Proton NMR

One Dimensional H-NMR

Common types of NMR experiments:

1-H NMR

a. Experiment – High field proton NMR (400MHz). single-pulse experiment.

b. Spectral Interpretation

i. Number of multiplets gives the different H-environments

ii. Splitting patterns indicate number of protons on ‘adjacent Cs’

iii. Integration, indicates relative number of types of protons.

iv. Chemical shift (ppm), indicates chemical environment.

A H nucleus that is surrounded by higher electron density will generally come into resonance at lower frequency than a nucleus surrounded by less electron density.

Thus the number of ‘multiplets’ gives the number of different H-environments in the molecule.

The ‘mean position’ of resonance of a group of nuclei is termed the chemical shift, δ, (ppm). δ indicates chemical environment.

A chemical shift a measure of the resonance frequency of a particular type of nucleus compared to that of a standard molecule, TMS in 1H-NMR, scaled to the frequency of the spectrometer and reported as parts per million, ppm.

Free rotation about sigma bonds make the nuclei equivalent on the NMR time scale.

Ratio of the integrated of peaks (peak areas/heights) indicates relative number of protons in different environs.

Peak (multiplet) area ∝ nH generating the signal, however area peaks are not perfect.
Hyperfine Splitting: (J-coupling/ scalar coupling)

NMR signals split into multiple peaks when molecules contain non-equivalent hydrogen atoms that are separated by covalent (usually no more than three bonds for saturated compounds).

The multiplets result from the spin-spin coupling between nuclei, an interaction in which nuclear spins of non-equivalent adjacent atoms influence each other.

Signal splitting allows the determination of how different H-carrying atoms are connected in a molecule, because atoms on adjacent 'functional' groups can generally split each other.

The general rule is that a signal will be split into \((n+1)\) peaks if there are \(n\) equivalent (or nearly equivalent) \(H\) atoms three bonds away.

Equivalent protons – protons that are having the same chemical shift and spin coupling.

Splitting (patterns) are indicative of the equivalence (nearly) or nonequivalence of the adjacent H (environ).
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In vicinal coupling is the dihedral angle \( \alpha \) between the adjacent C-H bonds and whether or not it is fixed is important. Coupling is highest when the angle 0° and 180°, and is lowest at 90°.

Bonds that rotate rapidly at room temperature do not have a fixed angle between adjacent C-H bonds, so an average angle and an average coupling is observed.

This latter concept is important for the interpretation of 1H-NMR spectra for alkanes and other flexible molecules.
Note the splitting constant $J$; for ‘groups’ of atoms with spins coupled, $J$ values are the same!!

The splitting arises because there are $n+1$ different possible spin state combinations of $n$ spins, aligned and against the external magnetic field arising from $n$ equivalent protons.

The probability of a molecule having a given set of spins is proportional to the number of possible spin alignments giving rise to that spin state.

Peaks in the multiplet pattern conforms to the coefficients of the Binomial expansion (Pascal triangle - first order spectra).

In a first-order spectrum where chemical shift difference is much larger than their coupling constant (nuclei $A$ and nuclei $X$), $\Delta \delta_{A,X} > 6 J_{A,X}$ the interpretation of splitting patterns is straightforward; multiplets are well separated.

The multiplicity of a multiplet is given by the number of equivalent neighboring equivalent atoms, $n$ plus 1, $(n+1)$ rule.

Equivalent nuclei do not interact with each other.

The coupling constant is independent on the applied field.

Multiplets can be easily distinguished from closely spaced chemical shifts.

Peaks in the multiplet pattern conforms to the coefficients of the Pascal triangle.

Splitting by more than one non-equivalent atoms:

To predict the splitting pattern use a tree diagram applying different couplings applied sequentially.

**General case**, a signal will be split into $(n + 1)(m + 1)$ peaks for an $H$ atom that is coupled to a set of $n$ $H$ atoms with $J$ value, and to another set of $m$ $H$ atoms with another $J$. 

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$J_{AB} > J_{BC}$
Note the splitting constant $J$: for ‘groups’ of atoms that are spin coupled, $J$ values are the same!!

$J_{AB} > J_{BC}$

Analysis of first order spectral clusters

Examine the area ratios starting from an end. Notice the area ratio patterns. Compare to the Pascal triangle values. The ratio values ordain the type of multiplet at this level. Determine the splitting at this (last) stage. (doublet here)

Repeat the procedure until the process end up in a single peak; i.e. the peak position without hyperfine splitting.
Equivalent protons – chemical shift and magnetic (spin coupling).

