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NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (NMR): A COMPREHENSIVE REVIEW

Anjanalakshmi[1]*, Mitali Dalwadi[2] and Umesh Upadhyay[3]

Student[1], Professor[2], Principal[3]

Sigma Institute of Pharmacy, Vadodara – 390 018, Gujarat, India.

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***Corresponding Author**
Anjanalakshmi
Student Sigma Institute of Pharmacy, Vadodara – 390 018, Gujarat, India.

ABSTRACT

A physicochemical method called nuclear magnetic resonance (NMR) spectroscopy which is used to identify the structural characteristics of molecules. The development of nuclear magnetic resonance (NMR) spectroscopy during the past few decades has been one of the most important developments in analytical methods. NMR has been used to examine a wide variety of biological and nonbiological applications, from a single cell through organs and tissues. Numerous facets of this method are still being investigated, and many NMR functions still need to be clarified and acknowledged. Solid-state NMR has the ability to characterize motions across a wide range of length and time, as well as to offer structural information with atomic resolution. Molecular dynamics, rotational and translational motions of the constituent parts, as well as the motion of the functional species themselves, such as protons or ions, are all examples of these movements. NMR investigations at high temperatures are used to examine the functional dynamics of ligand and partner protein complexes in a realistic membrane environment. NMR spectroscopy is a relatively new development, yet it is one that has great potential for the future. The method is significant because it offers a methodical way to identify and assess the thermodynamic stability of high-energy substates in proteins for the first time ever. In order to analyze complicated systems, such as membrane proteins, metabolically complex samples, or even biological tissues, scientists have created a wide range of unique approaches. One of the most effective methods for determining the structures of chemical species as well as for researching molecular dynamics and interactions is NMR spectroscopy.

1. Introduction of NMR Spectroscopy

1.1 Spectroscopy

Spectroscopy is the study of the spectrum produced by an atom, molecule, or other entity when its surface is illuminated with white light.

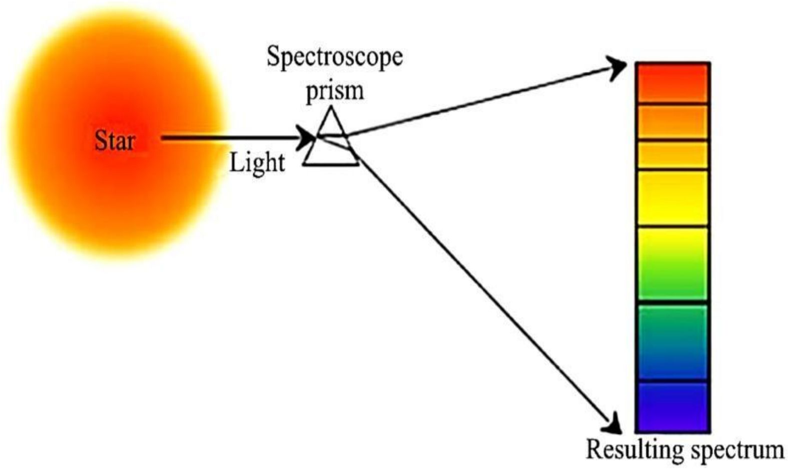

Fig. 1: Spectroscopy.

Here we can conclude from the figure that the defined atom, molecule, or other material influences the entire spectrum that is observed here. Additionally, spectroscopy is utilized in biology, chemistry, and physics. And the frequency is the lowest, while violet has the greatest frequency and the shortest wavelength.

Types of electromagnetic radiation

1. Gamma radiation
2. X- ray radiation
3. Ultra violet radiation
4. Visible light
5. Infrared radiation
6. Micro wave radiation
7. Radio wave radiation[1]

The practice of analyzing how electromagnetic radiation (light) interacts with matter isknown as spectroscopy. Scientists can gather both qualitative and quantitative data about atomic and molecular systems using the different spectroscopic techniques at their disposal. The wavelength of the incident light and the atomic or molecular events that these wavelengths cause are frequently used to classify various experimental techniques, which can entail the absorption, emission, or scattering of incident light.

The basic principles of ultraviolet/visible (UV/Vis), fluorescence, infrared (IR), Raman, and nuclear magnetic resonance (NMR) spectroscopy are reviewed, including the kinds of transitions that are involved in these techniques and some basic context for understanding the information they produce. Fundamental principles of electromagnetic radiation and the absorption process are also covered.[2]

A crucial tool for scientific research, spectroscopy has applications in everything from astronomy and medicine to characterization of materials. Spectroscopy methods are frequently divided into groups based on the wavelength range employed, the sort of interaction involved, or the type of material under study.

