Proton Nuclear Magnetic Resonance (^{1}H NMR)

Proton nuclear magnetic resonance (proton NMR, hydrogen-1 NMR, or ^{1}H NMR) is the application of nuclear magnetic resonance in NMR spectroscopy with respect to hydrogen-1 nuclei within the molecules of a substance, in order to determine the structure of its molecules. In samples where natural hydrogen (H) is used, practically all the hydrogen consists of the isotope ^{1}H. A full ^{1}H atom is called protium. Solvents used in NMR., Deuterated solvents especially for use in NMR are preferred, e.g. deuterated water, D_2O, deuterated acetone, $(CD_3)_2CO$, deuterated methanol, CD_3OD, deuterated dimethyl sulfoxide, $(CD_3)_2SO$, and deuterated chloroform, $CDCl_3$. However, a solvent without hydrogen, such as carbon tetrachloride, CCl_4 or carbon disulfide, CS_2, may also be used.

Proton NMR spectra of most organic compounds are characterized by chemical shifts in the range +14 to -4 ppm and by spin-spin coupling between protons. The integration curve for each proton reflects the abundance of the individual protons. Simple molecules have simple spectra. The spectrum of ethyl chloride consists of a triplet at 1.5 ppm and a quartet at 3.5 ppm in a 3:2 ratio. The spectrum of benzene consists of a single peak at 7.2 ppm due to the diamagnetic ring current.

Multiplicity

Multiplicity or coupling is useful because it reveals how many hydrogens are on the next carbon in the structure. That information helps to put an entire structure together piece by piece. In ethanol, CH_3CH_2OH, the methyl group is attached to a methylene group. The ^{1}H spectrum of ethanol shows this relationship through the shape of the peaks. The peak near 3.5 ppm is the methylene group with an integral of 2H.

The peak is split into four smaller peaks, evenly spaced, with taller peaks in the middle and shorter on the outside. This pattern is called a multiplet, and specifically a quartet. A quartet means that these hydrogens have three neighboring hydrogens on adjacent carbons. The peak is split into three smaller ones, evenly spaced, with a taller one in the middle and shorter ones on the outside. This pattern is called a triplet. A triplet means that these hydrogens have two neighboring hydrogens on adjacent carbons.

The number of lines in a peak is always one more than the number of hydrogens on the neighboring carbon. The triplet for the methyl peak means that there are two neighbors on the next carbon (3 - 1 = 2H); the quartet for the methylene peak indicates that there are three hydrogens on the next carbon (4 - 1 = 3H). Below table summarizes coupling patterns that arise when protons have different numbers of neighbors.

Number of Lines	Ratio of Lines	Term for Peak	Number of Neighbors
1	-	Singlet	0
2	1:1	Doublet	1
3	1:2:1	Triplet	2
4	1:3:3:1	Quartet	3
5	1:4:6:4:1	Quintet	4
6	1:5:10:10:5:1	Sextet	5
7	1:6:15:20:15:6:1	Septet	6
8	1:7:21:35:35:21:7:1	Octet	7
9	1:8:28:56:70:56:28:8:1	Nonet	8

The third peak in the ethanol spectrum is usually a "broad singlet." This is the peak due to the OH.

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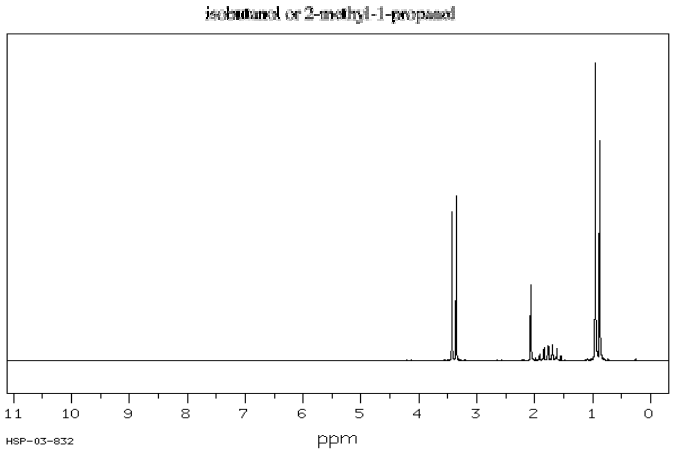
However, coupling is almost always lost on hydrogens bound to hetero atoms (OH and NH). The lack of communication between an OH or NH and its neighbors is related to rapid proton transfer, in which that proton can trade places with another OH or NH in solution. This exchange happens quite easily if there are even tiny traces of water in the sample.

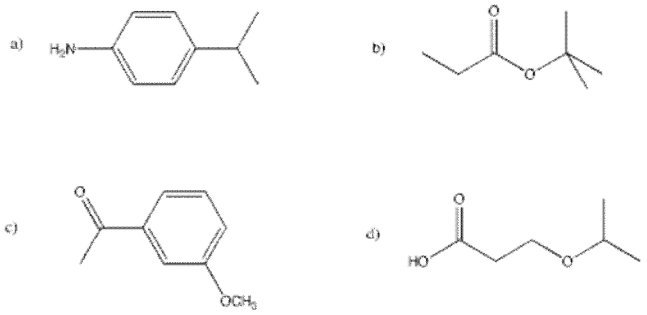
Multiplicity or coupling is what we call the appearance of a group of symmetric peaks representing one hydrogen in NMR spectroscopy. A proton can absorb at different frequencies because of the influence of neighboring hydrogens.

Protons on one carbon atom are affected by different protons on the next carbon atom, provided those two carbons are directly attached to each other. Stated another way, these neighboring hydrogens must be three bonds away (and so this phenomenon is sometimes called "three-bond coupling"). When a proton is coupled, the number of neighboring hydrogen is one less than the number of peaks in the multiplet.

The spectrum of isobutanol is shown below. Assign each peak to a different proton in the structure.

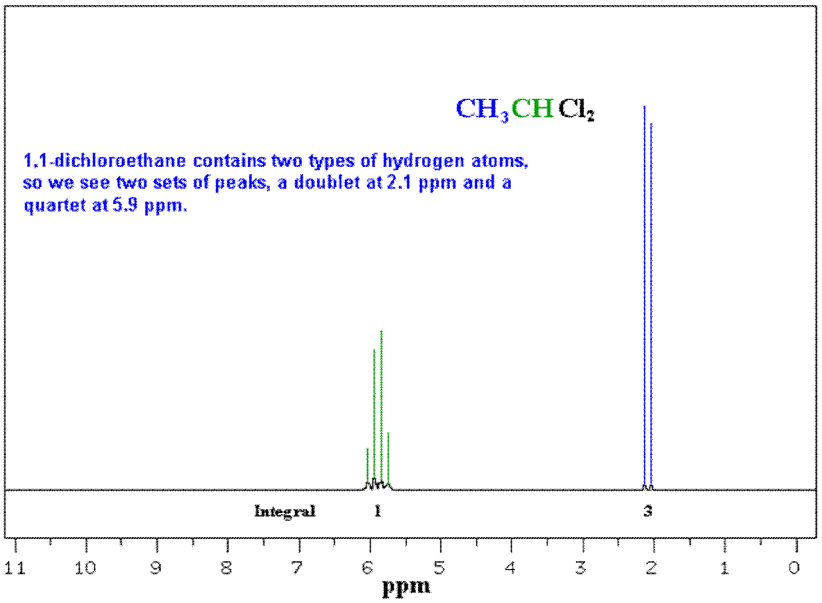


Sketch predicted ^{1}H NMR spectra, complete with coupling and integration, for the following structures:



Coupling in H-NMR

The H-NMR spectra usually have peaks that appear as groups of peaks due to **coupling** with neighboring protons, for example, see the spectra of 1,1-dichloroethane shown below.



δ = 5.9 ppm, integration = 1H Deshielded : Agrees with the **-$CHCl_2$** unit
δ = 2.1 ppm, integration = 3H : Agrees with **-CH_3** unit

Now, what about the coupling patterns ?

Coupling arises because the magnetic field of vicinal (adjacent) protons influences the field that the proton experiences. To understand the implications of this we should first consider the effect the -CH group has on the adjacent -CH3.

The proximity of "n" equivalent H on neighbouring carbon atoms, causes the signals to be split into "n+1" lines. This is known as the ***multiplicity*** or ***splitting***or***coupling pattern*** of each signal. Equivalent protons (or those with the same chemical shift) **do not couple** to each other. If the neighbours are not all equivalent, more complex patterns arise. To a first approximation, protons on adjacent sp^3 C tend to behave as if they are equivalent.

Now we can do more a complete analysis, including the application of the "n+1" rule to 1,1-dichloroethane:

δ = 5.9 ppm, quartet, integration = 1H, deshielded : agrees with the **-$CHCl_2$** unit next to a **-CH_3** unit (n = 3, so n + 1 = 4 lines). δ = 2.1 ppm, doublet, integration = 3H : agrees with **-CH_3** unit, next to a **-CH-** (n = 1, so n + 1 = 2 lines).

Coupling Constant (J)

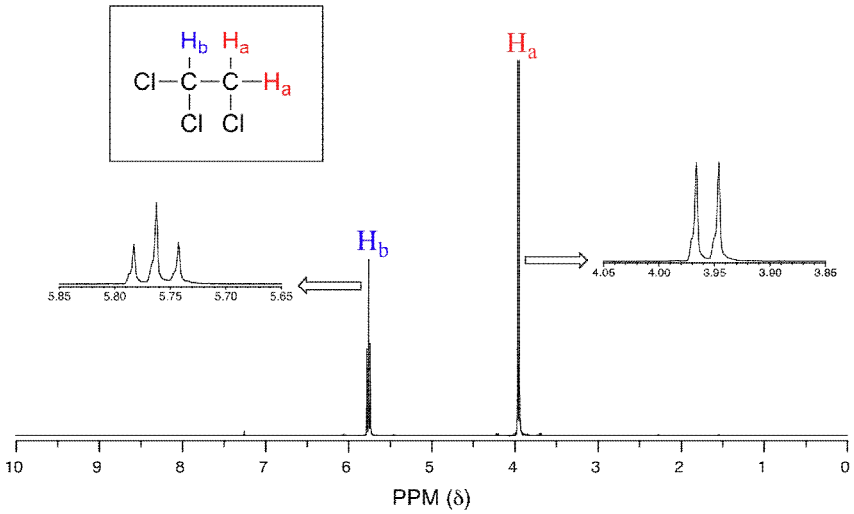
The coupling constant (J) is a measure of the interaction between a pair of protons. In a vicinal system of the general type, **H_a-C-C-H_b**then the coupling of **H_a** with **H_b**, J_{ab}, must be equal to the coupling of **H_b** with **H_a**, J_{ba}, therefore $J_{ab} = J_{ba}$. The implications are that the spacing between the lines in the coupling patterns are the same as can be seen in the coupling patterns from the H-NMR spectra of 1,1-dichloroethane (see left).

Spin-spin coupling

The source of spin-spin coupling

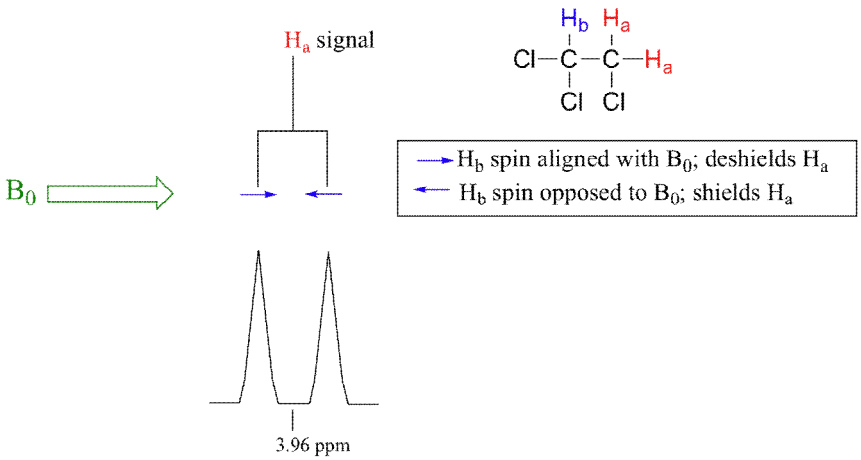
The ^{1}H-NMR spectra of most organic molecules contain proton signals that are 'split' into two or more sub-peaks. Rather than being a complication, however, this splitting behavior actually provides us with more information about our sample molecule.

Consider the spectrum for 1,1,2-trichloroethane. In this and in many spectra to follow, we show enlargements of individual signals so that the signal splitting patterns are recognizable.

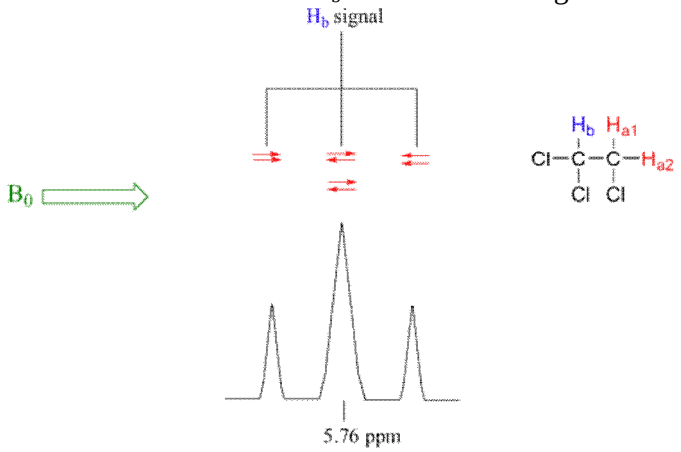


The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two sub peaks of equal height (and area) – this is referred to as a **doublet**. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were to integrate each sub peak, we would see that the area under the middle peak is twice that of each of the outside peaks. This is called a **triplet**.

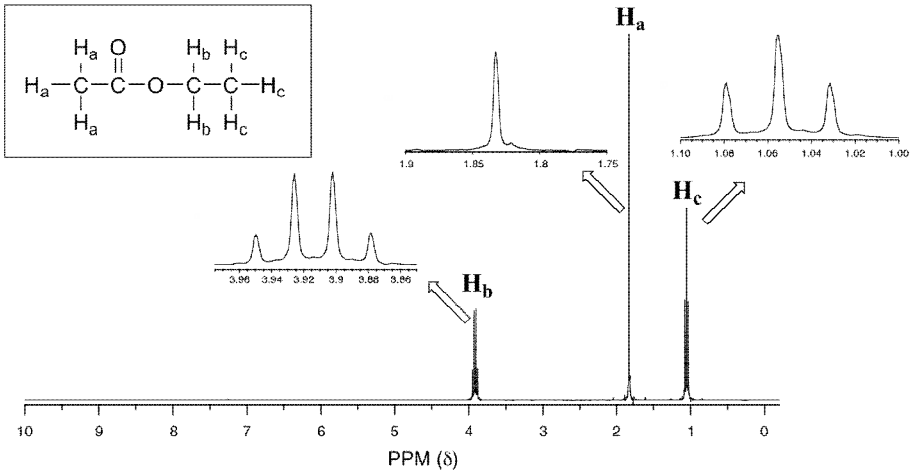
The source of signal splitting is a phenomenon called **spin-spin coupling**, a term that describes the magnetic interactions between neighboring, non-equivalent NMR-active nuclei. In our 1,1,2 trichloromethane example, the H_a and H_b protons are spin-coupled to each other. Here's how it works, looking first at the H_a signal: in addition to being shielded by nearby valence electrons, each of the H_a protons is also influenced by the small magnetic field generated by H_b next door. The magnetic moment of H_b will be aligned *with* B_0 inhalf of the molecules in the sample, while in the remaining half of the molecules it will be opposed to B_0. The B_{eff} 'felt' by H_a is a slightly weaker if H_b is aligned against B_0, or slightly stronger if H_b is aligned with B_0. In other words, in half of the molecules H_a is *shielded* by H_b and in the other half H_a is *deshielded* by H_b. What would otherwise be a single H_a peak has been split into two sub-peaks, one upfield and one downfield of the original signal. These ideas an be illustrated by a **splitting diagram**, as shown below.



Now, let's think about the $H_b$signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_{a1} and H_{a2}. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_{a1} and H_{a2} could be aligned with B_0, which would deshield H_b, shifting its NMR signal slightly downfield. Second, both the H_{a1} and H_{a2} magnetic fields could be aligned opposed to B_0, which would shield H_b, shifting its resonance signal slightly upfield. Third and fourth, H_{a1} could be with B_0 and H_{a2} opposed, or H_{a1}opposed to B_0 and H_{a2} with B_0. In each of the last two cases, the shielding effect of one H_a proton would cancel the deshielding effect of the other, and the chemical shift of H_b would be unchanged.

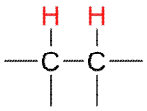


So in the end, the signal for H_b is a **triplet**, with the middle peak twice as large as the two outer peaks because there are *two* ways that H_{a1} and H_{a2} can cancel each other out.
Now, consider the spectrum for ethyl acetate:

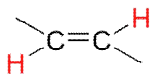


An unsplit '**singlet**' peak at 1.833 ppm that corresponds to the acetyl (H_a) hydrogens – this is similar to the signal for the acetate hydrogens in methyl acetate that we considered earlier. This signal is unsplit because there are no adjacent hydrogens on the molecule. The signal at 1.055 ppm for the H_c hydrogens is split into a triplet by the two H_b hydrogens next door. The explanation here is the same as the explanation for the triplet peak we saw previously for 1,1,2-trichloroethane.