Chemical Shift Equivalence

Symmetry makes atoms equivalent. Atoms or groups in identical physical locations relative to a plane of symmetry or center of symmetry in a molecule are equivalent.

Rapid processes makes atoms equivalent as well.

Diastereoscopic – no σ thro' CH2; nonequivalent.
Rapid Interconversions

- a. Keto-enol tautomerism
- b. Around partial double bonds
- c. Rings
- d. Rotation around sigma bonds

Magnetic Equivalence (Spin-Coupling equivalence):

Applicable (to be considered) for chemical shift equivalent protons only. The chemical shift equivalent protons must have the same spin couplings to other nuclei to be magnetically equivalent.

\[ J_{AX} = J_{AX'} \]

Non-equivalent protons at o,p positions

Note spectral symmetry

Splitting (patterns) are indicative of the equivalence (nearly) or nonequivalence of the adjacent H (environs).

Non-conformation to the ‘n+1’ rule

Unsymmetrical molecules with restricted bond rotation such as alkenes or rings, as well as molecules for which stereochemistry is important (where equivalence do not exist).

Note the splitting pattern for such systems are complex.

Geminal coupling

The dihedral angle between C-H bonds determines the extent of coupling (\( J \)). Therefore the bond rotation is a key parameter. Where free rotation about the C-C \( \sigma \) bonds exist, H - C bonds are equivalent (e.g. -CH\(_2\)- and -CH\(_3\)) due to the rapid bond rotation (exception -CH\(_2\)- is adjacent to a stereo-center).

Where there is restricted bond rotation (alkene or cyclic) H’s bonded to same C atom may not be equivalent, especially if the molecule is not symmetrical, the nonequivalent H nuclei on the same C atom will couple to each other and generating splitting of the peaks - geminal coupling.
The tree diagram is useful to identify the spin coupled atoms

Strongly Coupled (Second and Higher order) Spectra

In these spectra the simple rules used to construct multiplets (area ratios) are no longer valid. This is because the chemical shift differences between the spins (nuclei A and nuclei B) are small compared to the couplings $\Delta \delta_{A-B} < 8 J_{A-B}$. Peak splitting can range less to more than expected and unusual relative peak intensities arise; second-order spectra.

The overall effect of strong coupling is the roofing/tilting of multiplets.
The degree of leaning depends on proximity of the chemical shifts of the absorption, and The strength of the coupling. Closer $\nu$ values and larger $J$ values leads to greater leaning of the ‘roof’.

Exchangeable H atoms

- OH, -SH, -NH

1. OH, NH protons are exchangeable (fast in NMR scale – no coupling, single peak or merged into background). The acidic H signal broadens, do not undergo coupling. H-N would couple to ($^3J$) adjacent protons.

2. OH, SH, NH, H- bonded
   a. intermolecular (δ - solvent, concentration, temperature dependent)
   b. intramolecular

3. 14N (I=1, nuclear quadrupole interacts, lowers lifetime of H excited states, single broader peak or merged into bkg.)

Detection of acidic (exchangeable) protons

Acidic protons can be exchanged with deuterium ions. Mixing a compound with D₂O achieves this task. The H-NMR spectrum of the exchanged product would be absent of the acidic H peak.

The exchanged product is HOD, the H of which appears at 4.7ppm as a single peak.

Solvent Effect: Change of solvent generally changes chemical shifts slightly due to solvent-solute interactions changing the electronic environments of atoms.
Long Range Coupling

\( ^3J \); \( n>3 \) occur in rigid structures; alkenes, alkynes, aromatics, stained rings.

\( W \) conformation of four sigma bonds.

Appendix F for coupling constants.

Areas under multiplets

In principle the area under the multiplets are proportional to the number of protons generating the multiplets.

Integration and T₁

1-D Experiment

Usual H-NMR experiment is a single channel experiment repeated; a single pulse experiment, repeated.

Protons are excited via irradiation (Channel 1) and the same channel is used to observe the FID of the signal.

FID is then Fourier Transformed to obtain the NMR spectrum.

Note the FID decay characterized by a time constant that is related to the rate of re-equilibration
Signal intensity given by the integration of peaks is proportional to $M_0$'s the number of a given type of atoms resonating at it's frequency.