IR Spectroscopy

The intrinsic energy of the photons in the infrared area of the electromagnetic spectrum match those of molecular vibrations, IR spectroscopy is still the dominant method for examining the rotational and vibrational modes of molecules.

IR spectrometers typically assess a sample's relative IR absorption of various frequencies. The sorts of molecular bonds present in the sample can then be determined using this absorption spectrum, indicating the different types of molecular structures that are present.

UV Spectroscopy

The electromagnetic spectrum's ultraviolet (UV) and visible areas are where electron energy levels change in atoms and molecules. Thus, by investigating the electronic structure of molecules in a sample using UV/ Vis spectroscopy, it is possible to identify the compounds groups, and coenzymes can all be done using UV/VIS spectroscopy.

NMR Spectroscopy

The magnetic fields that are present around atomic nuclei can be measured using a technique called nuclear magnetic resonance spectroscopy. Radio waves are used in NMR spectroscopy to excite atomic nuclei in a sample. Sensitive radio receivers can pick up whennuclei begin to resonate.

NMR spectroscopy can provide extensive information on the structure and reaction state of molecules since the resonant frequency of an atomic nucleus depends on the electronic structure of the molecule of which it is a part. As a result, it is an effective tool for determining the precise makeup of monomolecular organic compound.

Raman spectroscopy

Raman spectroscopy focuses primarily on the inelastic scattering of photons, also known as Raman scattering, in which a photon's apparent wavelength changes as a result of its interaction with a sample.

Raman scattering illuminates the sample with a monochromatic light source. The energy of the photons is pushed up or down when the laser light interacts with molecular vibrations or other excitations in the chemical system. The types of chemical bonds that are present in the sample can be thoroughly analyed by accurate measurement of these energy shifts. IR spectroscopy and Raman scattering both produce similar but complementary data.

X-RAY Specroscopy

The innovation of X-ray crystallography in 1912 marked the beginning of the application of X-ray spectroscopy. William Henry Bragg and William Lawrence Bragg, a father-and- son team, demonstrated how one might determine the type of crystal structure from the diffraction patterns produced by X-rays passing through crystalline materials.

Current technologies include energy- and wavelength-dispersive X-ray spectroscopy (WDXS) (EDXS). By measuring distinctive X-rays within a specific part of the spectrum, both methods enable elemental analysis.

1.2 Nuclear Magnetic Resonance (NMR)

The study of molecules by nuclear magnetic resonance (NMR) spectroscopy involves observing how radiofrequency (Rf) electromagnetic radiations interact with molecule nuclei that are in a strong magnetic field. Zeeman originally noticed the peculiar behaviour of some nuclei in the presence of a strong magnetic field at the end of the nineteenth century, but it wasn't until the 1950s, when NMR spectrometers were made commercially available, that the so-called "Zeeman effect" was actually put to use.

It makes use of the phenomena of nuclear magnetic resonance and offers comprehensive data on the kinetics, reaction state, and chemical environment of molecules.[3]

Basics of NMR Spectroscopy

- Nuclear Magnetic Resonance (NMR) was discovered experimentally for the first time nearthe end of 1945.
- The Physical Review's same January 1946 issue featured the first of the NMR spectrum. The 1952 Nobel Prize in Physics was shared by Bloch and Purcell for their work on nuclearmagnetic resonance spectroscopy.
- For organic chemists, nuclear magnetic resonance (NMR) spectroscopy is a vital analyticaltool.
- The NMR has been used to indicate the results of the organic lab study. Not only may it reveal details about the molecule's structure, but it can also establish purity and substance of the sample. One of the NMR techniques that organic chemists utilize the most frequentlyis proton (1H) NMR.
- It is possible to determine the structure of a molecule by observing how the protons in it respond to the surrounding chemical environment.
- Over a number of decades, the method's evolution from physics to chemistry to biology will be highlighted by NMR.
- The chemical shift, the J-coupling, nuclear Overhauser effects, and residual dipolar couplings, which are NMR spectral parameters employed in structure.

