Journal of Advances and Scholarly Researches in Allied Education
Vol. 12, Issue No. 2, January-2017, ISSN 2230-7540

A Study on the NMR Spectroscopy

Raval Manish Kumar*

Department of Chemistry in OPJS University, Churu, Rajasthan

Abstract – Nuclear Magnetic Resonance (NMR) spectroscopy is an analytical chemistry technique used in quality control and research for determining the content and purity of a sample as well as its molecular structure. For example, NMR can quantitatively analyze mixtures containing known compounds. For unknown compounds, NMR can either be used to match against spectral libraries or to infer the basic structure directly. Once the basic structure is known, NMR can be used to determine molecular conformation in solution as well as studying physical properties at the molecular level such as conformational exchange, phase changes, solubility, and diffusion.

The principle behind NMR is that many nuclei have spin and all nuclei are electrically charged. If an external magnetic field is applied, an energy transfer is possible between the base energy to a higher energy level (generally a single energy gap). The energy transfer takes place at a wavelength that corresponds to radio frequencies and when the spin returns to its base level, energy is emitted at the same frequency. The signal that matches this transfer is measured in many ways and processed in order to yield an NMR spectrum for the nucleus concerned.

Keywords – Nuclear, NMR, Diffusion

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INTRODUCTION

The precise resonant frequency of the energy transition is dependent on the effective magnetic field at the nucleus. This field is affected by electron shielding which is in turn dependent on the chemical environment. As a result, information about the nucleus' chemical environment can be derived from its resonant frequency. In general, the more electronegative the nucleus is, the higher the resonant frequency. Other factors such as ring currents (anisotropy) and bond strain affect the frequency shift. It is customary to adopt tetramethylsilane (TMS) as the proton reference frequency. This is because the precise resonant frequency shift of each nucleus depends on the magnetic field used. The frequency is not easy to remember (for example, the frequency of benzene might be 400.132869 MHz) so it was decided to define chemical shift as follows to yield a more convenient number such as 7.17 ppm.

Nuclear magnetic resonance spectroscopy, most commonly known as NMR spectroscopy or magnetic resonance spectroscopy (MRS), is a spectroscopic technique to observe local magnetic fields around atomic nuclei. The sample is placed in a magnetic field and the NMR signal is produced by excitation of the nuclei sample with radio waves into nuclear magnetic resonance, which is detected with sensitive radio receivers. The intramolecular magnetic field around an atom in a molecule changes the resonance frequency, thus giving access to details of the electronic structure of a molecule and its individual functional groups. As the fields are unique or highly characteristic to individual compounds, in modern organic chemistry practice, NMR spectroscopy is the definitive method to identify monomolecular organic compounds. Similarly, biochemists use NMR to identify proteins and other complex molecules. Besides identification, NMR spectroscopy provides detailed information about the structure, dynamics, reaction state, and chemical environment of molecules. The most common types of NMR are proton and carbon-13 NMR spectroscopy, but it is applicable to any kind of sample that contains nuclei possessing spin.

NMR spectra are unique, well-resolved, analytically tractable and often highly predictable for small molecules. Different functional groups are obviously distinguishable, and identical functional groups with differing neighboring substituents still give distinguishable signals. NMR has largely replaced traditional wet chemistry tests such as color reagents or typical chromatography for identification. A disadvantage is that a relatively large amount, 2–50 mg, of a purified substance is required, although it may be recovered through a workup. Preferably, the sample should be dissolved in a solvent, because NMR analysis of solids requires a dedicated magic angle spinning machine and may

not give equally well-resolved spectra. The timescale of NMR is relatively long, and thus it is not suitable for observing fast phenomena, producing only an averaged spectrum. Although large amounts of impurities do show on an NMR spectrum, better methods exist for detecting impurities, as NMR is inherently not very sensitive - though at higher frequencies, sensitivity is higher.

Correlation spectroscopy is a development of ordinary NMR. In two-dimensional NMR, the emission is centered around a single frequency, and correlated resonances are observed. This allows identifying the neighboring substituents of the observed functional group, allowing unambiguous identification of the resonances. There are also more complex 3D and 4D methods and a variety of methods designed to suppress or amplify particular types of resonances. In nuclear Overhauser effect (NOE) spectroscopy, the relaxation of the resonances is observed. As NOE depends on the proximity of the nuclei, quantifying the NOE for each nucleus allows for construction of a three-dimensional model of the molecule.

