the rotation of the particle, of course conceptually we keep using this rotating about its own axis, precession, etc. But in principle though I said, it is not produced by the rotation of the particle then the question is why it is called spin? What do you mean by a spin? Why it is called spin? Remember it is described by the equations treating the angular momentum. Because I said all the rotating particles, I gave you examples, rotating objects possess angular momentum. These fundamental subatomic particles, like protons, neutrons and electrons are described by the equations governing the angular momentum. That is why it is called a spin.

And it is a vector quantity, it is a vector means, it has a direction and magnitude. All these properties can be described by the equation governing angular momentum.

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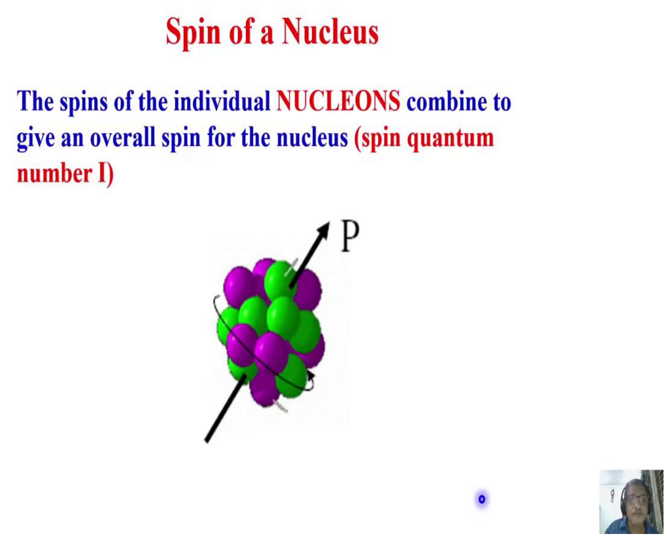

Now let us see, we know the subatomic particle properties of spin and charge. Let us consider the spin of the nucleus as a whole. Then we should know what are present inside the nucleus; what are the subatomic particles present inside the nucleus? Spins of the individual nucleons which are present inside the nucleus, they are nothing but protons and neutrons, which are collectively called nucleons. It is the protons and neutrons which are present inside the nucleus combine to give a overall spin for the nucleus.

Remember they combine in such a way, they align in a particular manner, so that whole nucleus as such will get a spin. That is overall spin will be given for the nucleus. This is called the spin quantum number I of the nucleus.

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Do Nuclei of all Elements/Isotopes Possess spin?

Now to make it understand that let us go further. The question that let us ask, do all nucleus of all the elements, or the isotopes of elements posses spin?

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Empirical rule to Predict NMR Activity of a Nuclear Spin

Atomic Mass	Atomic Number	Examples of Nuclei	Total Nuclear Spin	NMR Active
Odd	Odd / Even	$^{1}H_{1}$, $^{13}C_{6}$, $^{15}N_{7}$, $^{31}P_{15}$	Half integers 1/2, 3/2, 5/2	YES
Even	Odd	$^{14}N_{7}$, $^{2}H_{1}$, $^{10}B_{5}$	Integers 1, 3	YES
Even	Even	$^{12}C_{6}$, $^{16}O_{8}$, $^{32}S_{16}$	Zero	NO

Now there is a General empirical rule to predict the NMR activity of a nucleus spin, and you can find out whether a given nucleus, or a given isotope or a given element has a spin are not and then you can also say whether it is NMR active or not. Remember we have several information given and several parameters are mentioned here in this table containing 5 columns and five rows. Let us look at the second row.

Here the in first column we are discussing about atomic mass and in the second column atomic number and few examples of nuclei processing these properties in the third column. We can say what is it total nuclear spin and finally based on these, we know whether such nuclei is NMR nuclei or not. Take for example, if the atomic mass is odd number and atomic number is odd or even number, there are examples like Proton, ^{13}C which is an isotope of carbon, ^{15}N, again and isotope of nitrogen, ^{31}P. Look, in all these molecules all these nuclei which we have given examples, the atomic mass is an odd number 1, 13, 15 and 31. No matter what is a atomic number, atomic mass is odd number and atomic number would be even or odd. See it is even or odd it does not matter. So long as atomic mass is the odd number we can say such nuclei have the total nuclear spin angular momentum, or the spin of such nuclei are always in half integers. That means the spin value of such nucleus, such elements or such isotopes are always half integers like 1/2, 3/2, 5/2 etc. In the last column I am mentioning whether such nuclei are NMR active or not. Now I say such nuclei are NMR active. They are all NMR active nuclei. Look at the next row, atomic mass is even, atomic number is odd. There are examples like ^{14}N isotope of nitrogen, deuterium isotope of hydrogen and boron another isotope of boron. Look all these nuclei have their atomic mass even number, 14, 2 and 10; whereas the atomic numbers are odd 7, 1 and 5. Such nuclei will have the total nuclear spin always in integers, like 1, 3. They are integer numbers. Are there NMR active, yes such nuclei are also NMR active. Go to the last situation where atomic mass is even number, atomic number is even. For example, ^{12}C, the isotope of carbon, ^{18}O, ^{32}S, their atomic mass is even and atomic number, again even, even. Such a nuclei have total nuclear spin 0 and they are not NMR active, and they are NMR inactive nuclei. Remember what you understand from the table, given any element in the periodic table whatever may be the isotope which that you find out just by looking at the atomic mass and atomic number you can find out the spin of that nuclei, whether it is half integers spins or integers spins or their spin is 0. Depending on that we can say whatever may be the spin whether half integers or integers, if they have spin, such nuclei will be NMR active. Nuclei with spin angular momentum 0 are NMR inactive. This is the table which can tell you how to calculate spin of the nuclei how to find out empirically based on atomic mass and atomic number and then you will know that such nuclei are NMR active or not.

So next we can ask that question. How do I know they are spin half and spin 3/2, So far we did this in an empirical way. But there is a way you can find out how the nuclear spin get assemble themselves, and how the protons get assemble themselves and how neutrons get aligned themselves within the nucleus. From that we can work out what is the spin of the different nuclei. So, what I will do is, I will stop today and will continue from this point tomorrow.