  The prerequisite for any subsequent NMR research is resonance assignment, which resembles a jigsaw puzzle technique.
- Next, a bundle of structures is computed using constrained molecular dynamics utilizing the NMR spectral parameters8 translated into angles and distances.[5]
- The chemical structure can be fully revealed by NMR, which is unmatched by any other analytical technique.
- Beginning in the 1950s, NMR spectroscopy transformed organic chemistry and established itself as a vital technique for determining the structures of tiny, soluble compounds.
- NMR quickly dominated other fields of chemical sciences as the technique advanced. The method became a mainstay in materials characterization as well as it became possible to analyze macromolecules and solids as well.
- Since its inception, NMR spectroscopy has grown dramatically in all areas, including scientific and technological advancement and its applications in the natural sciences.
- As a result, it would be hard to discuss all pertinent issues pertaining to this

comprehensiveanalytical instrument.

- The reader will learn about the fundamentals of NMR spectroscopy, instrumentation, historical evolution, brands that are now on the market, practical cost considerations, sample preparation, and spectrum interpretation in this lesson.
- We demonstrate some cutting-edge methods pertinent to materials characterisation. We demonstrate the enormous scope of the technique in the examination of materials using a small number of examples from various areas of materials research.
- An extensive list of resources should aid the reader in exploring NMR spectroscopy further after our unavoidably constrained introduction.[6]

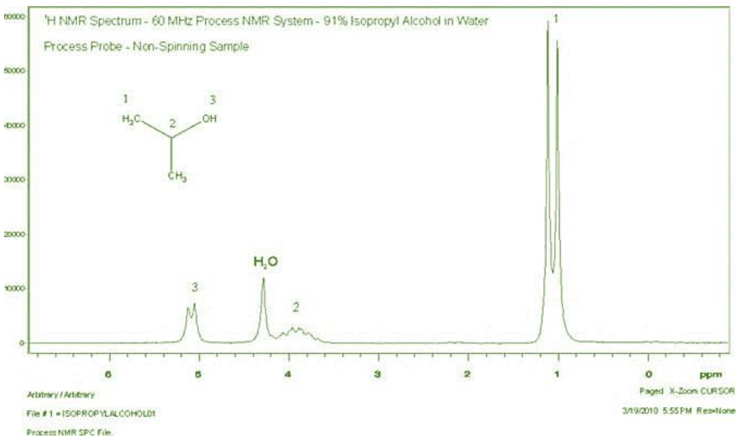

Fig. 2: A published NMR spectrum of isopropanol.

NMR spectroscopy is a common technique for identifying organic chemicals. It is based onthe phenomenon known as Larmor precession, in which the magnetic moment of a spin 1/2 particle in a magnetic field rotates around the magnetic field's axis.

We can obtain an extremely accurate measurement of the strength of the local magnetic field around the particle by measuring the frequency of this procession (the Larmor frequency). Because hydrogen nuclei are spin 1/2 particles, we can use proton NMR to uniquely identify many molecules containing hydrogen.[7]

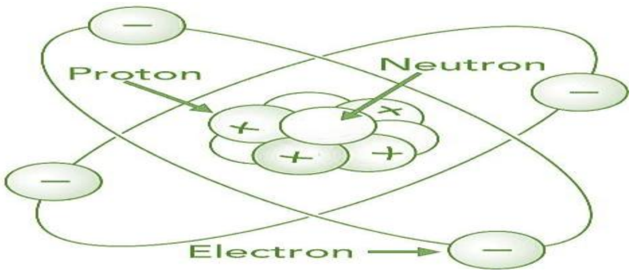

Fig. 3: Nuclei.

Consider a nucleus that contains a proton, with the proton serving as a symbol for the spin moment. As a result, the proton starts to behave like a little magnet. To determine whether nuclear magnetic resonance is active for an atom, a specific principle must exist. Thus, the nuclear magnetic resonance will only be active if an atom's spin quantum number is greater than 0. Nuclear magnetic resonance won't be triggered if the quantum number falls to zero. This will be achievable once the atomic number and mass are identical, or when their spin quantum is zero. Therefore, it may be claimed that nuclear magnetic resonance will only be active when the atomic number and atomic mass are not equal.