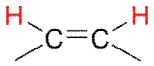
The $H_b$hydrogens give rise to a **quartet** signal at 3.915 ppm – notice that the two middle peaks are taller then the two outside peaks. This splitting pattern results from the spin-coupling effect of the *three* H_c hydrogens next door, and can be explained by an analysis similar to that which we used to explain the doublet and triplet patterns.



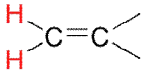
^3J = 6-8 Hz



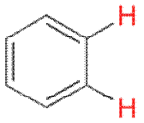
vinylic *trans*:
^3J = 11-18 Hz



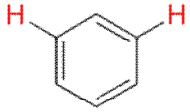
vinylic *cis*:
^3J = 6-15 Hz



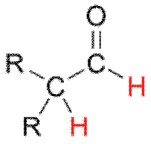
vinylic *gem*:
^2J = 0-5 Hz



ortho-benzylic:
^3J = 6-10 Hz

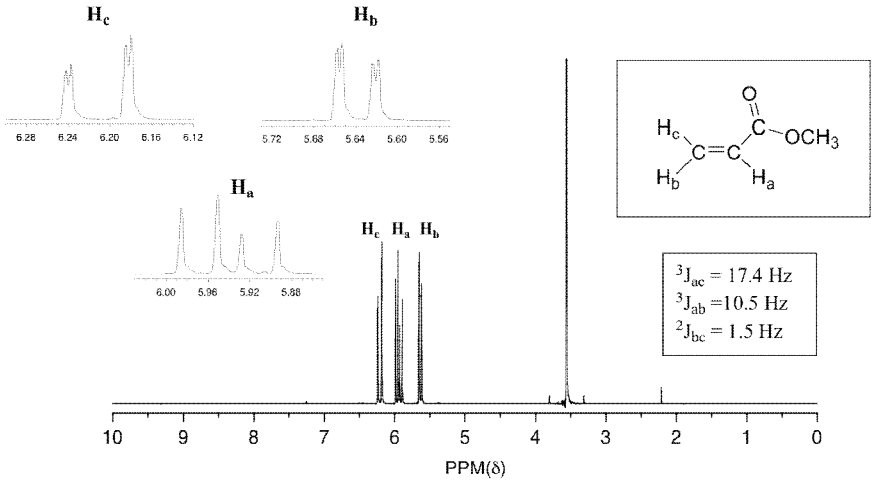


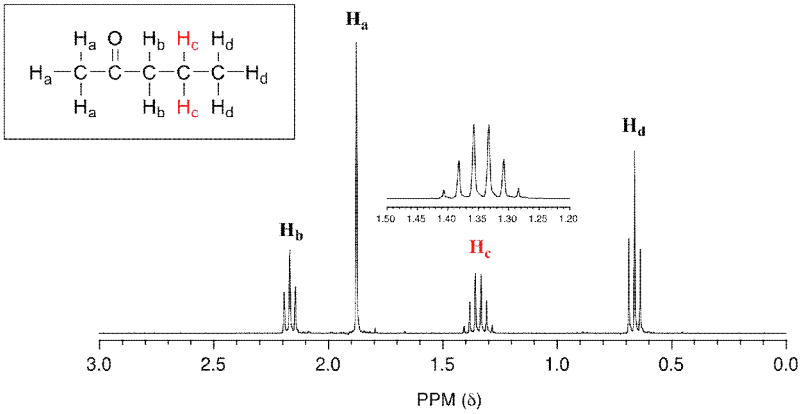
meta-benzylic:
^4J = 0-4 Hz

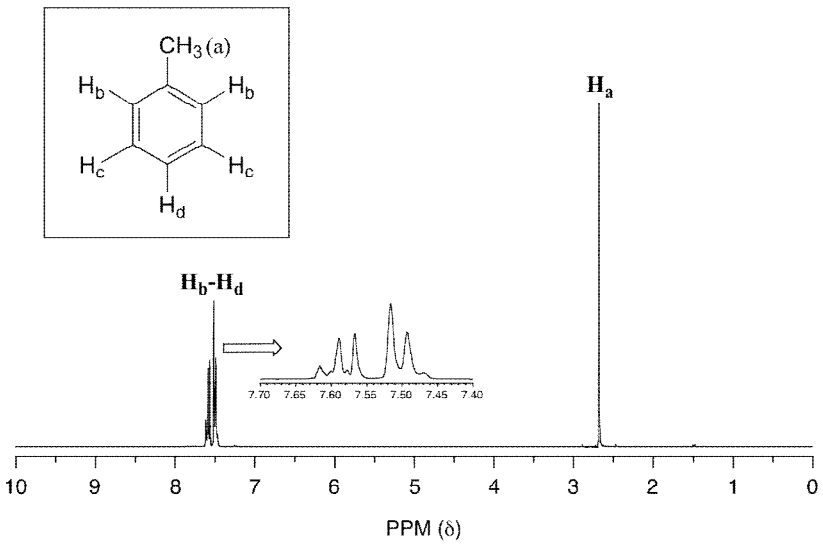


aldehyde:
^3J = 2-3 Hz

In all of the examples of spin-spin coupling that we have seen so far, the observed splitting has resulted from the coupling of one set of hydrogens to *just one* neighboring set of hydrogens. When a set of hydrogens is coupled to *two or more* sets of nonequivalent neighbors, the result is a phenomenon called **complex coupling**. A good illustration is provided by the ^{1}H-NMR spectrum of methyl acrylate:







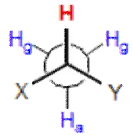
Vicinal Proton Coupling

The single most useful H-H coupling relationship is that between vicinal protons. The size of $^3J_{H\text{-}H}$ is predictable and provides detailed information about the special orientation between the two protons. Almost all $^3J_{HH}$ values are positive, but their magnitude varies widely depending on structural and conformational details.

Three bonds coupling across single bonds in acyclic systems with small conformational preferences, vicinal couplings are generally in the range 6-8 Hz, with electronegative substituent's causing smaller *J* values. Note in particular the reduced ^3J for protons on carbons bearing oxygen substituent's which is seen for all types of 3-bond couplings.

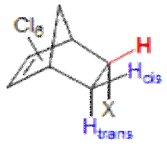
$CH_3–CH_2–X$

X	^3J	E	Ref.
Li	8.9	-1.0	*TL* **1963**, 767
$SiEt_3$	8.0	1.9	
H	8.0		*CJC* **1963**, 41,2114
I	7.45	2.5	
Br	7.33	2.8	
CH_3	7.26	2.5	*CJP* **1960**, 32, 67
Cl	7.23	3.1	
NEt_2	7.13	3.0	*JPC* **1964**, 68, 3430
OEt	6.97	3.5	*JPC* **1964**, 68, 3430
OH	6.97	3.5	*JCP* **1956**, 25, 362
F	6.9	4.0	*JACS* **1961**, 83, 4473
$^+OEt_2$	4.7		*JACS* **1959**, 81, 3826



For a methyl group, the observed coupling is the average of the three couplings, since these will be fully averaged by methyl rotation:

$$^3J_{obs} = \frac{J_g + J_g + J_a}{3} = \frac{4 + 4 + 13}{3} = 7$$



JACS **1962**, 84,516

X	J_{trans}	J_{cis}	E[a]
H	3.81	9.73	
CN	4.6	9.3	2.49
CO_2H	4.4	8.5	2.60
C_6H_5	4.2	8.9	2.75
Cl	3.2	8.0	3.25
OH	2.4	7.4	3.43
OAc	2.5	7.7	3.80

[a] *JCP* **1961**, **34**, 1099

When there are two electronegative substituents the vicinal coupling is reduced further, although adding a third such substituent does not seem to affect the coupling much.

CH_3-CHF_2
^3J = 4.5 Hz
JCP **1962**, *37*, 2907

CH_3-$CH(OH)_2$
^3J = 6.2 Hz
JCP **1956**, *25*, 362

CH_3-$CHCl_2$
^3J = 5.9 Hz
ASV

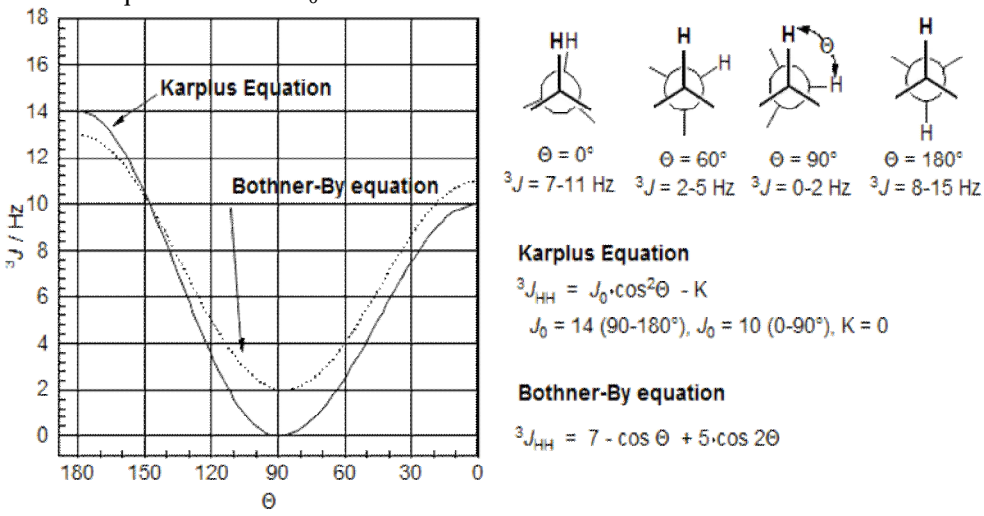
CH_3-$CH(OMe)_2$
^3J = 5.4 Hz
ASV

MeO-CH_2-$CHCl_2$
^3J = 5.8 Hz
ASV

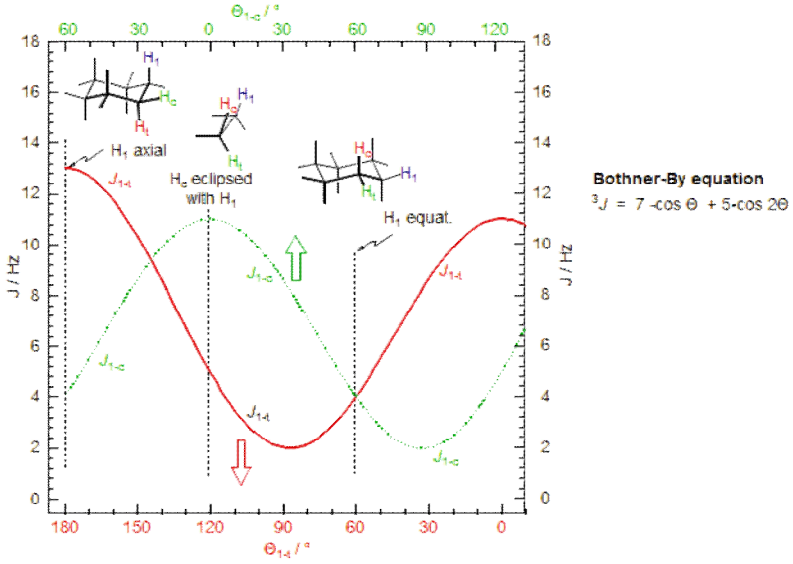
The Karplus Equation

The Karplus equation is based on the observation, supported by theoretical considerations, that vicinal H-H couplings will be maximal with protons with 180° and 0° dihedral angles (anti or eclipsed relationship results in optimal orbital overlap) and that coupling will be minimal (near 0) for protons that are 90° from each other. The equation gives us approximate values for $^3J_{HH}$ as a function of dihedral angle between the protons. The Karplus curve is the mainstay of conformational analysis for all ring systems, and has generally proved reliable if care is taken.

The constants J_o and K are used to correct for substituent effects in more sophisticated uses of the Karplus equation, different J_o values are also used for the 0 to 90° and the 90 to 180° sections of the curve. The Bothner-By equation provides an empirical "Karplus" curve that does not require different J_0 values for the 0-90 vs 90-180° sections:



A convenient graphical form of the Karplus relationship is given in below. Here two curves, separated by 120°, represent the predicted coupling constants for a proton H_1 coupled to an adjacent methylene group (H_{cis} and H_{trans}), as a function of the dihedral angle.



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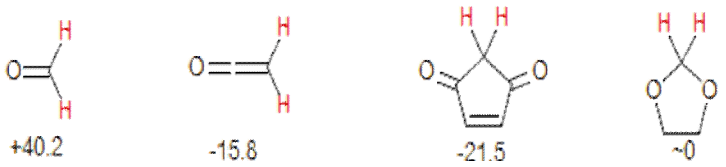
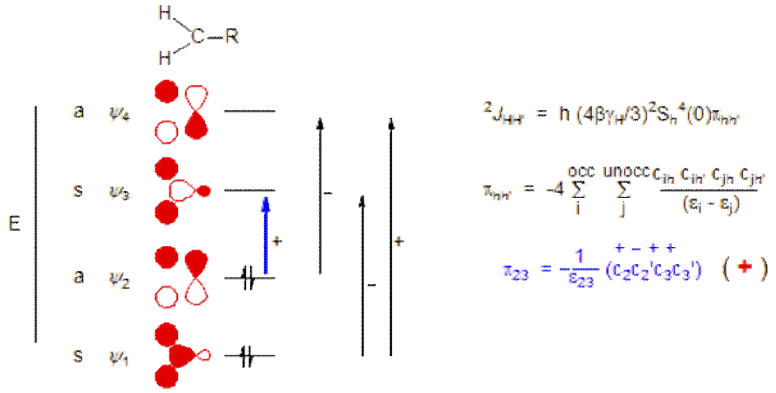
Geminal Proton Couplings ($^2J_{H\text{-}H}$)

Two-bond H-H couplings vary in a complicated way with structure, and they can only be understood if both magnitude and sign is taken into account. Some extreme examples are given below.

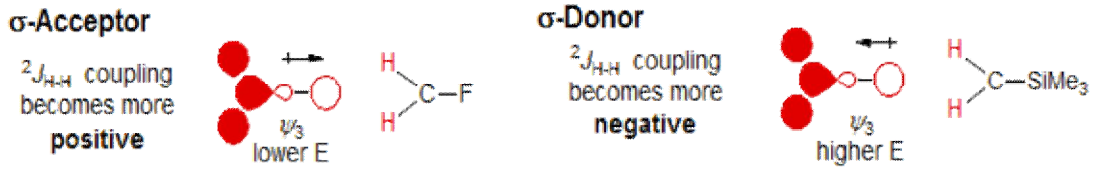


Most ^2J couplings fall into two well-defined groups. For unstrained sp^3 CH_2 protons with innocuous substituents, the coupling is typically around -12 Hz, whereas the 2-bond coupling of sp^2 (vinyl) protons is much smaller, typically 2 Hz. The molecular orbital perturbation theory of Pople and Bothner-By predicts the electronic effects of substituents on these coupling constants based on the interaction between filled and empty orbitals of the CH_2 fragment. Excitation between orbitals of the same symmetry has a negative effect on J, between orbitals of opposite symmetry has a positive effect.

The 1/E term is largest for the HOMO-LUMO transitions, so coupling effects are dominated by the ψ_2 ψ_3 transition. Substituents which reduce the energy gap between ψ_2 and ψ_3 (i.e. raise ψ_2 or lower ψ_3) will increase the size of 1/E and thus have a (+) effect on the coupling, whereas those which increase the energy gap (i.e. lower ψ_2 or raise ψ_3) will have a (-) effect. There are also changes in the orbital coefficients which affect the magnitude of the coupling.

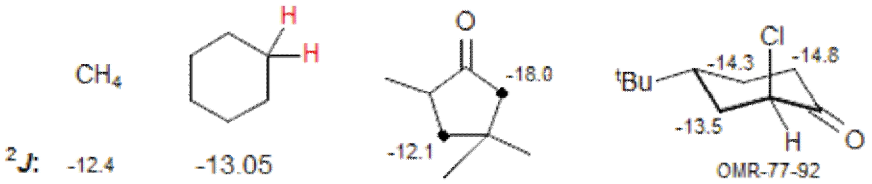


σ-Acceptor substituents (electronegative atoms like F, O, N) interact mainly with ψ_3 and ψ_1 because of symmetry restrictions. The most important effect is to lower ψ_3, and thus have a (+) effect on the coupling, whereas σ-donor substituents like Si or other metals will raise ψ_3 and thus have a (-) effect.