However the above fact is dependent on how well the experiment parameters are set up.

Pulse experiments (FT-NMR) are repeated, single pulse experiments, where the nuclei are 'excited' and their decay is followed (during which time an FID is captured) after each pulse.

All FIDs from the repeated application of a series of pulses (scans) are summed.

The summed FID is then transformed into the frequency domain to generate the traditional spectrum.

The 'decay' of excited nuclei restores the system to equilibrium. It takes time to restore, 'relaxation time', $T_1$.

It is imperative that all nuclei relaxes back to equilibrium. However every type of nuclei do not decay at the same rate.

Therefore, if the 'next' pulse in the multi-pulse protocol is applied before complete relaxation; without giving sufficient delay time ($5T_1$) between pulses, the signal size in the transformed spectrum is not proportional to the number of nuclei slow decaying nuclei (usually less).
Selective Spin Decoupling: Double Resonance

Decoupling is done as a two channel experiment.

Channel 1: Excite and observe protons (pulse)
Channel 2: Excite the nucleus to be decoupled (CW)

Heteronuclear decoupling: different types of atoms involved (observed atom and decoupled atom type different)

Homonuclear decoupling: same types of atoms involved (observed atom and decoupled atom type same)

If the spin states of the nucleus/nuclei adjacent to a certain nucleus is/are flipped between their two spin states very fast, equalizing the populations then that particular nucleus would not be able to distinguish (feel) the spin states of the fast spin flipping neighbors.

The resonance peak appears as if the neighbor ‘do not exist’.

That is, the particular nucleus gets decoupled from the neighbors.

The result is the elimination of scalar (J) coupling and it results in the merging of the otherwise spin coupled ‘peaks’.

Further the peaks of the decoupled nuclei vanishes.

Homonuclear decoupling

Scalar (J) coupling arises due to through bond interactions of nuclei in close proximity.

Another type of interaction is dipolar coupling which occurs through space and is dependent on the direct distance between nuclei. This interaction manifests in decoupling experiments.

The excess energy provided to the molecule via the Channel 2 (much larger than in double resonance experiment, inverts populations) finds a ‘way’ to dissipate via dipolar coupling to the ‘nearby’ nuclei. The excess energy shifts population of spin states from the ‘equilibrium states’. Thus sets up the need to reestablish the populations.
This in turn increases the population of protons low energy spin states in close proximity, usually ~5 Angstroms from the decoupled nucleus.

In NOE difference experiments, a $^1$H is selectively pre-irradiated until saturation is achieved. During the pre-irradiation period, NOE buildup occurs at other $^1$H nuclei close in space.

Then a 90° pulse is applied, 90° pulse then creates an observable magnetization, which is detected during the acquisition period.
The final NOe difference spectra are displayed as the difference between a spectrum recorded with on-resonance pre-irradiation and a reference spectrum that has all proton absorptions at the same conditions but off resonance.

Nuclear Overhauser Effect:

Consider a two channel experiment where one channel excites a spin I and the other saturates a spin S.

Assume the spins I and S are close enough to have a dipole-dipole coupling (the through-space interaction) and there is no spin-spin coupling (i.e. scalar coupling) among I and S.

This experiment leads to the enhancement of the signal from spin I. This phenomenon is known as the Nuclear Overhauser Effect (NOE).

This enhancement is due to the change in relative populations of the energy levels brought about by the saturation of S spins and the subsequent relaxation processes.
The NOE effect occurs through space and is operational within a ~5Å sphere centered around the irradiated nuclei ("NOE range"). It does not enhance resonance signals away from "range" from the irradiated 'centre'. NOE allows determination of the proximity of the nuclei to the irradiated ones, thus is an excellent technique to ascertain the inter-proton distances/stereochemistry of molecules.

Note:
NMR signals with high multiplicities (> 5) may have very low intensities and may be less than the level in the output. E.g. (CH₃)₂CHCH₂OH, multiplicity = 21.

Multiple overlapping may give complex peak ‘splitting’.

"Long-range"-couplings (> 3 bond) may be stronger (π bonds). E.g. CH₃COOCH₃C=CCCH₂OH.

Higher order spectra. Relative intensities of peaks of multiplets changes extensively; usual patterns not followed.

Spin-spin couplings between protons and other magnetically active nuclei (e.g., ³¹P, ¹³C or ¹⁹F) leads to additional peak splitting.