The term nuclear magnetic resonance is made up of three words: nuclear, magnetic, and resonance. This implies that the nucleus should include all of the information about a nucleus with protons and neutrons, where the proton has a positive charge and the neutron has not. When an electron rotates around the nucleus, the electron itself revolves in its place, indicating that the electron has some spin. The electron can have a clockwise or counterclockwise spin moment. The other term, magnetic, suggests that the magnetic field is also involved. When electrons rotate, an angular moment develops, and magnetism is seen.[1]

The Significantly Used NMR

1 H may be used to identify the kind and quantity of atoms in an atom.

2 Used to identify the different sorts of carbon atoms in an atom. In hydrogen nuclear magnetic resonance, atoms are evaluated using hydrogen atoms. When an atom is examinedusing a carbon atom as the foundation of a carbon nuclear magnetic resonance. Different compounds can have their structures determined using nuclear magnetic resonance methods.[1]

Various kinds of nuclear magnetic resonance spectroscopy

I. Solid-state NMR

For chemical analysis, solid state nmrs are utilized to identify any structural alterations that occur during phase transitions and other solid state transformations. Magic angle spinning is the most often employed method in a solid-state NMR (MAS). The smaller NMR lines produced by this magic angle result in narrower signals that give isotropic values and spinning sidebands to determine the CS of the nuclei for structural characterization of solid materials, improving sample resolution.

II. Phosphorus nuclear resonance spectroscopy

Phosphorus is one of the isotopes utilised in solid-state NMR to examine the molecules and structures of various materials. Orthophosphate diesters, polyphosphate, phosphonates, orthophosphate monoesters, and orthophosphates were among the phosphorus compound classes discovered.

III. Proton nuclear magnetic resonance

The first and most common atom employed in NMR spectroscopy is the proton. It is also known as hydrogen-NMR (1 H-NMR), because it offers details on the various types of hydrogen that are present in the molecule as well as details on its surroundings. Small CS range is visible in the 15 1 H-NMR spectra of the primary materials for the chemical under study. There is a significant variance in the magnitude of the coupling constant for this CS, which runs from +14 to -14 ppm.

IV. 27 Silicon magic angle spinning nuclear magnetic resonance

The 29 Si isotope of silicon, which is employed in 29 Si-NMR, has a 4.70% natural occurrence with the half spin nucleus and is a crucial ingredient. It is an additional spectroscopic method for examining the structures of organic molecules. Its magnetic moment value is a bit low, which results in a low resonance frequency. Between +50 and -200 ppm, there is a preponderance of 29 Si-NMR shifts.

V. 19 Fluorine magic angle spinning nuclear magnetic resonance

All fluoride isotopes save for the 19 F isotope are incredibly rare in nature. The only stable isotope of fluorine that can be discovered in significant amounts is F-19. It is employed in the 19 F MAS NMR method because of its excellent nuclear properties and large amount. When compared to 1 H-NMR, the 19 F-NMR approach is more faster, and the 19 F nucleus is unquestionably one of the most accessible NMR nuclei. The spin of fluorine is half- nuclear. Its binding energy is 147,801 keV, and nine electrons typically surround its nucleus in molecules. Fluorine is extremely reactive because 19 F-NMR spectroscopy has a high sensitivity to its CS (to analyse the fine features of the local environment).

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VII. 13 Carbon nuclear magnetic resonance spectroscopy

This method is an important resource for identifying carbon atoms in any biological substance. Additionally, it provides thorough details on the chemical composition of the investigated organic component. Only 1.1% of carbon is found naturally in the isotope 13 C, which has a spin quantum number of 1, and may be found via 13 C-NMR. Given that the primary isotope of carbon, 12 C, is not magnetically active and cannot be identified using this method, 13 C-NMR is less sensitive to carbon. In carbon-NMR, the signal intensities are typically not comparable to the number of matching 13 C atoms. They heavily rely on the numbers of nearby spins.

VIII. 27 Aluminum magic angle spinning nuclear magnetic resonance

The nuclear spin is 5/2 and the natural abundance of 27 Aluminum MAS-NMR is 100% The aluminum's incredibly sensitive core produces wide lines throughout a wide range of CS. This NMR's primary use is to detect the presence of aluminium and track any potential structural changes in the various types of aluminium. In a prior work, the transformation of Al (IV) into Al (VI) in the setting glass carbomer cement was seen using 27 Al-NMR.[3]