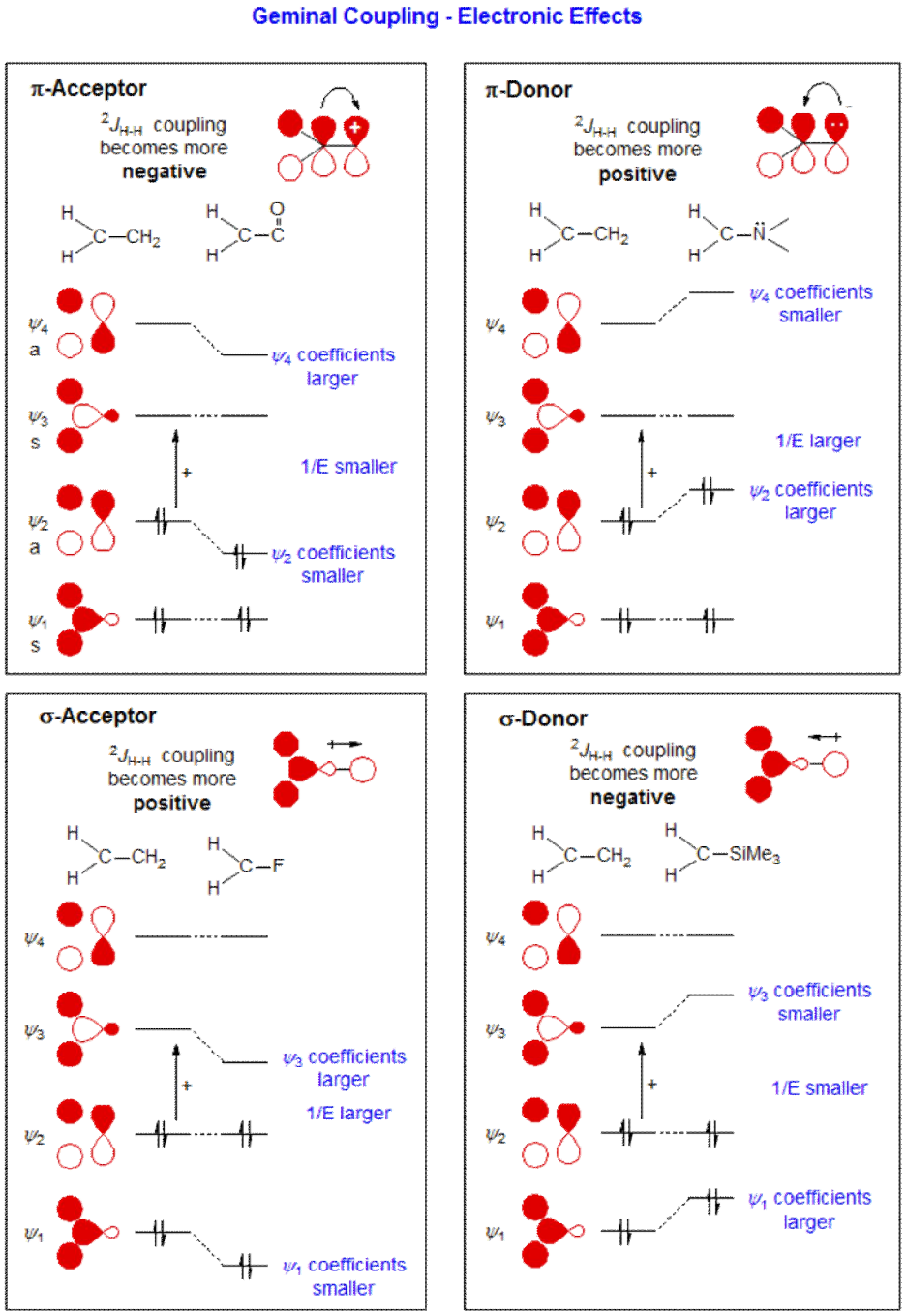


Remarkably, π-donors and acceptors have the opposite effect -- symmetry requires that these will interact mainly with ψ_2. Thus π-donor substituents (directly attached atoms with lone pairs, or adjacent electron rich bonds) will raise ψ_2, and result in a (+) effect, and π-acceptor substituents (carbonyl groups and related functions, or adjacent electron poor bonds) will lower ψ_2 and have a (-) effect.

Gem coupling in Saturated Carbons (sp^3): In acyclic and unstrained ring systems the gem coupling is typically from -10 to -13 Hz.

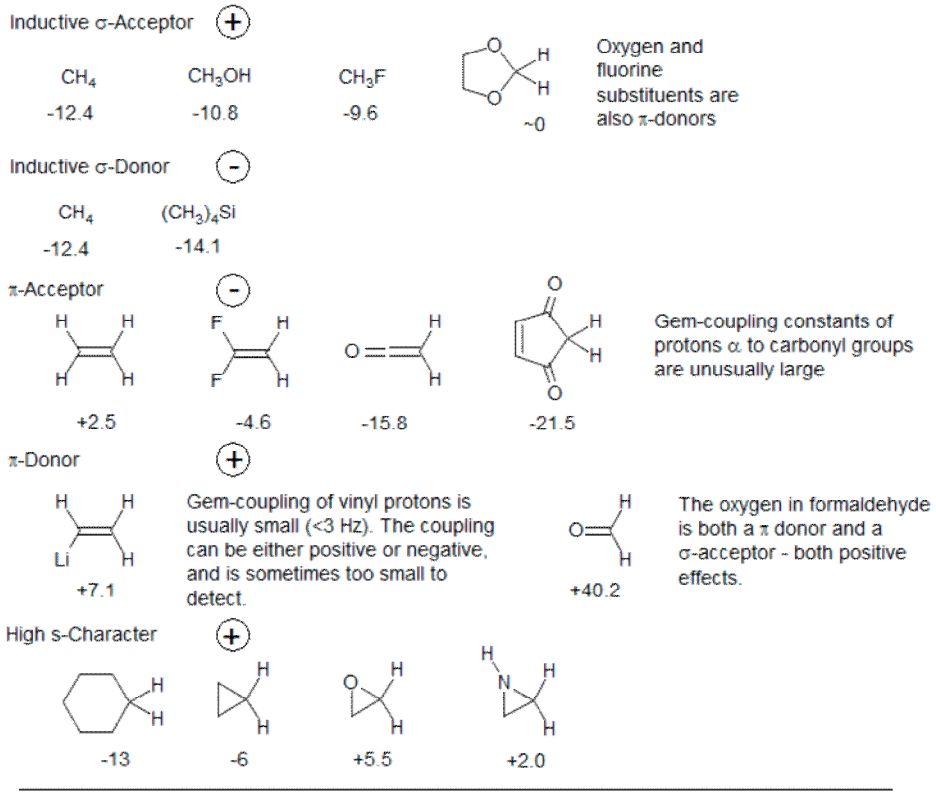


Substituents will change these couplings as described above: when the CH_2 group is substituted with a π-acceptor like a carbonyl, imino or cyano group, the coupling becomes more negative, i.e. larger in magnitude, ranging from -15 to -25 Hz.



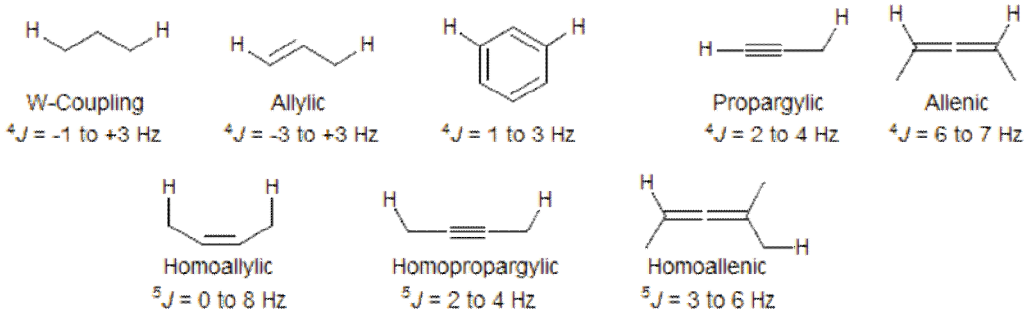
Geminal couplings between protons vary widely in sign and magnitude. There are both positive and negative substituent effects on the coupling, as summarized below. The

remarkable feature is that σ and π acceptors have opposite effects on the coupling, as do σ and π donors.



Long-Range (^4J and higher) Proton Couplings

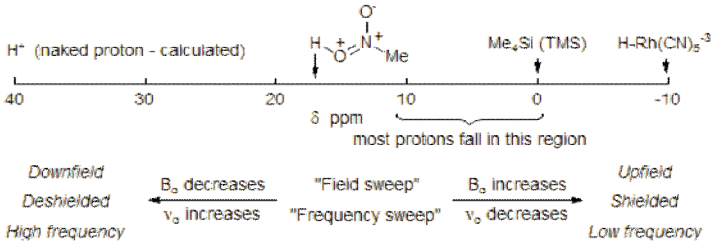
Proton-proton couplings over more than three bonds are usually too small to detect easily (< 1 Hz). However, there are a number of important environments where such couplings are present, and can provide useful structural information. Coupling across π-systems are the most frequently encountered ^4J couplings: the *meta*-coupling in aromatic compounds, and the 4-bond allylic, propargylic and allenic couplings. 4-Bond couplings across saturated carbons (sp^3) or heteroatoms are rarer, and are usually seen only in cyclic compounds when there is a favorable geometric alignment along the H-C-C-C-H chain ("W-Coupling"). Longer range couplings are also observed, particularly in acetylenes and allenes.



The Proton Chemical Shift Scale

Experimentally measured proton chemical shifts are referenced to the ^1H signal of tetramethylsilane (Me_4Si). For NMR studies in aqueous solution, where Me_4Si is not sufficiently soluble, the reference signal usually used is DSS ($Me_3Si\text{-}CH_2CH_2\text{-}SO_3^-Na^+$. For aqueous solution of cationic substrates where may be interactions between the anionic reference compound and the substrates, an alternative reference standard, DSA ($Me_3Si\text{-}CH_2CH_2\text{-}NH_3^+$ $CF_3CO_2^-$ has been suggested. Proton chemical shifts cover a range of over 30

ppm, but the vast majority appear in the region δ 0-10 ppm, where the origin is the chemical shift of tetramethylsilane.

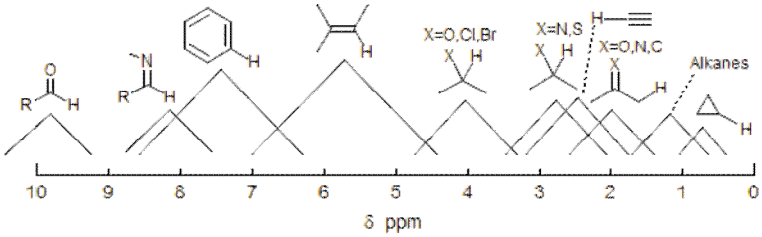


In the original continuous wave (CW) method of measuring NMR spectra, the magnetic field was scanned from left to right, from low to high values. We thus refer to signals on the right as upfield or shielded and signals to the left as downfield or deshielded. Later spectrometers gained the capability of scanning frequency, which then had to decrease from left to right during the scan, hence the "backwards" nature of NMR scales. δ units are defined as follows:

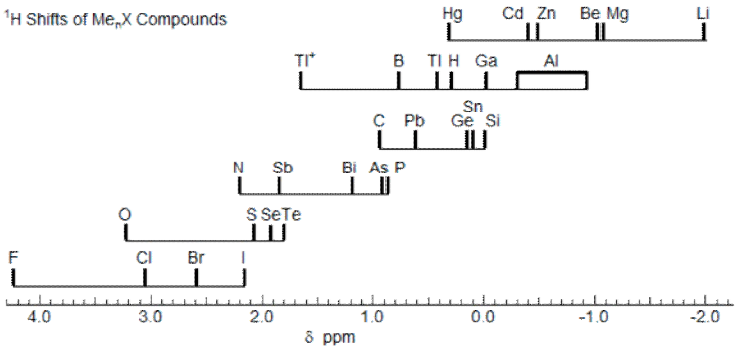
$$\delta = \frac{[\nu_o(H) - \nu_o(TMS)]}{[\text{Spectrometer Frequency in MHz}]}$$

Chemical shifts of all nuclei should be reported using δ values, with frequency and δ increasing from right to left. Many early papers on proton and multinuclear NMR used the opposite convention (not to mention other references) - in particular the τ scale was used in the early days: $\delta = 10 - \tau$.

The chemical shifts of protons on carbon in organic molecules fall in several distinct regions, depending on the nature of adjacent carbon atoms, and the substituents on those carbons. The scale below should be used only as a rough guideline, since there are many examples that fall outside of the indicated ranges. To a first approximation, protons attached to sp^3 and sp carbons appear at 0-5 ppm, whereas those on sp^2 carbons appear at 5-10 ppm.



Within these ranges, for a given type of C-H bond (sp^3, sp^2 or sp) the chemical shift is strongly affected by the presence of electronegative substituents as can be seen in the methyl shifts summarized below, which range from δ -2 for MeLi to δ 4 for MeF.



The ^1H chemical shifts of protons attached to heteroatoms (H-X) show a very wide chemical shift range, with no obvious correlation to the electronegativity of X or the acidity of HX.

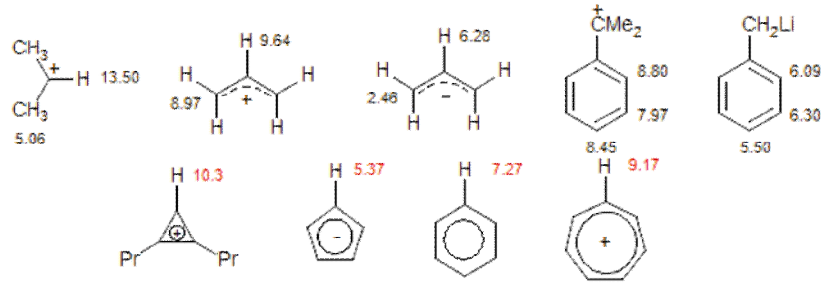
Influencing factors on chemical shifts

Chemical Shift Effects - Electronegativity

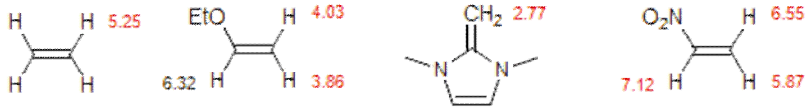
Proton shifts move downfield when electronegative substituents are attached to the same or an adjacent carbon. Alkyl groups behave as if they were weakly electron withdrawing, although this is probably an anisotropy effect.

CH_3F	CH_3Cl	CH_3Br	CH_3I	CH_3CH_3	CH_4	CH_3SiMe_3	CH_3Li
4.26	3.05	2.69	2.19	0.96	0.2	0.0	-2.1

The chemical shifts of protons attached to sp^2 hybridized carbons also reflect charges within the π system.

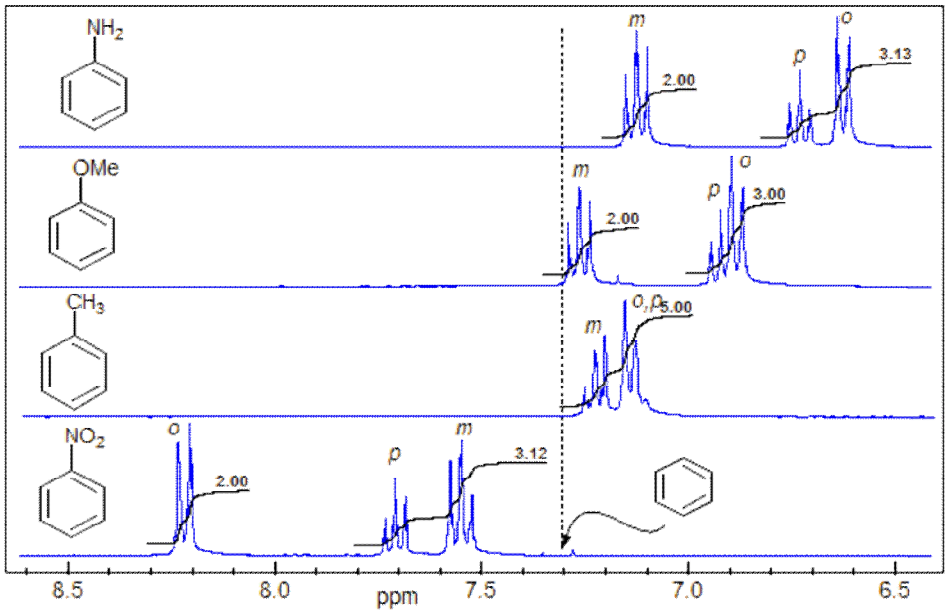


Even without formal charges, resonance interactions can lead to substantial chemical shift changes due to π polarization.



This is especially useful in the interpretation of the NMR chemical shift of protons in aromatic systems. The protons ortho and para to electron donating and electron withdrawing substituents show distinct upfield and downfield shifts.