NMR spectrometers are relatively expensive; universities usually have them, but they are less common in private companies. Between 2000 and 2015, an NMR spectrometer cost around 500,000 - 5 million USD.

Modern NMR spectrometers have a very strong, large and expensive liquid helium-cooled superconducting magnet, because resolution directly depends on magnetic field strength. Less expensive machines using permanent magnets and lower resolution are also available, which still give sufficient performance for certain applications such as reaction monitoring and quick checking of samples. There are even benchtop nuclear magnetic resonance spectrometers. NMR can be observed in magnetic fields less than a millitesla. Low-resolution NMR produces broader peaks which can easily overlap one another causing issues in resolving complex structures. The use of higher strength magnetic fields result in clear resolution of the peaks and is the standard in industry.

When placed in a magnetic field, NMR active nuclei (such as ^{1}H or ^{13}C) absorb electromagnetic radiation at a frequency characteristic of the isotope. The resonant frequency, energy of the radiation absorbed, and the intensity of the signal are proportional to the strength of the magnetic field. For example, in a 21 Tesla magnetic field, hydrogen atoms (commonly referred to as protons) resonate at 900 MHz. It is common to refer to a 21 T magnet as a 900 MHz magnet since hydrogen is the most common nucleus detected, however different nuclei will resonate at different frequencies at this field strength in proportion to their nuclear magnetic moments.

An NMR spectrometer typically consists of a spinning sample-holder inside a very strong magnet, a radio-frequency emitter and a receiver with a probe (an antenna assembly) that goes inside the magnet to surround the sample, optionally gradient coils for diffusion measurements, and electronics to control the system. Spinning the sample is usually necessary to average out diffusional motion, however some experiments call for a stationary sample when solution movement is an important variable. For instance, measurements of diffusion constants (*diffusion ordered spectroscopy* or DOSY) are done using a stationary sample with spinning off, and flow cells can be used for online analysis of process flows.

NMR SPECTROSCOPY

The vast majority of molecules in a solution are solvent molecules, and most regular solvents are hydrocarbons and so contain NMR-active protons. In order to avoid detecting only signals from solvent hydrogen atoms, deuterated solvents are used where 99+% of the protons are replaced with deuterium (hydrogen-2). The most widely used deuterated solvent is deuterochloroform ($CDCl_3$), although other solvents may be used for various reasons, such as solubility of a sample, desire to control hydrogen bonding, or melting or boiling points. The chemical shifts of a molecule will change slightly between solvents, and the solvent used will almost always be reported with chemical shifts. NMR spectra are often calibrated against the known solvent residual proton peak instead of added tetramethylsilane.

To detect the very small frequency shifts due to nuclear magnetic resonance, the applied magnetic field must be constant throughout the sample volume. High resolution NMR spectrometers use shims to adjust the homogeneity of the magnetic field to parts per billion (ppb) in a volume of a few cubic centimeters. In order to detect and compensate for inhomogeneity and drift in the magnetic field, the spectrometer maintains a "lock" on the solvent deuterium frequency with a separate lock unit, which is essentially an additional transmitter and RF processor tuned to the lock nucleus (deuterium) rather than the nuclei of the sample of interest. In modern NMR spectrometers shimming is adjusted automatically, though in some cases the operator has to optimize the shim parameters manually to obtain the best possible resolution.

Upon excitation of the sample with a radio frequency (60–1000 MHz) pulse, a nuclear magnetic resonance response - a free induction decay (FID) - is obtained. It is a very weak signal, and requires sensitive radio receivers to pick up. A Fourier transform is carried out to extract the frequency-domain spectrum from the raw time-

domain FID. A spectrum from a single FID has a low signal-to-noise ratio, but it improves readily with averaging of repeated acquisitions. Good ^{1}H NMR spectra can be acquired with 16 repeats, which takes only minutes. However, for elements heavier than hydrogen, the relaxation time is rather long, e.g. around 8 seconds for ^{13}C. Thus, acquisition of quantitative heavy-element spectra can be time-consuming, taking tens of minutes to hours.