2. Principles of NMR Spectroscopy

Basic mechanism of action of nuclear

The fundamental tenet of NMR is that the nuclei of different substances, which have their own unique magnet field, may be used to determine their structural and chemical composition. The fundamental NMR spectrometer measures the changes using a magnetic field and a particular detector. Electrically charged nuclei move from a lower energy level (E1) to a higher energy level (E2) as a result of the strength of the external magnetic field. The difference between E2 and E1 is represented by the symbol E, which depends on the strength of the magnetic field and the size of the nuclear field moment. The nuclei migrate to a higher energy level (E1/E2) when the NMR signal is attained by the electromagnetic radiation rhythm at a frequency (v). Stopping this electromagnetic radiation results in the nuclei to relax and accomplish thermal equilibrium. This release of energy from the nuclei is recorded in the form of spectra on the computer, and these spectra are exclusive for every nucleus and are equivalent to the energy levels between the two states (E2/E1).[3]

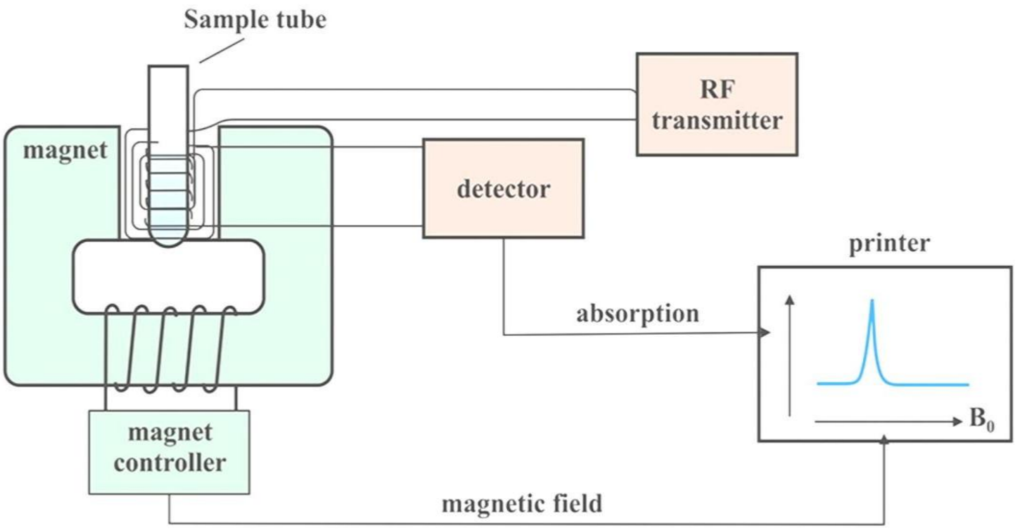


Fig. 4: NMR Spectrometer.

Nuclear spin

An atom's protons and neutrons have spin. In some substances, such as carbon 12C, oxygen 16O, and sulphur 32S, the protons and neutrons have paired spins that cancel each other out and prevent the nucleus from spinning. In some substances, such as proton 1H, phosphorus 31P, and fluoride 19F, the number of protons and neutrons in an atom is unpaired.

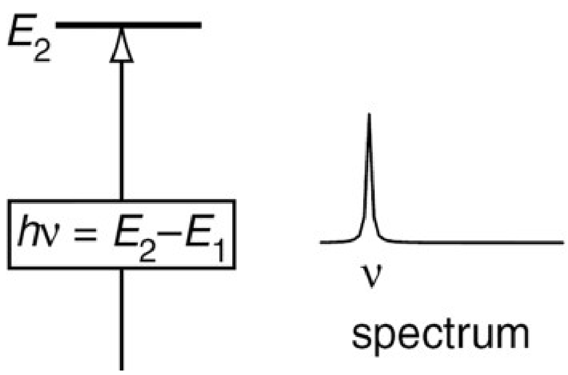


Fig. 5: Applied magnetic Field and The nuclear moment.

A magnetic moment is produced in the atomic nucleus of an atom by the spin of the protons and neutrons. This magnetic moment may point in the direction of the external magnetic field or The nuclear moment with the applied magnetic field away from it. B0 denotes this applied magnetic field. The more desired direction of the nuclear moment is toward the magnetic field which is at lower energy level denoted as α compared with the path opposite to the magnetic field denoted as β5. The magnetic field is accountable for retaining the distinction in the energy levels. If it does not happen, all the orientations of the spin of 21+ 1 would be of equal energy.[3]

Magnetic field strength

NMR necessitates a high and homogenous magnetic field. The strength of the magnetic field is measured in Tesla or MHz. To represent the nucleus in NMR, a reference nucleus is required the magnetic field's strength**.**[11]

Chemical shift

The flow of electrons generates a magnetic field inside and outside the nucleus. This magnetic field is formed in a different direction than the surrounding magnetic field.