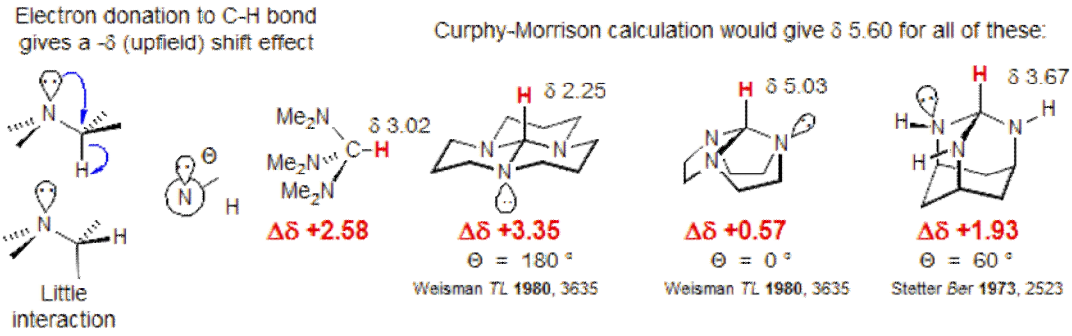
Click for Spectrum



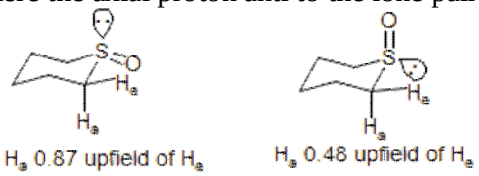
Chemical Shift Effects - Lone-Pair Interactions

When lone pairs on nitrogen or oxygen are *anti* to a C-H bond, the proton is shifted upfield, presumably the result of n --> σ* interaction. There is thus a strong conformational dependence of chemical shifts of protons α to heteroatoms. Whereas for an acyclic tris-amino methane the Curphy-Morrison chemical shift calculations give a substantial positive error (δ_{calc} - δ_{obs} = +2.58), for constrained systems the shifts are highly variable, with the largest upfield shift when there is an enforced anti-arrangement between the lone pair and the C-H

bonds (Θ = 180°). This effect is also present in ^{13}C chemical shifts. C-H bonds anti to lone pairs also show Bohlmann bands in the IR spectra, as a result of weakening of the C-H bond by hyperconjugation. Thus compound **E** shows IR absorption C-H stretch at 2450 cm^{-1}, as well as at 2690-2800 cm^{-1}.

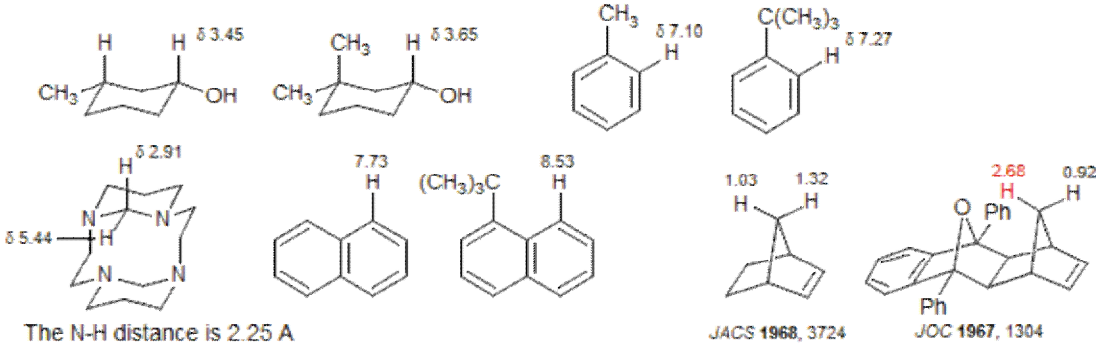


A similar interaction may be responsible for the shift effects noted for the sulfoxides below, where the axial proton anti to the lone pair on sulfur is upfield compared to the stereoisomer.

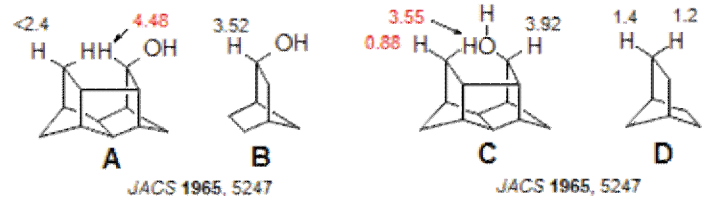


Chemical Shift Effects - Steric Compression

When molecular features cause a proton to be forced close to other protons, or to various functional groups, the proton will in general be deshielded (dispersion interactions). Shifts of this type are hard to distinguish from magnetic anisotropy interactions.



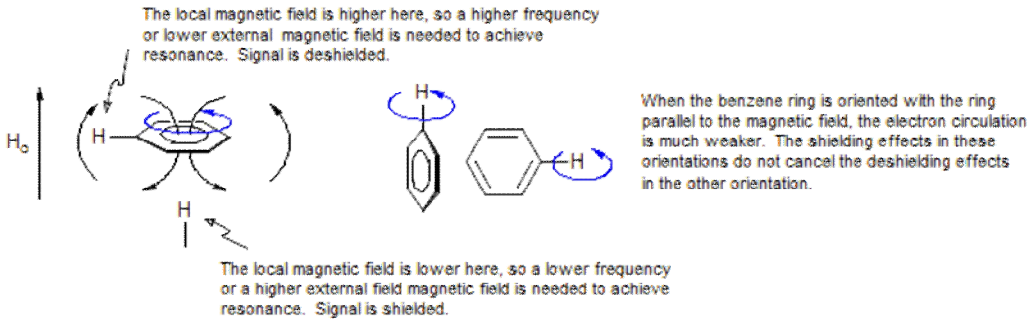
These shifts are especially large in highly compressed compounds like the "birdcage" molecules. The inside proton in the "out" alcohol **A** at δ 4.48 is downfield by 0.96 ppm from the model **B**. Even more striking are the shifts in the "in" alcohol **C**, where the proton jammed into the OH group at δ 3.55 is downfield by 2.3 ppm from the model **D**, and the gem partner at δ 0.88 is actually upfield by 0.5 ppm from its position in **D**, suggesting a migration of electron density from the sterically compressed inside H to the outside H.



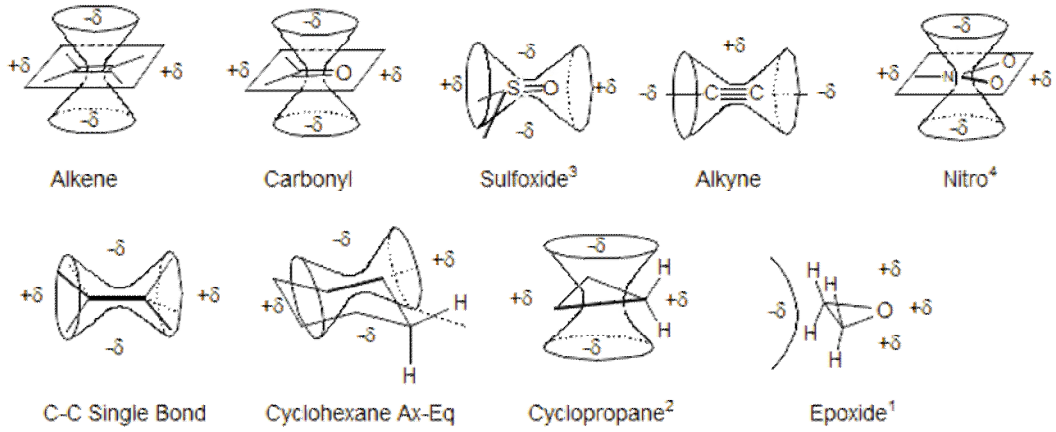
Chemical Shift Effects - Magnetic Anisotropy

Whereas the local circulation of electrons around H_A is a shielding effect (i.e., to the *right* in the NMR spectrum, -δ), there can be both shielding and deshielding effects on H_A from electron motion in other parts of the molecule. We refer to such interactions as magnetic anisotropy effects, since they are caused by anisotropic electron circulation.

The most dramatic examples of anisotropy effects are seen with benzene and other aromatic rings, which cause very large *shielding* (-δ) effects for protons placed above the ring, and smaller *deshielding* (+δ) effects for protons to the side of it. These chemical shift effects occur because electron circulation is stronger when the plane of the benzene ring is perpendicular to the magnetic field than when it is parallel to it

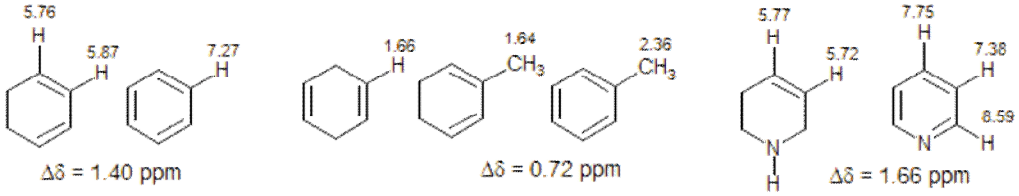


The consequence of magnetic anisotropy effects is to provide a stereochemical component to the chemical shift of a nucleus: the chemical shift changes depending on the spacial relationship between a proton and nearby functional groups. Such effects can be valuable for making stereochemical assignments. Some proposed magnetic anisotropy shielding/deshielding cones are shown below:

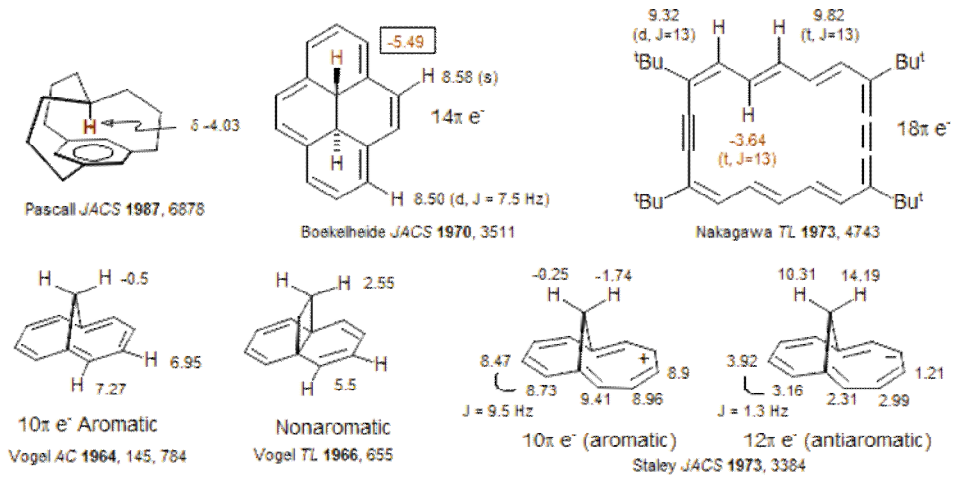


Chemical Shift Effects - Aromatic Rings

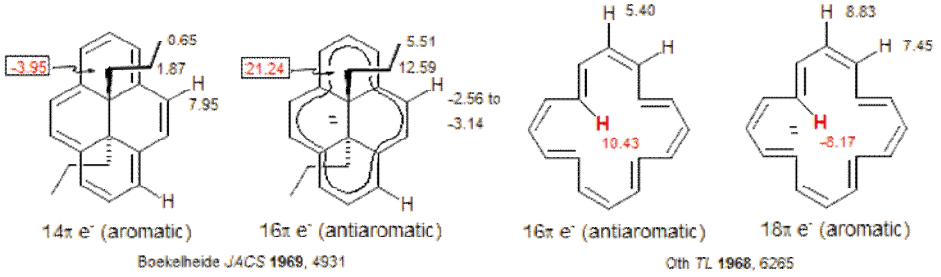
The ring current in Huckel aromatic systems, i.e., those with 4n + 2 π electrons (2, 6, 10, 14, 18 ...) causes downfield shifts in the plane of aromatic ring.



When protons are above or below the plane (or in the middle) of the aromatic ring then large upfield shift effects are observed.



When a cyclic conjugated system is planar and antiaromatic, i.e., 4n π electrons (4, 8, 12, 16) then chemical shift effects are in the opposite direction: downfield over the ring, and upfield in the ring plane. This is seen in the Staley 10 and 12-electron methano annulene cation and anion above, as well as in the 14-electron dihydropyrene below. The normal chemical shift effects are seen in the 10 and 14π-electron systems. In the 12 and 16 π-electron anions the methylene bridge and propyl groups over the ring show very large downfield shifts as a result of the antiaromatic ring current. The paramagnetic ring currents are a consequence of the small HOMO-LUMO separation that is characteristic of 4n π (antiaromatic) systems.

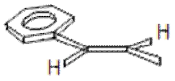


In the [16]-annulene the neutral compound has antiaromatic character. The shifts were measured at low temperature, where conformational averaging has stopped. In the 18π-electron dianion, large aromatic shifts are reported.

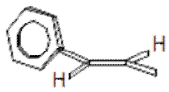
Chemical Shift Effects of Phenyl Groups.

The presence of phenyl groups in molecules often results in substantial chemical shift perturbations: unusually large diastereotopic effects, odd chemical shifts, and large differences between isomers compared to similar molecules with less magnetically potent substituents. These effects are sometimes predictable and can help with structure assignments.

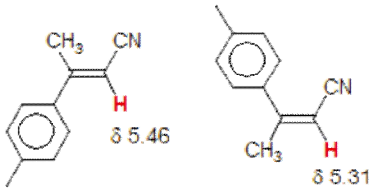
The effects of a phenyl substituent are highly dependent on conformation. For example, for styrenes the chemical shift effect of the phenyl is downfield (+δ) when the phenyl is in the plane of the double bond (the usually more stable conformation), but upfield (-δ) when the rotamer with the phenyl group perpendicular is the more stable one, usually as the result of steric interactions:



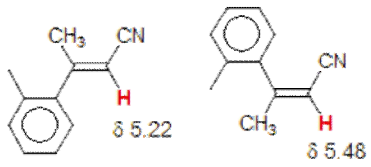
If ring is flat, get downfield shifts (+δ)



If ring is perpendicular, get upfield shifts (-δ)



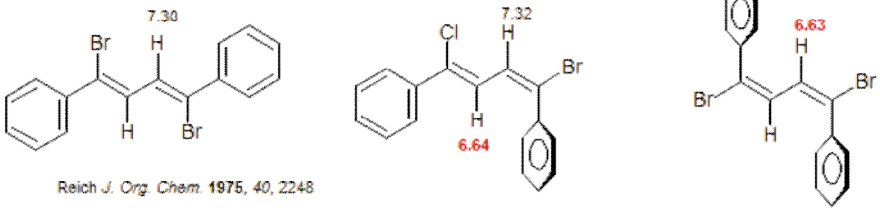
H cis to Ph is downfield



H cis to Ph is upfield - the ortho-methyl substituent presumably rotates the Ph group out of the C=C plane.

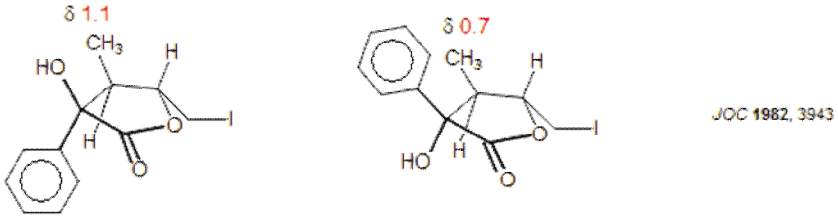
TET **1970**, 4783

The large differences in chemical shifts of the butadienes below can be used to assign stereochemistry, based on the effect of the "rotated" benzene ring when it is cis to the other vinyl group.



Reich *J. Org. Chem.* **1975**, *40*, 2248

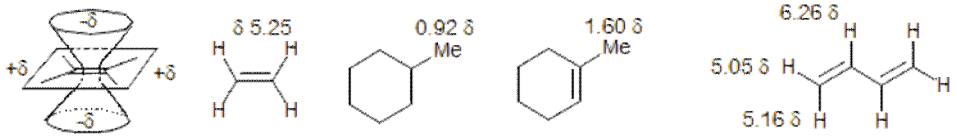
If steric effects force a phenyl to adopt a face-on conformation (as in the lactone example below) then a cis CH_3 group will be shifted upfield compared to a trans group.



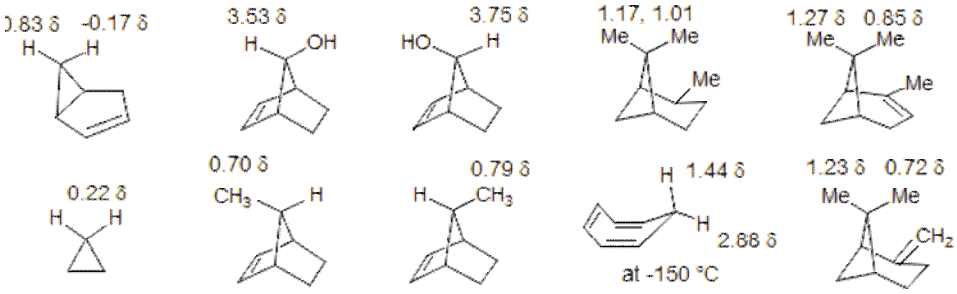
JOC **1982**, 3943

Chemical Shift Effects - Anisotropy of Double Bonds

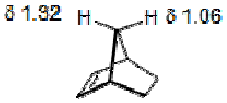
C=C Double Bonds. The magnetic anisotropy of C-C double bonds has generally been assumed to be similar to that of aromatic rings, with a deshielding region in the plane of double bond. This explains both the downfield shifts of vinyl protons, and the larger downfield shifts of the internal (which are affected by the anisotropy of both π systems) versus the terminal protons in conjugated dienes. It also explains the downfield shifts of allylic protons.



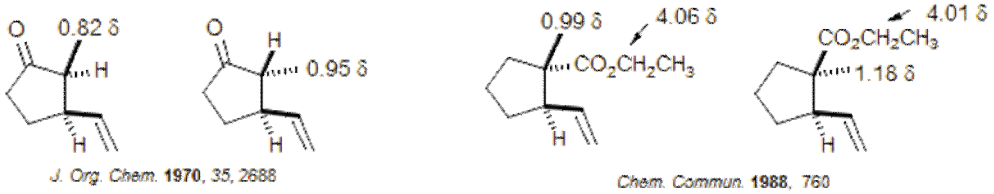
The shielding region above and below the plane of the double bond is more controversial. A number of examples show the expected upfield shifts of protons above double bonds.