Following the pulse, the nuclei are, on average, excited to a certain angle vs. the spectrometer magnetic field. The extent of excitation can be controlled with the pulse width, typically ca. 3-8 μs for the optimal 90° pulse. The pulse width can be determined by plotting the (signed) intensity as a function of pulse width. It follows a sine curve, and accordingly, changes sign at pulse widths corresponding to 180° and 360° pulses.

Decay times of the excitation, typically measured in seconds, depend on the effectiveness of relaxation, which is faster for lighter nuclei and in solids, and slower for heavier nuclei and in solutions, and they can be very long in gases. If the second excitation pulse is sent prematurely before the relaxation is complete, the average magnetization vector has not decayed to ground state, which affects the strength of the signal in an unpredictable manner. In practice, the peak areas are then not proportional to the stoichiometry; only the presence, but not the amount of functional groups is possible to discern. An inversion recovery experiment can be done to determine the relaxation time and thus the required delay between pulses. A 180° pulse, an adjustable delay, and a 90° pulse is transmitted. When the 90° pulse exactly cancels out the signal, the delay corresponds to the time needed for 90° of relaxation.[13] Inversion recovery is worthwhile for quantitive 13C, 2D and other time-consuming experiments.

A spinning charge generates a magnetic field that results in a magnetic moment proportional to the spin. In the presence of an external magnetic field, two spin states exist (for a spin 1/2 nucleus): one spin up and one spin down, where one aligns with the magnetic field and the other opposes it. The difference in energy (ΔE) between the two spin states increases as the strength of the field increases, but this difference is usually very small, leading to the requirement for strong NMR magnets (1-20 T for modern NMR instruments). Irradiation of the sample with energy corresponding to the exact spin state separation of a specific set of nuclei will cause excitation of those set of nuclei in the lower energy state to the higher energy state.

For spin 1/2 nuclei, the energy difference between the two spin states at a given magnetic field strength is proportional to their magnetic moment. However, even if all protons have the same magnetic moments, they do not give resonant signals at the same frequency values. This difference arises from the differing electronic environments of the nucleus of interest. Upon application of an external magnetic field, these electrons move in response to the field and generate local magnetic fields that oppose the much stronger applied field. This local field thus "shields" the proton from the applied magnetic field, which must therefore be increased in order to achieve resonance (absorption of rf energy). Such increments are very small, usually in parts per million (ppm). For instance, the proton peak from an aldehyde is shifted ca. 10 ppm compared to a hydrocarbon peak, since as an electron-withdrawing group, the carbonyl deshields the proton by reducing the local electron density. The difference between 2.3487 T and 2.3488 T is therefore about 42 ppm. However a frequency scale is commonly used to designate the NMR signals, even though the spectrometer may operate by sweeping the magnetic field, and thus the 42 ppm is 4200 Hz for a 100 MHz reference frequency (rf).

However, given that the location of different NMR signals is dependent on the external magnetic field strength and the reference frequency, the signals are usually reported relative to a reference signal, usually that of TMS (tetramethylsilane). Additionally, since the distribution of NMR signals is field dependent, these frequencies are divided by the spectrometer frequency. However, since we are dividing Hz by MHz, the resulting number would be too small, and thus it is multiplied by a million. This operation therefore gives a locator number called the "chemical shift" with units of parts per million.[14] In general, chemical shifts for protons are highly predictable since the shifts are primarily determined by simpler shielding effects (electron density), but the chemical shifts for many heavier nuclei are more strongly influenced by other factors including excited states ("paramagnetic" contribution to shielding tensor).

DISCUSSION

The chemical shift provides information about the structure of the molecule. The conversion of the raw data to this information is called assigning the spectrum. For example, for the 1H-NMR spectrum for ethanol (CH3CH2OH), one would expect signals at each of three specific chemical shifts: one for the CH3 group, one for the CH2 group and one for the OH group. A typical CH3 group has a shift around 1 ppm, a CH2 attached to an OH has a shift of around 4 ppm and an OH has a shift anywhere from 2–6 ppm depending on the solvent used and the amount of hydrogen bonding. While the O atom does draw electron density away from the attached H through their mutual sigma bond,

the electron lone pairs on the O bathe the H in their shielding effect.