Any change in the magnetic field induces a corresponding change in the NMR spectra. The nature of the nucleus and the migration of electrons in its surrounding atoms and molecules govern the sum of the shift. This is known as "chemical shift (CS)." A reference chemical is required to measure CS9 and to identify and distinguish magnetically inequivalent nucleiin a molecule.

Coupling of spins

Due to the divergent magnetic fields of the nearby nuclei, an incident known as spin-spin coupling (SS) is caused. NMR signals can be separated if this direction is either toward or away from the magnetic field. Depending on the unique nuclei having characteristic distance and relative potency, this magnetic field direction could either strengthen or diminish the signals of NMR signals that can split into two or more components.

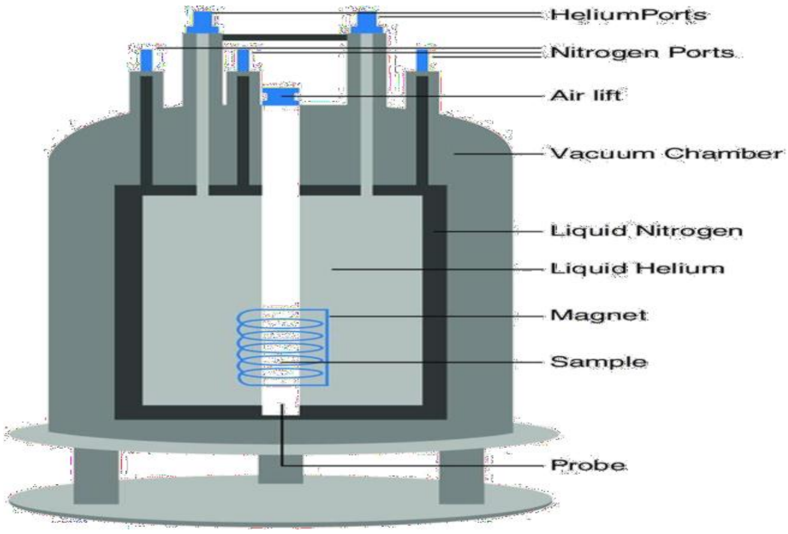
Spin Relaxation (SR)

Energy levels stabilize as a result of spin relaxation. This happens as a result of the loss of resonance signals over time after releasing the resonance frequency. The nuclear spin can stabilize again through two relaxation processes: spin-spin relaxation and spin-lattice relaxation.11 T1 is the duration it takes for a given nucleus to regain thermal stability. This process may be affected by a number of factors, including solution composition, temperature, molecular mass, and structure.[3]

3. Instrumentation of NMR Spectroscopy

3.1 Instrumentation and Working of NMR

Three primary parts make up an NMR spectrometer: a superconducting magnet, a probe, and a sophisticated electronic apparatus (console) run by a workstation.



The creation of a powerful magnetic field by the magnet causes the atoms in the sample to align their nuclear spins. These days, the magnets used in NMR spectroscopy are made of superconducting materials, necessitating extremely low temperatures for them to function (around 4 K). This is why NMR spectrometers include a cooling system made up of many layers of thermal isolating materials, an inner jacket filled with liquid helium, a second jacket filled with liquid nitrogen, and all of these together.[12]

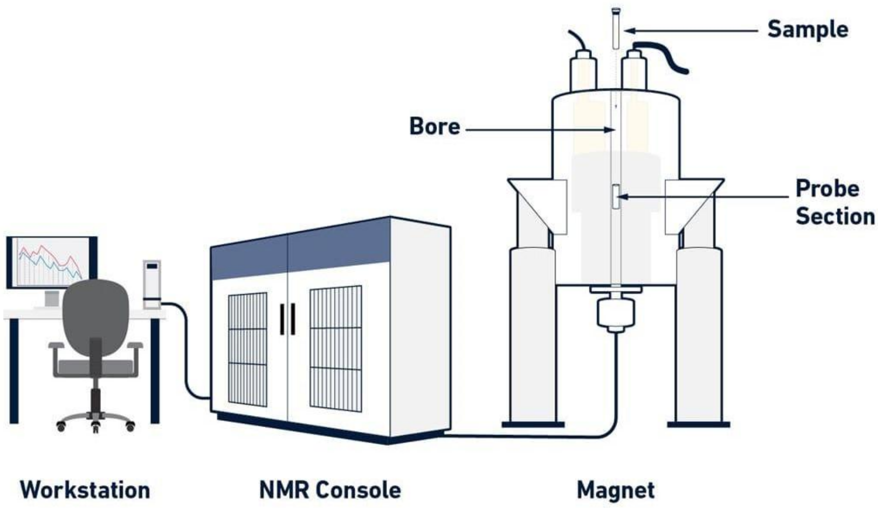


Fig. 7: General design of an NMR spectrometer with principal components.