There is, however, one major exception. In norbornene itself, the proton shifts are in the opposite direction than seen in the 7-substituted norbornenes above. Both the proton assignment and the absence of a -δ region above the double bond are supported by high level *ab initio* MO chemical shift calculations. Thus the deshielding region above double bonds shown in the figure must be viewed with some skepticism.

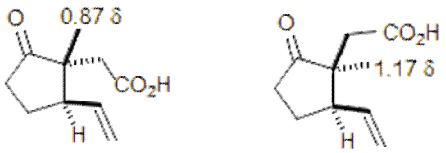


For this reason, assignment of stereochemistry in cyclopentanes based on an assumed anisotropy of double bonds, as in the examples below, should be used with caution. Possibly the shifts are the result of C-C single bond anisotropy of the C-vinyl bond.



J. Org. Chem. **1970**, *35*, 2688

Chem. Commun. **1988**, 760

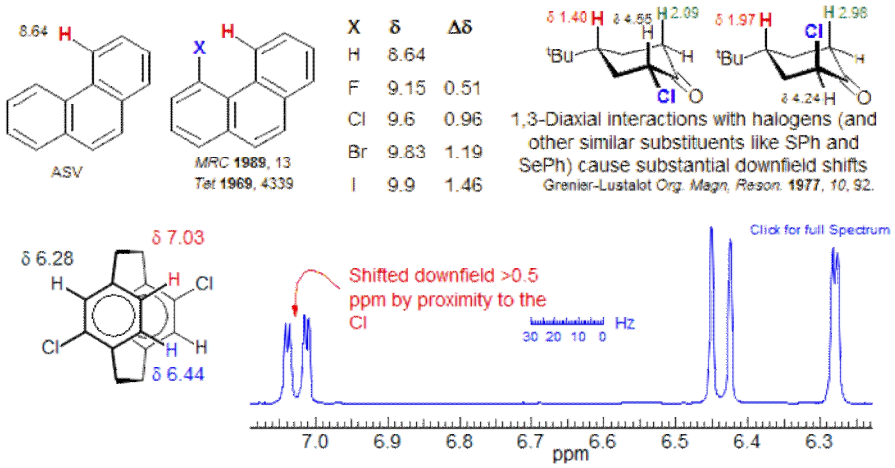


When the methyl and vinyl groups are cis, the methyl group is shifted upfield.

Vollhardt *J. Am. Chem. Soc.* **1980**, *108*, 5253.

Chemical Shift Effects - Anisotropy of Single Bonds

Anisotropy of Halogens. Protons positioned near lone-pair bearing atoms such as the halogens generally show downfield shifts, as in the phenanthrene examples below. Interpretation of these Δδ values is complicated by the close approach of the X and H atoms, which can cause geometry and orbital distortions that also affect the chemical shifts.



C-C Single Bond Anisotropy. Because of the many single bonds in typical organic molecules, each with local anisotropic effects, it has been hard to define single bond chemical shift effects, and even harder to make practical use of them. Nevertheless, useful stereochemical effects have been identified in several situations, loosely based on a magnetic anisotropy of C-C single bonds in which flanking hydrogens are shifted upfield, end-on hydrogens downfield.

Chemical Shift Effects of OH Protons

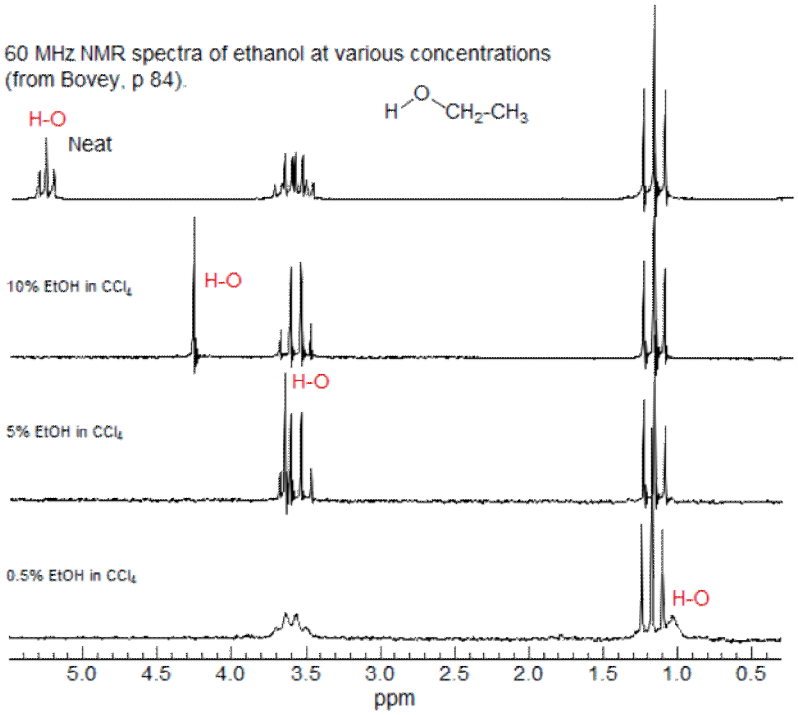
Hydrogen Bonding Effects.

The chemical shifts of OH and NH protons vary over a wide range depending on substrate structure, solvent, temperature and concentration. The shifts are very strongly affected by hydrogen bonding, with large downfield shifts of H-bonded groups compared to free OH or NH groups. Thus OH signals tend to move downfield at higher substrate concentration because of increased hydrogen bonding. Both OH and NH signals move downfield in H-bonding solvents like DMSO or acetone.

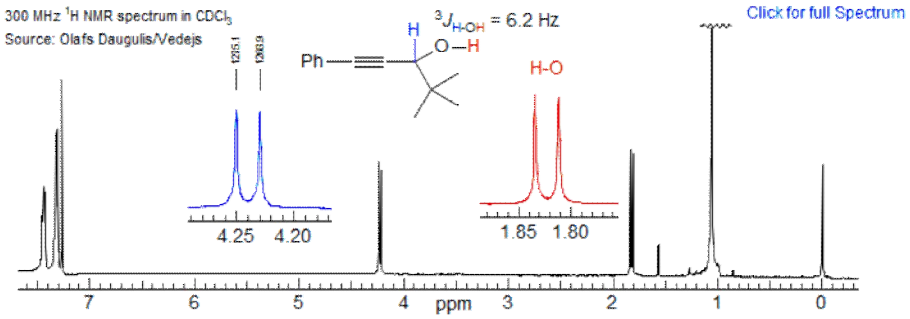
There is a general tendency for the more acidic OH and NH protons to move further downfield. This effect is in part a consequence of the stronger H-bonding propensity of acidic protons, and in part an inherent chemical shift effect. Thus carboxylic amides and sulfonamides NH protons are shifted well downfield of related amines, and OH groups of phenols and carboxylic acids are downfield of alcohols.

Recognizing Exchangeable Protons. In many samples NH and OH protons can be recognized from their characteristic chemical shifts or broadened appearance. When this fails, the labile protons can be identified by shaking the sample with a drop of D_2O, which results in disappearance of all OH and NH signals. This works best if the solvent is water immiscible and more dense than water ($CDCl_3$, CD_2Cl_2, CCl_4) since the formed DOH is in the drop of water floating at the top of the sample where it is not detected. In water miscible solvents (acetone, DMSO, acetonitrile, pyridine, THF) the OH and NH signals are largely converted to OD and ND, but the DOH formed remains in solution and will be detected in the water region.

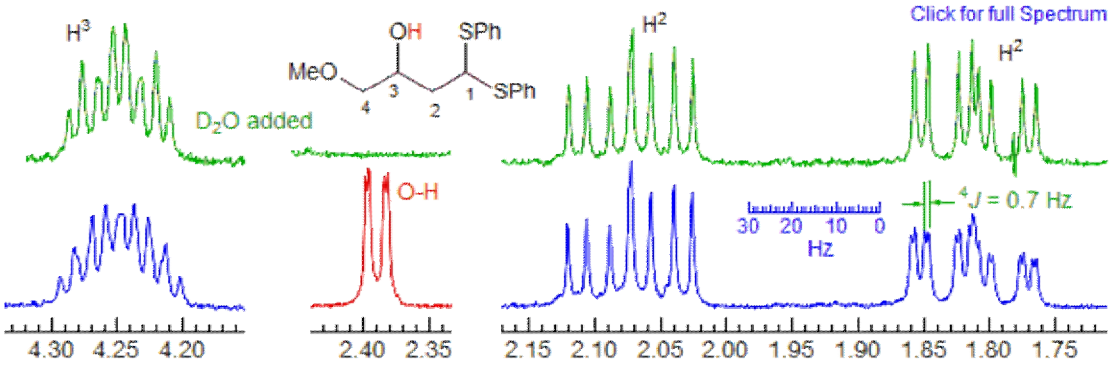
Alcohol OH Protons. In dilute solution of alcohols in non-hydrogen-bonding solvents (CCl_4, $CDCl_3$, C_6D_5) the OH signal generally appears at δ 1-2 At higher concentrations the signal moves downfield as a result of increased fraction of H-bonded alcohols, e.g. the OH signal of ethanol comes at δ 1.0 in a 0.5% solution in CCl_4, and at δ 5.13 in the pure liquid.



Dynamic Exchange OH. Under ideal conditions OH groups of alcohols can show sharp signals with full coupling to neighboring protons, as in the spectrum of neat ethanol above, and in the spectrum of 1-phenyl-4,4-dimethyl-1-pentyn-3-ol below.

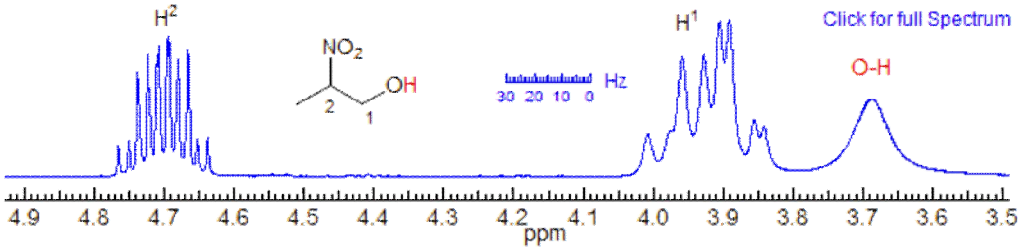


Even long-range coupling can be seen, as in the example below, where the OH proton is a dd, from ^{3}J coupling to the C^{3} proton (4.3 Hz), and a ^{4}J coupling of 0.7 Hz to one of the diastereotopic C^{2} protons (presumably a W-type coupling).



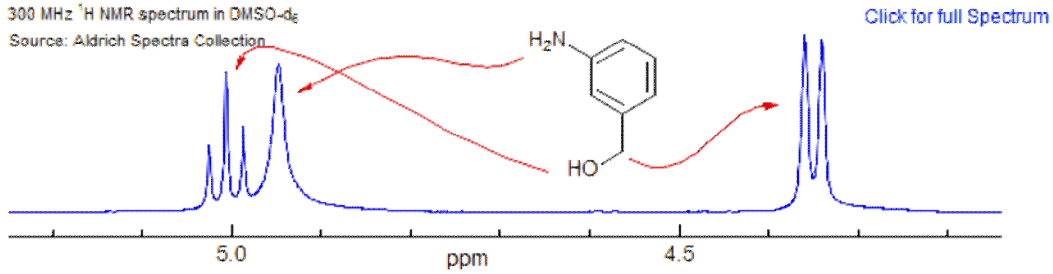
More typically, signals for OH protons are subject to rapid (on the NMR time scale) intermolecular exchange processes, which may result in broadening or complete loss of coupling to neighboring protons. In the example below, the **ABMX$_3$** signal H^{1} at δ 3.9 is

broadened by partial averaging of coupling to the OH group. Note that the **AB<u>M</u>X$_3$** signal (H^2) at δ 4.7 is sharp.

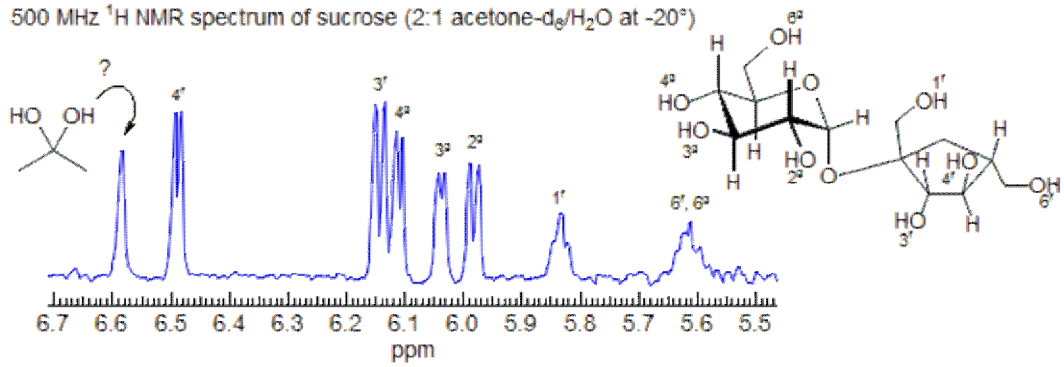


Such exchange can also broaden or average the signals of multiple OH, NH or SH groups in the sample, if more than one is present. Any water present might also exchange with the R-OH protons. The rates of exchange are a complex function of temperature, solvent, concentration and especially the presence of acidic and basic impurities. In $CDCl_3$ the presence of acidic impurities resulting from solvent decomposition often leads to rapid acid catalyzed exchange between OH groups.

Solvents like DMSO and acetone form strong hydrogen bonds to the OH group. This has the effect of slowing down intermolecular proton exchanges, usually leading to discrete OH signals with observable coupling to nearby protons. Note the triplet and doublet for the $HOCH_2$ group in the spectrum below taken in DMSO.

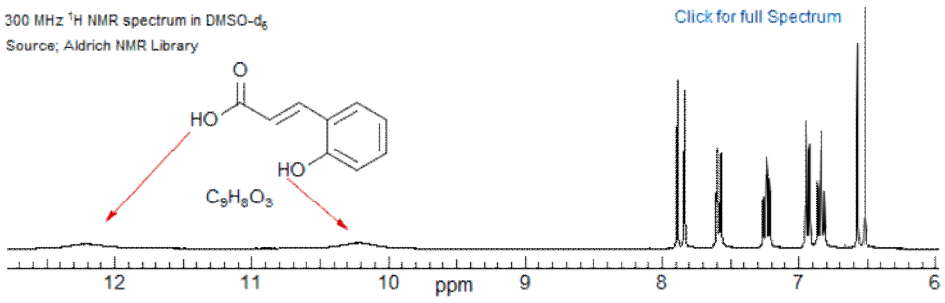


In the remarkable NMR spectrum of the OH region of sucrose below taken in aqueous acetone solvent all of the OH signals and their coupling are resolved.

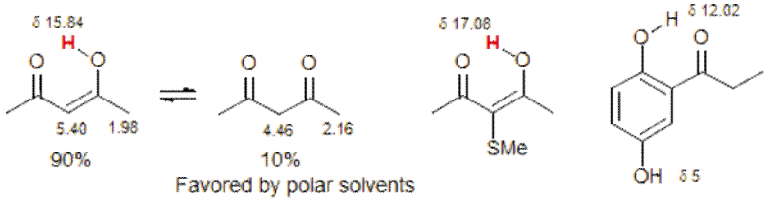


Phenol OH Protons. The OH signals of phenols are generally well downfield of those of alcohols, appearing at δ 5-7 in $CDCl_3$, and δ 9-11 in DMSO. The higher acidity of phenols results in faster exchange rates, so that polyphenolic compounds will usually show only one OH signal.

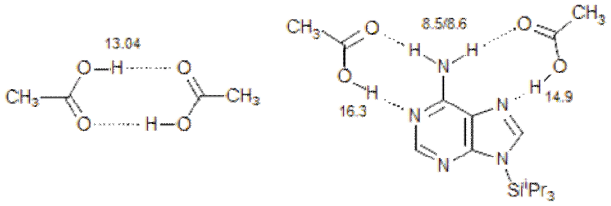
In DMSO solution, even the exchange between carboxylic acid protons and other OH groups can be slowed enough to allow individual observation, as in the spectrum of 2-hydroxycinnamic acid below.



β-Dicarbonyl Compounds. Especially dramatic shifts are observed for the strongly intramolecular H-bonded enol forms of β-dicarbonyl compounds, o-ketophenols and related structures.