In paramagnetic NMR spectroscopy, measurements are conducted on paramagnetic samples. The paramagnetism gives rise to very diverse chemical shifts. In 1H NMR spectroscopy, the chemical shift range can span up to thousands of ppm.[15]

Because of molecular motion at room temperature, the three methyl protons average out during the NMR experiment (which typically requires a few ms). These protons become degenerate and form a peak at the same chemical shift.

The shape and area of peaks are indicators of chemical structure too. In the example above—the proton spectrum of ethanol—the CH3 peak has three times the area of the OH peak. Similarly the CH2 peak would be twice the area of the OH peak but only 2/3 the area of the CH3 peak.

Software allows analysis of signal intensity of peaks, which under conditions of optimal relaxation, correlate with the number of protons of that type. Analysis of signal intensity is done by integration—the mathematical process that calculates the area under a curve. The analyst must integrate the peak and not measure its height because the peaks also have width—and thus its size is dependent on its area not its height. However, it should be mentioned that the number of protons, or any other observed nucleus, is only proportional to the intensity, or the integral, of the NMR signal in the very simplest one-dimensional NMR experiments. In more elaborate experiments, for instance, experiments typically used to obtain carbon-13 NMR spectra, the integral of the signals depends on the relaxation rate of the nucleus, and its scalar and dipolar coupling constants. Very often these factors are poorly known - therefore, the integral of the NMR signal is very difficult to interpret in more complicated NMR experiments.

Some of the most useful information for structure determination in a one-dimensional NMR spectrum comes from J-coupling or scalar coupling (a special case of spin–spin coupling) between NMR active nuclei. This coupling arises from the interaction of different spin states through the chemical bonds of a molecule and results in the splitting of NMR signals. For a proton, the local magnetic field is slightly different depending on whether an adjacent nucleus points towards or against the spectrometer magnetic field, which gives rise to two signals per proton instead of one. These splitting patterns can be complex or simple and, likewise, can be straightforwardly interpretable or deceptive. This coupling provides detailed insight into the connectivity of atoms in a molecule.

Coupling to n equivalent (spin ½) nuclei splits the signal into a n+1 multiplet with intensity ratios following Pascal's triangle as described on the right. Coupling to additional spins will lead to further splittings of each component of the multiplet e.g. coupling to two different spin ½ nuclei with significantly different coupling constants will lead to a doublet of doublets (abbreviation: dd). Note that coupling between nuclei that are chemically equivalent (that is, have the same chemical shift) has no effect on the NMR spectra and couplings between nuclei that are distant (usually more than 3 bonds apart for protons in flexible molecules) are usually too small to cause observable splittings. Long-range couplings over more than three bonds can often be observed in cyclic and aromatic compounds, leading to more complex splitting patterns.

For example, in the proton spectrum for ethanol described above, the CH3 group is split into a triplet with an intensity ratio of 1:2:1 by the two neighboring CH2 protons. Similarly, the CH2 is split into a quartet with an intensity ratio of 1:3:3:1 by the three neighboring CH3 protons. In principle, the two CH2 protons would also be split again into a doublet to form a doublet of quartets by the hydroxyl proton, but intermolecular exchange of the acidic hydroxyl proton often results in a loss of coupling information.

CONCLUSION

Coupling to any spin-1/2 nuclei such as phosphorus-31 or fluorine-19 works in this fashion (although the magnitudes of the coupling constants may be very different). But the splitting patterns differ from those described above for nuclei with spin greater than ½ because the spin quantum number has more than two possible values. For instance, coupling to deuterium (a spin 1 nucleus) splits the signal into a 1:1:1 triplet because the spin 1 has three spin states. Similarly, a spin 3/2 nucleus splits a signal into a 1:1:1:1 quartet and so on.

Coupling combined with the chemical shift (and the integration for protons) tells us not only about the chemical environment of the nuclei, but also the number of *neighboring* NMR active nuclei within the molecule. In more complex spectra with multiple peaks at similar chemical shifts or in spectra of nuclei other than hydrogen, coupling is often the only way to distinguish different nuclei.

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Corresponding Author

Raval Manish Kumar*

Department of Chemistry in OPJS University, Churu, Rajasthan