A essential element of the equipment, the "probe" is a cylindrical chamber encircled by the superconducting magnet. The sample is inserted into the probe and exposed to the magnetic field as a result. The probe also has a number of magnetic coils that are positioned all aroundthe sample (Fig 4.2). These coils serve a variety of functions. On the one hand, they are utilised to irradiate the radiofrequency pulses as well as to find and gather the NMR signalthe sample emits. However, they also make it possible to regulate the magnetic field's homogeneity and apply pulse gradients, which are both employed in some NMR research.

Finally, the electronic system of the spectrometer controls all the experimental conditions and enables the set up and modification of every parameter of the NMR experiment through the workstation. This system is also responsible for data acquisition and subsequent mathematical transformation into an NMR spectrum. The spectrum contains a series of peaks of different intensities as a function of a magnitude known as the chemical shift thatis derived from the Larmor frequency of the different atomic nuclei present in the sample.

Where, both in Hz, vL is the measured Larmor frequency of a nucleus and vL0 is the reference nucleus's Larmor frequency. Chemical shift is generally stated in parts per million (ppm). Using a reference substance, such as sodium trimethyl silyl propane sulfonate (DSS)for 1H or tetramethylsilane (TMS), the chemical shift scale's zero value is established.[13]

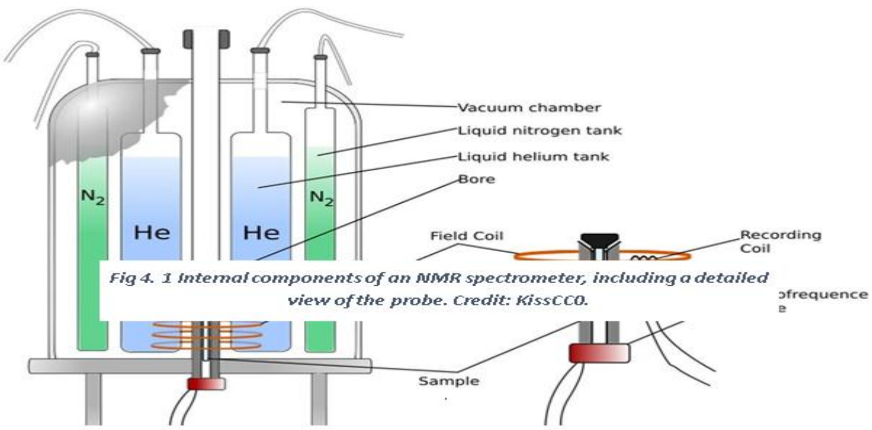


Fig. 8: Internal components of an NMR spectrometer.

An NMR spectrum provides a lot of information about the molecules present in the sample. First, chemical groups within a molecule can be identified from chemical shift values. In the example provided in Figure 5, acetic acid (H3C-COOH) has four protons so you could be forgiven for expecting to see four signals in the spectrum. However, the three protons of the methyl group (CH3) are magnetically equivalent and therefore have the same chemical shift.

This means that one signal comes from the CH3 group and the other one, from the proton.[13]

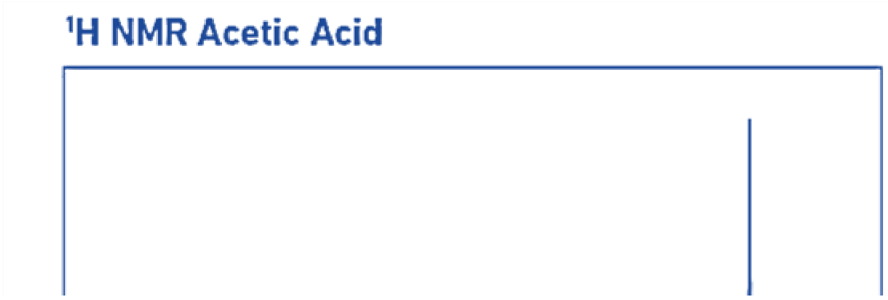


Fig. 9: Shows an illustration of a proton (1H) NMR spectrum.