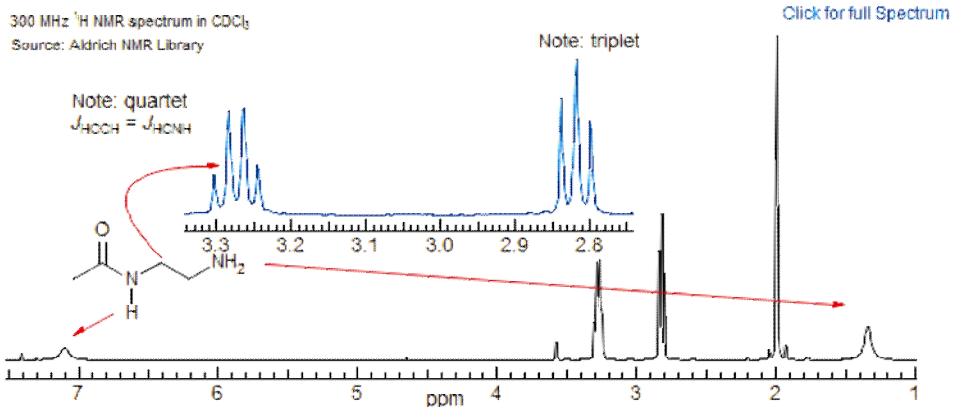


Carboxylic Acids. Most carboxylic acids are strongly hydrogen bonded in non-polar solvents, and the OH protons are correspondingly downfield shifted. Acetic acid dimer in Freon solvent ($CDClF_2/CDF_3$) at 128 K appears at δ 13.04, and the OH signals of acetic acid hydrogen bonded to a protected adenosine under conditions of slow exchange appear at even lower field.

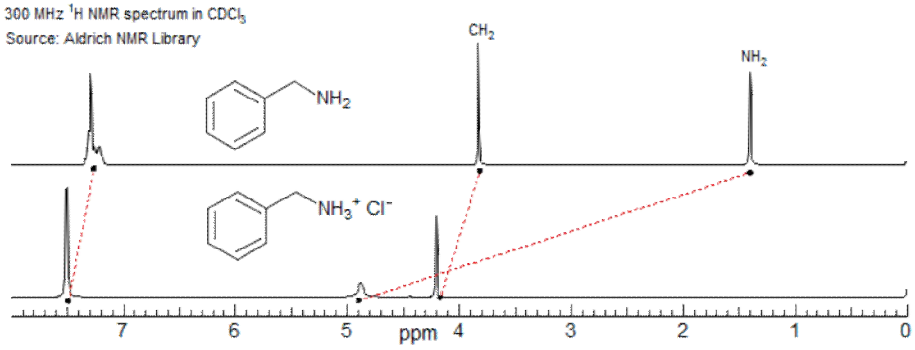


Chemical Shift Effects of NH Protons

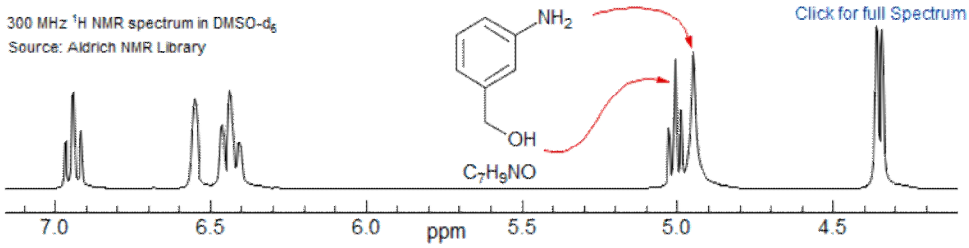
Amine N-H protons: NH_2 protons of primary alkyl amines typically appear as a somewhat broadened signal at δ 1-2 in $CDCl_3$. The broadening has several sources: partially averaged coupling to neighboring protons, intermolecular exchange with other NH or OH protons, and partially coalesced coupling to the quadrupolar ^{14}N nucleus ($I = 1$), which usually has a short T_1. In the example below, the CH_2 group bonded to amino (δ 2.82) shows little indication of coupling to the NH_2 protons, so NH exchange must be rapid on the NMR time scale. The amide proton at δ 7.1 is broadened by residual coupling to ^{14}N, not by exchange, since the N-CH_2 signal is a sharp quartet (the vicinal HN-CH_2 and CH_2-CH_2 couplings are accidentally equivalent).



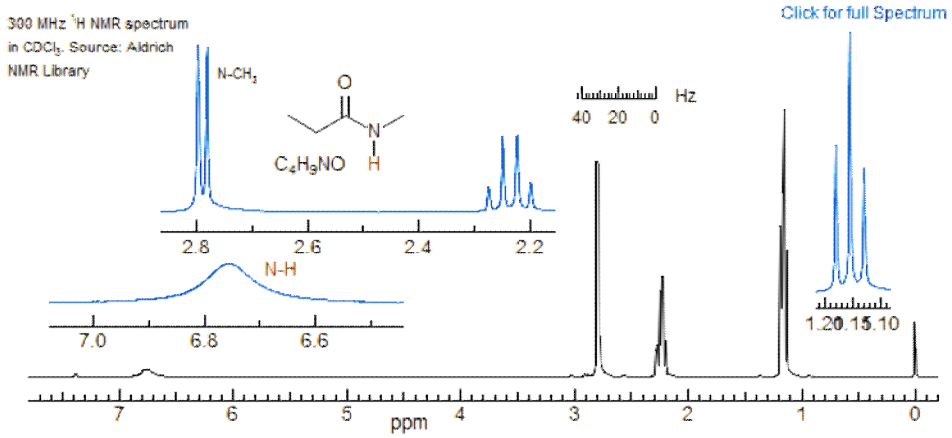
Ammonium N-H protons. The N-H signals of ammonium salts are strongly downfield shifted, typically appearing at δ 4-7 in $CDCl_3$ and δ 8-9 in DMSO. If spectra are taken in strongly acidic solvents (e.g. trifluoroacetic acid), where intermolecular exchange is slowed, the signals are sometimes very broad, and can show poorly resolved ^{1}H-^{14}N *J* coupling (1:1:1 triplet, $J_{HN} \approx 70$ Hz). Under these conditions N-H protons in ammonium salts show coupling to neighboring C-H protons.



Aniline NH Protons. The NH protons of anilines are typically at δ 3.5-4.5 in $CDCl_3$ solution, moving downfield by 1-2 ppm in DMSO solution. ortho-Nitroanilines (ca δ 5-6) and heterocyclic amines such 2-aminopyridines (δ 4.5) have signals downfield of this range.



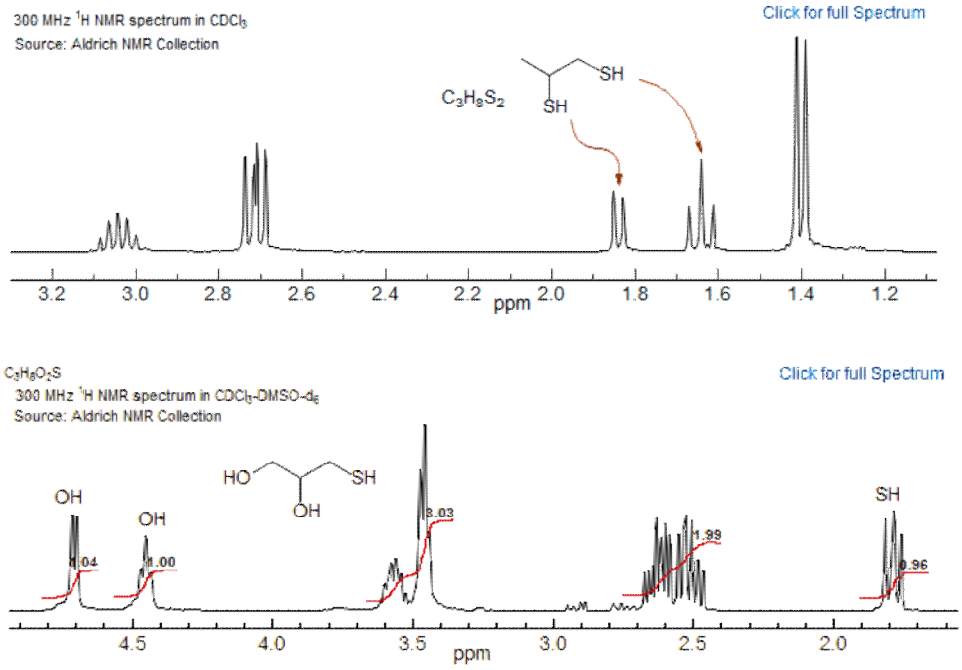
Amide NH Protons. Amide NH signals typically appear around δ 7, as in the example of N-acetylethylenediamine above and N-methylpropionamide below. They are generally in slow exchange with other NH and OH signals. Thus, neighboring protons will show coupling to the NH proton, as in the examples, where the CH_2 bonded to the amide nitrogen is a quartet and the N-Me group is a doublet. The amide N-H protons are typically broad from poorly resolved coupling to ^{14}N, so the coupling to neighboring protons is usually not resolved, or barely resolved in the NH signal.



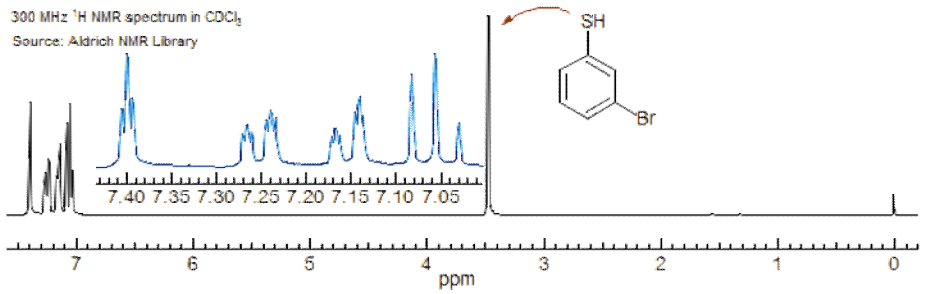
Chemical Shift Effects of SH, SeH and TeH Protons

Thiol S-H Protons. S-H protons of alkyl thiols typically appear between δ 1.2 and 2.0 in $CDCl_3$. The position is not strongly affected by hydrogen bonding solvents like acetone or DMSO, since SH protons are only weakly hydrogen bonded. Coupling to nearby protons is

usually seen, although broadened or fully averaged signals are not uncommon, especially in molecules containing OH protons (or in impure samples).



Aryl thiol S-H signals are further downfield, typically δ 3.5-4.5, as a result of normal ring-current effects, and the greater electron withdrawing effect of aryl vs. alkyl groups.



Simplification of complex proton NMR spectrum

The complete analysis of a compound is frequently made difficult, when signals overlap and as a result, useful information is often buried due to complexity of the spectrum. In a spectrum several signals may overlap as is the case, e.g., of closely related methylene groups in a molecule. In such a situation an intense, broad and compulsory unresolved signal, termed the methylene envelope may appearsbetween δ 1-2. Another cause of complexity is where a coupling constant is comparable with the chemical shift different between the coupled protons. For these problems following techniques may use to solve them.

NMR spectra may be complex with following complicating factors

1. Overlap: - Overlap is a serious problem in NMR spectroscopy. Integration (which is used to determine the ratio of different kinds of magnetically non-equivalent protons in a sample by measuring the relative intensities of the associated peaks) is of greatest help in demonstrating the presence of overlap. Perhaps the great difficulty encountered in the application of electronic integration is overlap or resonance peaks, either partial or complete. If facilities for operating a spectrometer at considerably different frequency are available and there is no overlap of peaks on centre, it may be impossible to obtain a spectrum which allows the overlap to be disintegrated.

2.Exchange: Complications in the spectrum also arise when two or molecular species are present and both of them carry labile protons which may exchange with each other. If the rate is very slow, then the peak of each type of labile proton will be seen at the usual position and of almost normal appearance. But as the rate of exchange increases, the peak broaden still further and moves towards each other and when the rate became greater than the chemical shift between them, the peaks coalesce. Further increase in the rate only sharpness up the line. Spin spin coupling may also be destroyed by exchange.

3. Hydrogen bonding:-if the structure of the sample molecule is such that strong hydrogen bonding takes place, then the proton involved will have a chemical shift to a much lower field than would otherwise be expected. The same effect of a low field shift may also occur, but somewhat diminished, when hydrogen bonding is molecular as in acids and alcohols.

4. Solvent effects: - The presence of solvent also affects the NMR spectrum. The effect cannot be eliminated. However, it may be standardized. Solvents which are particularly suspected include acetone, benzene, and acetonitrile carbon disulphide usually has little effect on proton spectra, but may strongly influence those of fluorine. The behavior of cyclohexane, carbon tetrachloride and tetra-methylsilane are generally satisfactory

Spectroscopy tricks used in the complex proton NMR spectra:
There are number of tricks which may be used to assist in the interpretation of spectrum For example (1) Active hydrogen atoms of hydroxyl and amine groups may be removed by shaking the solution of the compound in deuterated chloroform with heavy water and then separating the aqueous layer. The signal due to the hydroxyl and amino groups would have disappeared when the spectrum was recorded again. Hence any coupling between the hydroxyl and amino groups and other hydrogen atoms would also have been removed as a result of deuteration of these groups. (2) Double resonance is another important technique which assists in sorting out the spectra. Whether two groups of resonance signals are interacting by spin coupling or not may be ascertained by applying a strong radio frequency irradiation at the centre of the first signal (while observing the second signal). The two groups will be interacting if the second signal is collapsed to a singlet or is simplified.

Some other approaches used in simplify a complex spectrum:-
1. Magic angle spinning and cross polarization: it is also a technique of simplify a complex spectra and the procedure consist of four basic timed sequences of rf pulses. The four part procedure are.,
a.Polarizing the 1H spin system by applying a 900rf pulse at the 1H resonance frequency.
b. Spin locking in the rotating frame by applying a 900 phase shift to the foregoing field
c. Establishing 13C -1H contact by applying a rf field at the 13C resonance frequency
d. Observing the 13C free induction decay while the 1H field is maintained for decoupling
The entire sequence is repeated many times until a suitable signal-to-noise ratio for 13C is achieved.

Shift Reagents:
Shift reagents provide a useful technique for spreading out 1H NMR absorption patterns which normally overlap, without increasing the strength of the applied magnetic field. The 1H NMR spectrum of n-hexanol is reproduced in fig 1.9, 100 MHz which is the normal record. In this spectrum the high field triplet is distorted which represents the absorption of a methyl group adjacent to a –CH2- group.

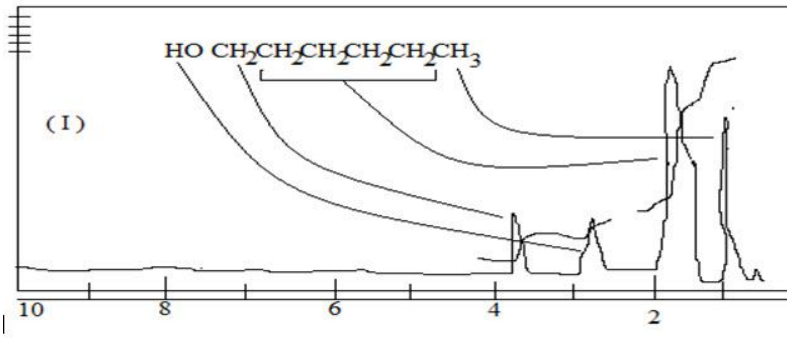


Figure 3.12

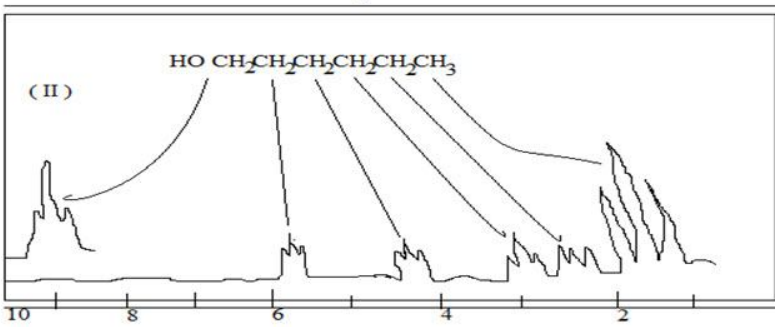


Figure 3.13

The low field broad multiplet (presumably not first order) is due to the methylene group adjacent to the hydroxyl group. The protons of the remaining methylene groups areall buried in the methylene envelope between δ 1.2 & 1.8. When the same spectrum is recorded (fig. 1.10) after the addition of a soluble europium (III) complex, Eu (DMP)3 , i.e., the shift-reagent, the spectrum is spread out over a wider range of frequencies so that it is now simplified almost to first order. In the spectrum (fig 1.10) the OH absorption signal is shifted too far to be observed. In complexes of this type, the lanthanide ion can increase its co-ordination by bonding interaction with lone pair electrons of groups like NH2, OH, C=O, -O-, COOR, CN. The magnetic field associated with the metal ion, which is a paramagnetic moiety, causes marked changes in the observed shifts of the protons in the substrate- thus the name shift reagent.

Spin Decoupling: Coupling between neighbouring nuclei gives splitting patterns and their analysis is useful for structure determination of compounds. In some situations, however these patterns are so complex that simplification of the spectra is desirable and spin decoupling provides one such techniques. Example of the 1H NMR spectrum of ethanol serves as good example where the spin spin splitting of the methyl signal by the methylene protons is due to the three possible spins states, which the two methylene protons can adopt. If one irradiates strongly the methylene protons with an additional radio frequency at their resonance position, the methylene protons will get induced to change their spin states very rapidly. The methyl protons will therefore only "see an average CH2 state" and coupling will disappear, consequently the methylene absorption will be eliminated and the methyl signal will be recorded at its usual frequency only as a singlet.

Deuterium Labelling and Exchange: Deuterium 2H or D, the heavy isotope of hydrogen, has been used extensively in 1H NMR spectroscopy for two reasons. First, it is easily introduced into a molecule. Second, the presence of deuterium in a molecule is not detected in a 1H NMR spectrum. Deuterium has a much small magnetic dipole moment than hydrogen, and therefore it absorbs at different field strengths. Although it broadens the peak of a neighbouring proton, it does not split it because it couples only slightly with a proton. When deuterium replaces the methyl hydrogen's in, for e.g., ethyl bromide. Note that the multiplicity of the $-CH_2-$ peaks changes from a quartet (3+1 peaks) to a triplet (2+1 peaks) to

a doublet (1+1 peaks) and finally to a singlet as the hydrogen's on the $-CH_3$ group are replaced by D. In $Br-CH_2-CD_3$ no splitting occurs between the remaining hydrogen's and the neighbouring methyl, which is now completely deuterated. Carboxylic acid and aldehyde protons appear between δ 12 and 9. Acidic compounds can be differentiated from aldehyde because protons attached to a heteroatom exchange readily with D_2O.

Exchangeable Protons (-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)

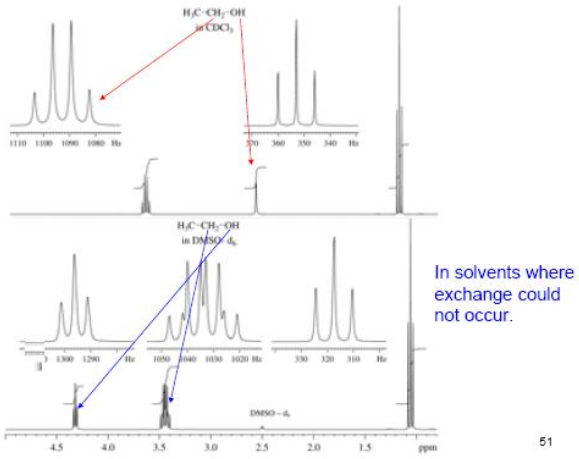
b. intramolecular

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.



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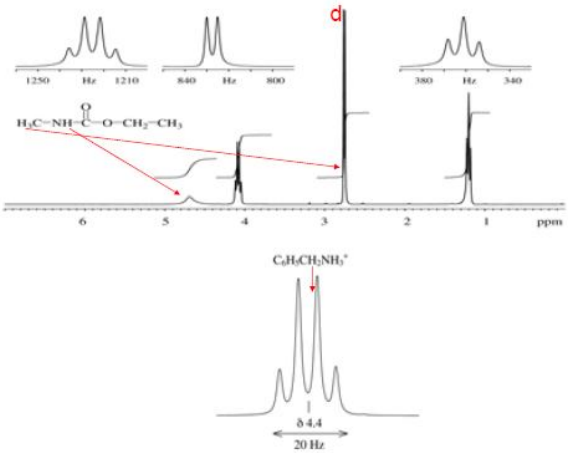
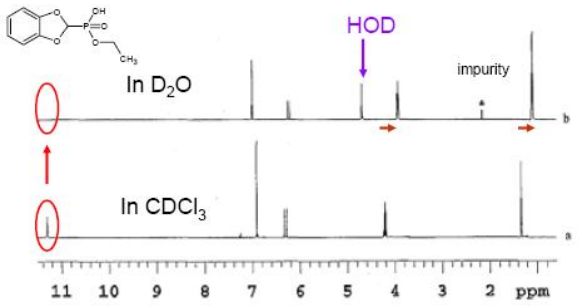




Nuclear Overhauser (NOE) Effect:

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.

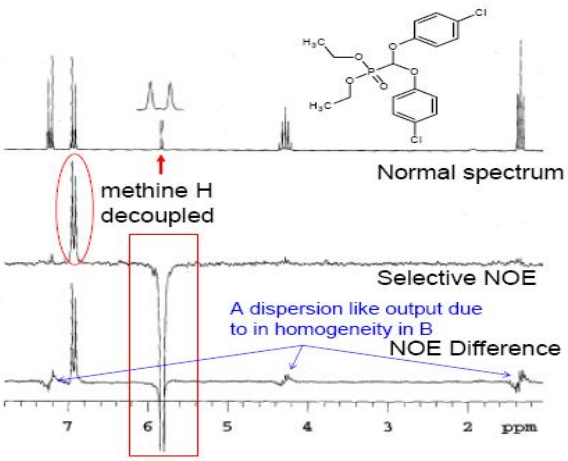
The NOE effect occurs through space and is operational within a ~5A sphere centered around the irradiated nuclei ("NOE range"). It does not enhance resonance signals away from "range" from the irradiated 'centre'. NOE allows determination of the proximity of the nuclei to the irradiated ones, thus is an excellent technique to ascertain the inter-proton distances/stereochemistry of molecules.

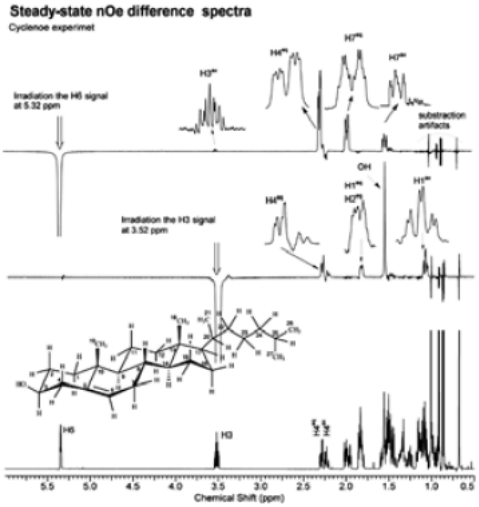
NOE and through space interactions: Scalar (J) coupling arises due to *through bond* interactions of nuclei in close proximity. Another type of interaction is *dipolar coupling* which occurs *through space* and is dependent on the direct distance between nuclei. This interaction manifests in decoupling experiments.

NOE Effect $\alpha\ 1/r^6$

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 1H is selectively pre-irradiated until saturation is achieved. During the pre-irradiation period, NOE buildup occurs at other 1H nuclei close in space. Then a 90o pulse is applied, 90^o pulse then creates an observable magnetization, which is detected during the acquisition period.

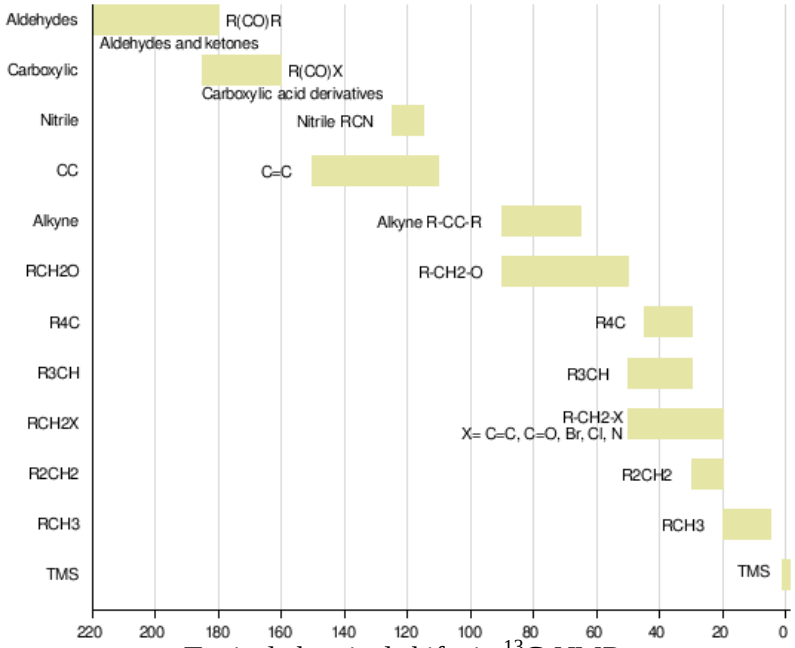




Carbon-13 Nuclear Magnetic Resonance

Carbon-13 nuclear magnetic resonance (known as carbon-13 NMR or ^{13}C NMR or sometimes simply referred to as carbon NMR) is the application of nuclear magnetic resonance (NMR) spectroscopy to carbon. It is analogous to proton NMR (1H NMR) and allows the identification of carbon atoms in an organic molecule just as proton NMR identifies hydrogen atoms. As such ^{13}C NMR is an important tool in chemical structure elucidation in organic chemistry. ^{13}C NMR detects only the 13C isotope of carbon, whose natural abundance is only 1.1%, because the main carbon isotope, 12C, is not detectable by NMR since it has zero net spin.

^{13}C chemical shifts follow the same principles as those of ^{1}H, although the typical range of chemical shifts is much larger than for ^{1}H (by a factor of about 20). The chemical shift reference standard for ^{13}C is the carbons in tetramethylsilane (TMS), whose chemical shift is considered to be 0.0 ppm.



Typical chemical shifts in ^{13}C-NMR

Broad band decoupling and off resonance decoupling in 13C NMR

Broad band decoupling: To eliminate the complicating effects of the proton couplings in the 13C spectra, we must decouple the 1H nuclei by double irradiation at their resonant frequencies (80 MHz at 1.9 T, etc.).

This is an example of heteronuclear decoupling, but we do not wish merely to decouple specific protons; rather we wish to double irradiate all protons simultaneously while recording the 13Cspectrum. A decoupling signal is used that has all the 1H frequencies spread around 80 MHz, and is therefore a form of radiofrequency noise; spectra derived thus are 1H-decoupled, or noise decoupled. The alternative name broad band decoupled spectra simply takes cognizance of the fact that a widespread of decoupling radiofrequency can be produced by several electronic techniques, other than by simple noise modulation. The convenient notation 13C-{1H] can be used to identify proton decoupled carbon 13 NMR spectra; in the same way 31P-{1H} spectra are phosphorus-31 NMR spectra with all proton coupling to phosphorus removed by broad band or noise decoupling, and 15N-{1H} corresponds for nitrogen-15, etc

Off resonance decoupling: In an off resonance-decoupled 13C spectrum, the coupling between each carbon atom and each hydrogen attached directly to it is observed. The n+1 rule can be used to determine whether a given carbon atom has three, two, one, or no hydrogens attached. However, when off resonance decoupling is used, the apparent magnitude of the coupling constants is reduced, and overlap of the resulting multiplets is a less frequent problem. The off-resonance-decoupled spectrum retains the couplings between the carbon atom and directly attached protons (the one-bond couplings) but effectively removes the couplings between the carbon and more remote protons. In this technique, the frequency of a second radiofrequency transmitter (the decoupler) is set either upfield or downfield from the usual sweep width of a normal proton spectrum (i.e. off resonance). In contrast, the frequency of the decoupler is set to coincide exactly with the range of proton resonances in a true decoupling experiment. Furthermore, in of resonance decoupling, the power of the decoupling oscillator is held low to avoid complete decoupling. The off resonance decoupled spectrum is usually obtained separately, along with the proton decoupled spectrum.Off resonance decoupled spectrum of 1-propanol, in which the methyl carbon atom is split into a quartet, and each of the methylene carbons appears as a triplet. The observed multiplet patterns are consistent with the n+1 rule. If TMS has been added, its methyl carbons would have appeared as a quartet centered at $\delta = 0$ ppm.

Nowadays, NMR probably is the most important technique for structure elucidation, material characterization and studying molecular motion. Continuing efforts have been made to develop different NMR methods so as to obtain more information from NMR measurements, a number of experiments such as 1D-NMR (^{1}H DEPT, ^{13}C, ^{15}N, ^{19}F, ^{31}P, etc.), 2D-NMR (COSY, DQFCOSY, MQFCOSY, HETCOR, HSQC, HMQC, HMBC, TOCSY, NOESY, EXSY, etc.) and Multidimensional-NMR (Homonuclear and Heteronuclear) are developed [7-26]. This paper focuses mainly on interpretation of structure of different organic compounds by different NMR techniques. A few of the strategies of NMR experiments that are used in determination of different compounds are described as follows.

1D-NMR

^{1}H-NMR: In ^{1}H-NMR spectroscopy, spin transitions of only hydrogen nuclei are noticed. Interpretation of ^{1}H-NMR spectra can be well understood from data presented in **table 1** representing different δ values, couplings, coupling constants and chemical shifts of ^{1}H nuclei processing in different chemical environments. Commonly, δ value scale of ^{1}H-NMR ranges from 0-10 ppm with respect to Tetra methyl Silane (TMS) as internal standard.

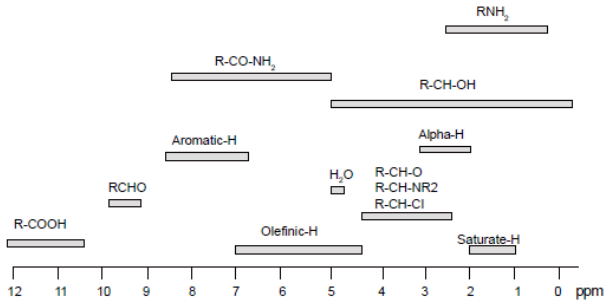


Figure 1: Chart representing ^{1}H nuclei chemical shift due to different chemical environments.

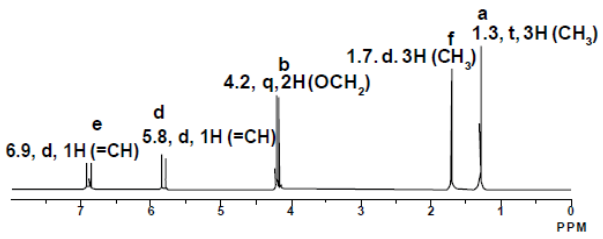


Figure 2a: ^{1}H-NMR proton coupled spectrum of Ethyl-2-butenoate in $CDCl_3$.

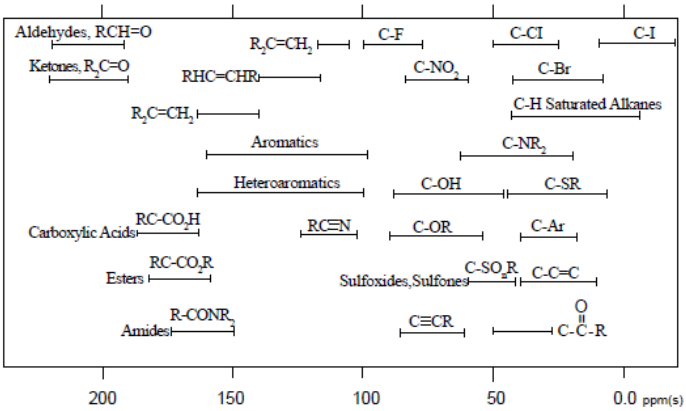


Figure 3: Chart representing ^{13}C nuclei chemical shift due to different chemical environments.

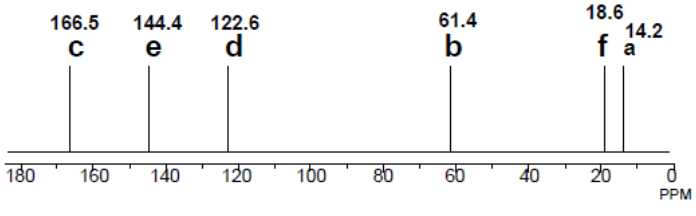


Figure 4: ^{13}C-NMR proton decoupled spectrum of Ethyl-2-butenoate in $CDCl_3$.

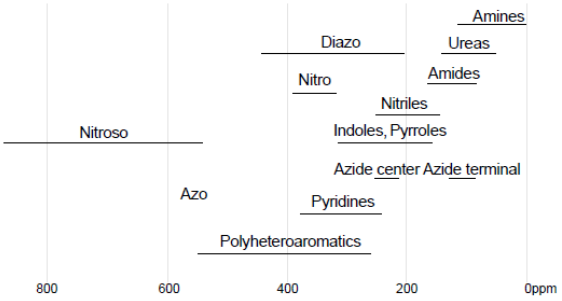


Figure 5: Chart representing ^{15}N nuclei chemical shift due to different chemical environments.

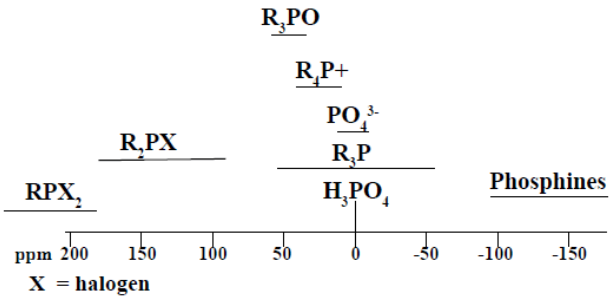


Figure 7: Chart representing ^{31}P nuclei chemical shift due to different chemical environments.

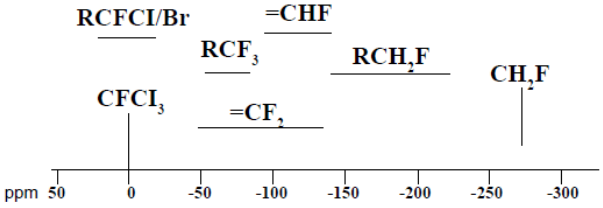


Figure 9: Chart representing ^{19}F nuclei chemical shift due to different chemical environments.