The carboxylic acid group (COOH). Secondly, in 1H-NMR spectra, signal area is proportional to the number of atomic nuclei producing that signal (this does not apply to 13C-NMR spectra). In this example, if the areas of both signals were to be calculated, the most. Will be three times larger than the other.[13]

Intensesignal

3.2 Advantages and Disadvantages of NMR

3.2.i Advantages

- The molecular mechanisms and chemical interactions have been largely determined because of NMR.
- This method has made it possible to learn more about the intricate aspects of the physical and chemical properties of structures.
- The characteristics of CS can also be examined using NMR, and it can provide information on the local bonding environment surrounding a specific atom that can be estimated over alonger period of time.[28]
- It makes use of the pseudo wave function to learn more about complex large-scale structures.
- NMR can help with studies of biological processes carried out invivo, which is difficult to accomplish with current imaging methods.
- X-ray diffraction is inferior to NMR in terms of quality when determining the structure of ancient bones.[19]
- The ability to obtain highly detailed and accurate data on the molecular structure of a sampleis one of the major benefits of NMR Spectroscopy.
- The ability to obtain rich data from intact molecules.

- NMR instruments have allowed researchers to measure self-diffusion coefficients and extract valuable physical data from samples. This includes viscosity, molecular size and ionic conductivity and transference.[3]

3.2.ii Disadvantage

- An unavoidable outcome when performing the NMR technique is the requirement to perform in a surrounding which has a high magnetic field.
- The presence of the magnetic field can affect the proper functioning of monitors and computer-controlled devices.
- If any sharp objects such as a scalpel, scissors, or stapler are present in the NMR magneticfield area, it can get attracted to the magnet field which can cause severe injuries to the workers.
- Nowadays, monitoring devices used in the magnetic field area are being designed to function properly under the magnetic field.
- Furthermore, instruments being used in NMR studies are made nonferromagnetic to reduce the problems encountered with high magnetic field surroundings.
- NMR system cannot be purchased by a single investigator or for single research because ofits high cost.[3]

3.3 Application of NMR

- NMR spectroscopy is widely employed in a variety of disciplines, but it is most frequentlyused in chemistry and the life sciences.
- Chemical applications of NMR: The identification and structural clarification of organic, organometallic, and biological compounds is the primary use of NMR spectroscopy in chemistry.[2]
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- Chemical applications of NMR: The identification and structural clarification of organic, organometallic, and biological compounds is the primary use of NMR spectroscopy in chemistry.
- Chemistry: purification determination, product quality control, and structural determinationof novel chemicals
- Pharmaceutics: Is the study of structure, dynamics, and molecular interactions with the goal of discovering new medications, monitoring their quality, and determining their

purity.

- Petrochemistry: evaluation of rock materials to determine whether the oil reserve is suitable for exploitation, composition analysis of petroleum derivatives using solid state NMR, andproduct quality control.
- Materials: characterization of new materials by solids state NMR.[26]
- The application of NMR in the life sciences : NMR spectroscopy has been widely used in the life sciences to resolve the structural details of biological macromolecules, such as peptides, proteins, lipids, carbohydrates, and nucleic acids. Because of the immense complexity of these systems, a unique strategy must be used.
- This comprises: Using isotopic labelling to increase the sample's 13C, 15N, or even 2H contentthe use of unique NMR pulses to increase resolution and minimise signal overlapping Using high-dimensional NMR experiments (2D, 3D or even higher).[23]

4. CONCLUSION

In terms of the broad range of systems that may be researched and the kinds of information that can be gathered about the system of interest, nuclear magnetic resonance is a very efficient analytical tool. Data should be available both qualitative and quantitative. Considering the NMR technique's positive advantages, it can be stated with assurance that it has become a preferred method for any diagnosis, treatment planning, maintenance of treatment, and also to monitor how foreign substances interact with the human body. The NMR spectroscopic method is an excellent analytical method that complies to the basic principles of green chemistry. NMR incorporates statistical tools that can aid in understanding any disease, but especially the immunogenicity in the field of immunology. Without fractionation or derivatization, NMR may examine several compounds in different biochemical mixtures in an untargeted method. Human infections, diseases, treatments, immunology, and NMR spectroscopy are all attempting to address existing and future health issues in the subject of genomics. Since some basic work has already been done in these NMR areas, more investigation must yet be conducted. There will be development and commercialization of NMR techniques, particularly high-throughput combined LC-MS NMR techniques and processes.

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