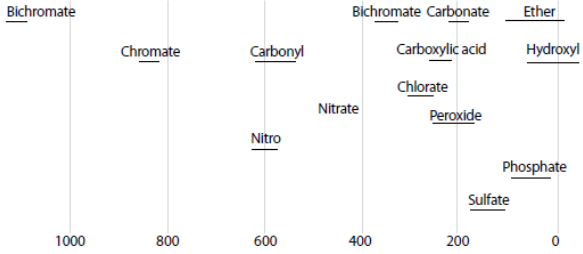


Figure 11: Chart representing ^{17}O nuclei chemical shift due to different chemical environments.

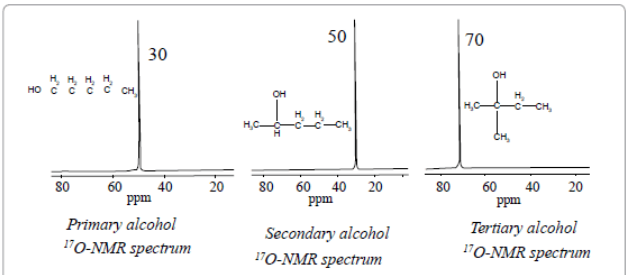


Figure 12: Chart representing ^{17}O nuclei proton decoupled chemical shift due to different chemical environments.

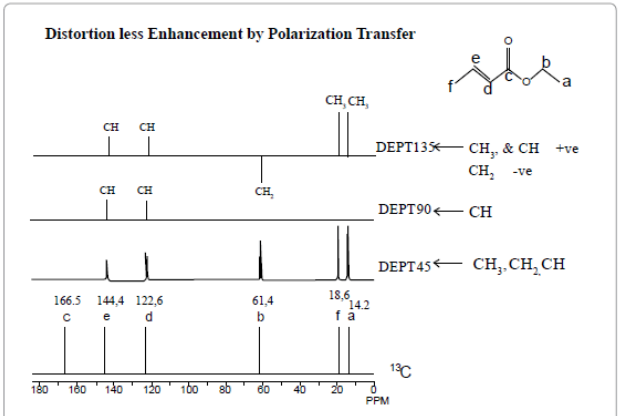


Figure 13: DEPT spectrum of Ethyl-2-butenoate.

2D NMR

COSY: COSY is a homonuclear 2D NMR correlation spectroscopy. COSY correlates chemical shift of two hydrogen nuclei located on two different carbons that are separated by a single bond via J coupling. Thereby detects the chemical shift for hydrogen's on both F1 and F2 axis. COSY experiment is categorized as follows:

- Simple COSY
- DQF COSY
- TQF COSY
- MQF COSY

Simple COSY

Simple COSY technique involves simple pulse sequence in which firstly a $(\pi/2)_x$ pulse is introduced in ^{1}H channel to create an evolution phase. There after some time a second $(\pi/2)_y$ pulse is introduced to create an acquisition phase. In ^{1}H-^{1}H COSY pulse sequence contains variable relaxation delay time (t_1) and acquisition time (t_2). Experiment is repeated with different values of $t_1$and t_2. So that value of t_1 is increased at regular intervals, to generate a series of different FID data during t_2. COSY offers three bond coupling ($^3J_{H\text{-}H}$). The COSY interpretation can be best understood from COSY spectrum of Ethyl-2-butenoate given in **figure 14**. The off diagonal peaks at point 1, 2, and 3 represents coupling of protons of hydrogens on 'a' with 'b', 'e' with 'f ', and 'e' with 'd' protons of molecule of Ethyl-2-butenoate. There is no cross peak for c because it does not possess any hydrogens.

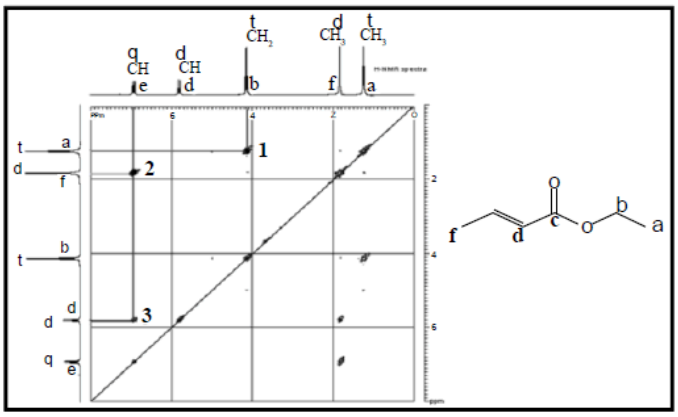


Figure 14: COSY spectrum of Ethyl-2-butenoate.

DQFCOSY

^{1}H-^{1}H DQF COSY is a modified technique of COSY that incorporates a typical pulse sequence, in which firstly a $(\pi/2)_x$ pulse is introduced in ^{1}H channel. Nextly, after first pulse a second $(\pi/2)_y$ pulse with just immediate third $(\pi/2)_z$ pulse is introduced to eliminate singlet peaks. This simplifies the complex COSY spectrum. The DQF COSY interpretation can be best understood from Ethyl acetate (liquid) in $CDCl_3$, simple COSY and DQF COSY spectra given in **figure 15**. In simple COSY spectrum of ethyl acetate the isolated 'd' hydrogen produces a singlet cross peak at spot '1'. But in case of ^{1}H-^{1}H DQF COSY spectrum of ethyl acetate spot '1' is removed and the spectra is simplified.

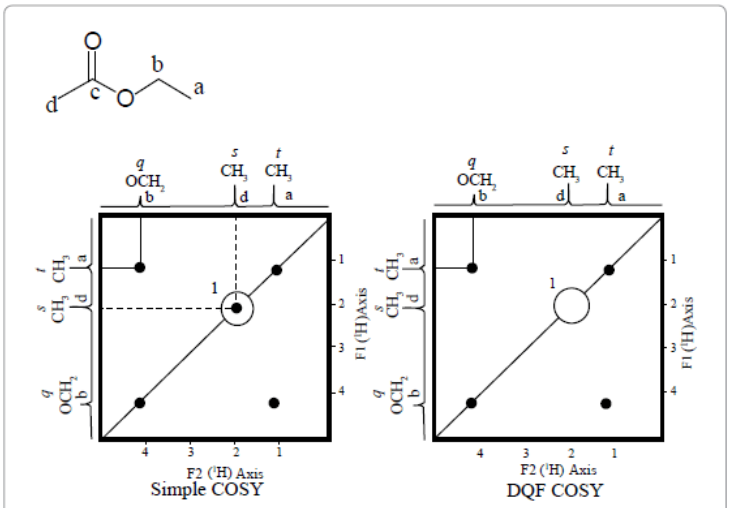


Figure 15: Ethyl acetate simple COSY and DQF COSY spectra.

TQF COSY

^{1}H-^{1}H TQF COSY employs further typical pulse sequence, in which initially a $(\pi/2)_x$ pulse is introduced in ^{1}H channel. Which is followed by introduction of a second $(\pi/2)_y$ pulse along with just immediate third $(\pi/2)_z$ and fourth $(\pi/2)_{z1}$ pulse. This eliminates singlet and doublet peaks.

MQF COSY

^{1}H-^{1}H MQF COSY employs a pulse sequence, in which firstly a $(\pi/2)_x$ pulse is introduced in ^{1}H channel. This initial pulse is followed by introduction of a second $(\pi/2)_y$ pulse along with a just immediate multiple number of $(\pi/2)_{zm}$ pulse (as desired). This eliminates triplets or any unwanted multiple peaks and simplifies complex COSY spectrum.

HETCOR:

HETCOR is a heteronuclear 2D NMR correlation experiment, which correlates two nuclei e.g. ^{13}C or ^{15}N with hydrogens separated by single bond. This detects chemical shift for hydrogen's on F1 axis and hetero nucleus on F2 axis. No cross peak signifies no hydrogen present over carbon. One cross peak indicates there can be one, two or three hydrogens. Two cross peaks indicates presence of diastereotype carbon (hydrogen). Interpretation of HETCOR spectra can be understood from HETCOR spectrum of ethyl-2-butenoate given in **figure 16**.

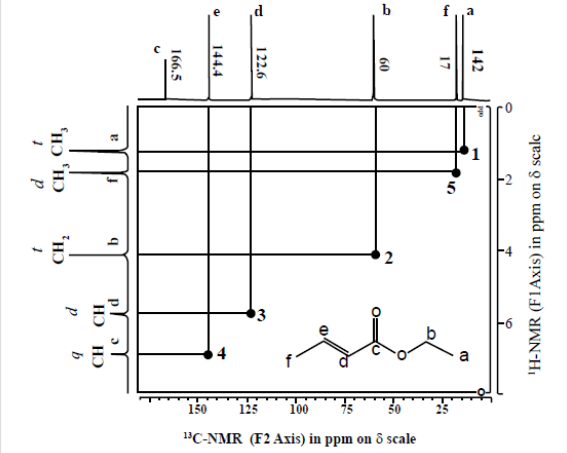


Figure 16: HETCOR spectrum of Ethyl-2-butenoate.

Peaks at point 1, 2, 3, 4 and 5 accounts for *a*, *b*, *d*, *e* and *f* carbons and attached hydrogens couplings. No cross peak for '*c*' as does not contain any hydrogen so no coupling. Hence, with HETCOR, one can easily determine the single bonded hetero nuclear correlation.

HMQC and HSQC: HSQC is better than HMQC. This can be best supported from HSQC and HMQC spectrum of menthol given in **figure 17**. So, when high ^{13}C resolution is required, then pulses should be calibrated on a well tuned and matched probe and HSQC should be run. But when high ^{13}C resolution is not an essential requirement then HMQC can be run.

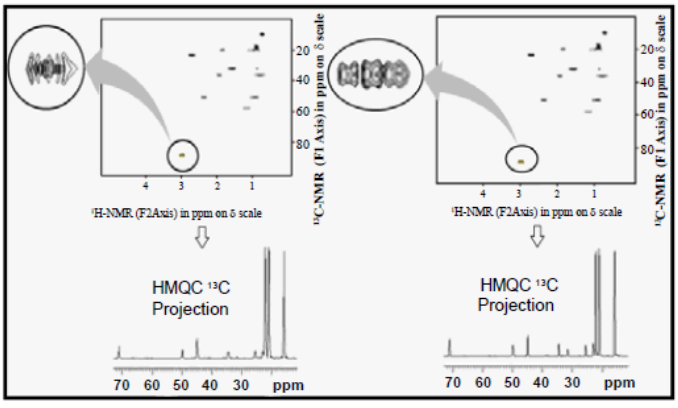


Figure 17: HSQC and HMQC spectrum of menthol.

HMBC: HMBC is a heteronuclear 2D-NMR correlation spectroscopy. This technique correlates chemical shift of hetero nuclei e.g. ^{13}C or ^{15}N with hydrogens, through a multiple bond. So, detects chemical shift for hydrogen's nuclei on F2 axis and hetero nuclei on F1 axis. Interpretation of HMBC can be understood from HMBC spectrum given in **figure 18**.

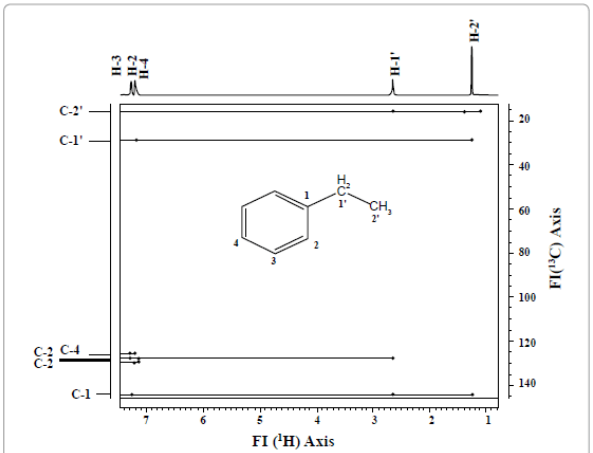


Figure 18: HMBC spectrum of ethyl benzene.

Line drawn from 16.2 (C-2') ppm, parallel to ^{1}H axis, intersects three cross peaks of H-1', which correlates C-2' with two H attached on C-1'. Other cross peaks doesn't show correlation. The line drawn from C-1' at 29 ppm, intersects one cross peak correlates C-1' to hydrogens present on C-2'. Similarly, C-1 correlated with hydrogens of C-1', C-2' and C-3; C-2 with hydrogens of C-3, C-4, and C-of 1'; C-4 with hydrogens of C-3 and C-2; C-3 with hydrogens of C-2 and C-4; C-4 with hydrogens of C-3 and C-2.

TOCSY:

2D TOCSY (Total Correlation Spectroscopy) is a homonuclear experiment which produces a COSY-like plot. TOCSY possesses two dimensions or axis of ^{1}H-NMR. A 2D-TOCSY, gives correlations between all protons in a given spin system. Interpretation of TOCSY spectrum can be best learnt from the TOCSY and COSY spectrum of 3-heptanone given in **figure 19**. TOCSY and COSY spectrum of 3-heptanone can be easily distinguished on the basis of correlation, such as COSY correlations occurs among hydrogens 4-5, 5-6 and 6-7, but not between 4-7 and 5-7. TOCSY correlation occurs between hydrogens 4-7 and 5-7 also. Similarly, other correlations can also be easily distinguished between two spectra of TOCSY and COSY for any given compound.

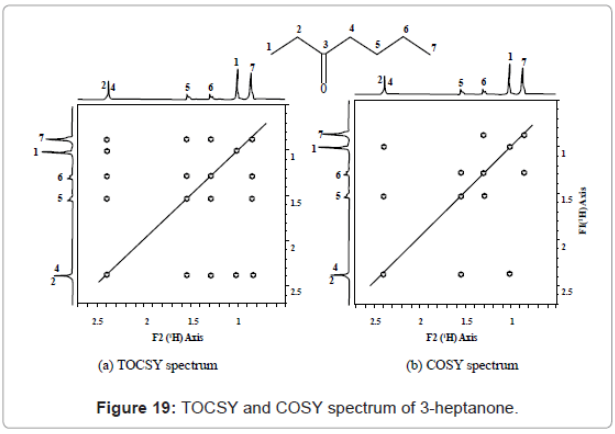


Figure 19: TOCSY and COSY spectrum of 3-heptanone.

EXSY:

This is a homonuclear correlation spectroscopy that correlates between nuclei which are physically close to each other regardless of whether there is a bond between them exists or not. Interpretation of EXSY spectrum can be understood from **figure 20**.

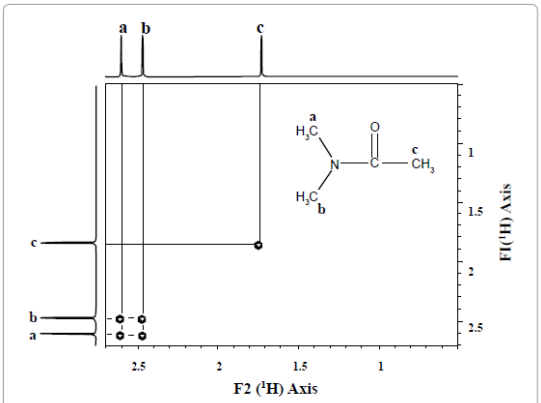


Figure 20: EXSY spectrum of N,N-dimethyl acetamide.

^{1}H EXSY spectrum of N, N-dimethyl acetamide is recorded at room temperature. At this temperature, the molecule exhibits slow rotation about the $(CH_3)_2N$-C bond such that both methyl groups represented as 'a' and 'b' exchange with one another rotationally yet are distinct in the spectrum. This is evident by the cross peaks in the spectrum between the two methyl groups on the nitrogen.

NOESY:

NOESY is a homonuclear correlation spectroscopy that correlates between the nuclei which are physically close to each other regardless of whether there is a bond between them exists or not. The interpretation can be understood from NOESY and COSY spectrum of a quinoline derivative given in **figure 21**. The two experiments differentiates on the diastereotopic protons of the CH_2 group. NOESY spectrum, shows two NOE correlations at (4.29, 1.28) and (4.29, 3.13) ppm. There are no NOE's to the proton signal at 2.68 ppm. The DQFCOSY below shows ^{2}J and ^{3}J correlations at (4.29,3.13), (4.29,1.28) and (3.13, 2.68) ppm. There are no four-bond correlations present as the ^{4}J coupling constants are close to zero. [7-14].

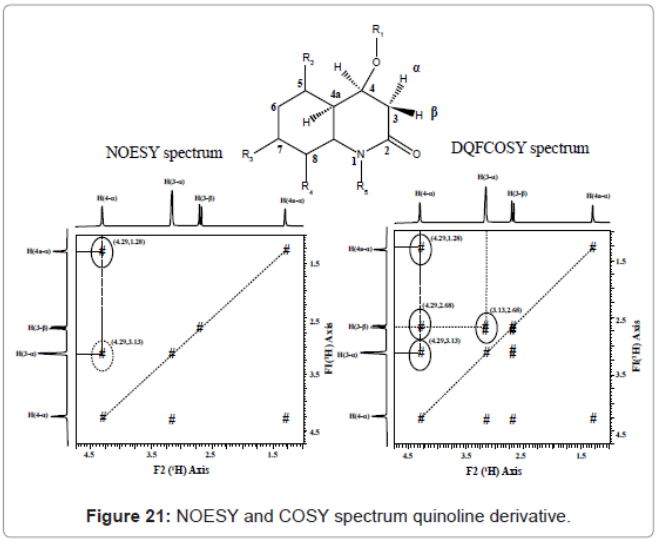


Figure 21: NOESY and COSY spectrum quinoline derivative.