5. Proton Nuclear Magnetic Resonance Spectroscopy

5.0 The NMR Experiment

Nuclear Properties

We are used to thinking of chemical properties in terms of elements (atomic number). For nuclear properties we have to think in terms of isotopes (mass number) - different isotopes of the same element have different nuclear properties. The main nuclear property we are interested in connection with NMR is the nuclear angular momentum spin quantum number I, the "spin" of the nucleus.

I = 0 no spin, the nucleus has no magnetic moment and no NMR properties

I > 0 the nucleus has spin (I = 1/2, 1, 3/2, 2, etc) and a magnetic dipole μ, and thus may be suitable for NMR observation.

$^{x}N_{y}$	$^{even}N_{even}$	I = 0 $^{12}C_6$ $^{16}O_8$ $^{32}S_{16}$
x = mass number y = atomic number	$^{odd}N_{either}$	I = 1/2 $^{1}H_1$, $^{13}C_6$, $^{15}N_7$, $^{19}F_9$, $^{31}P_{15}$
		I = 3/2, 5/2, etc $^{7}Li_3$ (3/2), $^{11}B_5$ (3/2)
	$^{even}N_{odd}$	I = 1, 2, 3, etc $^{6}Li_3$ (1), $^{14}N_7$ (1), $^{2}H_1$ (1),

Nuclei with I = 1/2 have especially advantageous NMR properties, and the vast majority of all NMR experiments are done with such isotopes.

Nuclei with I > 0 have angular momentum P (spinning mass) whose direction is the spin axis. The angular momentum is quantized, and can only have one value:

$$P = \sqrt{I(I+1)} \cdot \frac{h}{2\pi}$$

Nuclei with I > 0 also have a magnetic dipole μ (spinning charge). For the NMR experiment it is the ratio of μ to P that matters (much in the way that m/e is what matters in mass spectrometry). We define γ, the gyromagnetic ratio:

$$\gamma = \frac{\mu}{P}$$

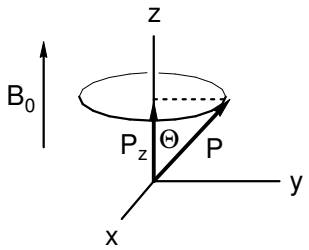
Interaction of Nuclei with a Magnetic Field

When we place a nucleus with spin in a magnetic field the nuclei tend to align with the field. The observable component of the angular momentum P_z is also quantized, and can only have the following values:

$$P_z = m \cdot \frac{h}{2\pi}$$

where m is the magnetic quantum number which can have the values I, I - 1, I - 2, ... -I

Quantum restrictions prevent the nuclei from aligning exactly with B_o, since both the angular momentum (P) and the observable component (P_z) are quantized. For spin ½ nuclei there is a tip angle of 54.7°.



$\cos(\Theta) = P_z/P = 1/\sqrt{3}$

For m = +½ Θ = 54.74°

For m = -½ Θ = 125.26°

For I = 1, m = 1 Θ = 45°, m = 0 Θ = 90°, m = -1 Θ = 135°

There are 2I + 1 allowed orientations of the nucleus in the magnetic field

The nuclei precess around the direction of B_o, with a frequency ν_o (Larmor precession frequency). The frequency is a function of the magnetic field strength (B_o), the angular momentum and the magnetic dipole (Gyromagnetic ratio γ).

$$\nu_o = \frac{\gamma B_o}{2\pi}$$

Interaction with Radiofrequency

A radiofrequency (at the Larmor precession frequency ν_0) applied in the x-direction causes transitions between the spin states if $\nu_{RF} = \nu_o$. These transitions are detected by the spectrometer and plotted as an NMR spectrum.

The NMR Spectrometer

An NMR spectrometer consists of a powerful magnet, and the associated electronics to control the properties of the magnet and create and detect radiofrequency signals. In the first spectrometers (up to 60 MHz proton frequency) permanent magnets were used, then electromagnets (to 100 MHz), and now most spectrometers use superconducting magnets to achieve field strengths which give proton resonances from 200 to as high as 900 MHz. The magnetic field must be very stable over a period of hours and very homogeneous over the sample volume (better than 1 part in 10^9). A complex array of tuning coils is mounted in the magnet and probe to correct for magnetic field inhomogeneities. The radiofrequency generators (at least two are required) must also be very stable, and capable of providing frequencies accurate to 1 part in 10^9, and with short (microsecond range) very accurately timed pulses. All of these very stringent requirements, together with the inherent insensitivity of the NMR experiment, mean that NMR spectrometers have very complex electronics and are hence the most expensive of all common analytic devices used by chemists, running from $100K to $3M (physicists, of course, use analytic devices that cost billions of dollars).

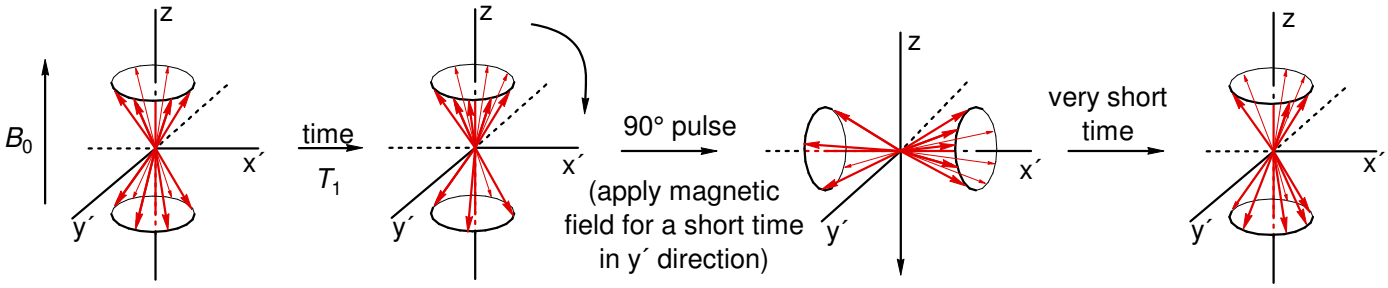
At the heart of an NMR spectrometer is the probe, which is a removable cylinder inserted into the center of the magnet. The probe contains: the sample tube holder and air spinner outlets; the radiofrequency coils for signal detection, decoupler irradiation, and locking of the magnetic field; the electronics, dewar, gas inlets and outlets for cooling and heating of the sample; the tuning coils for fine adjustments of the magnetic field, as well as (in advanced probes) coils for producing precise field gradients. The very latest probes have the electronics for signal detection cooled to liquid nitrogen or liquid helium temperatures (cryoprobes) to provide substantially improved sensitivity (at a factor of 10 increase in cost). Just an ordinary probe can cost more than a low-end IR or UV spectrometer, and a cryoprobe alone can cost as much as an entire mass spectrometer or X-ray diffraction instrument.

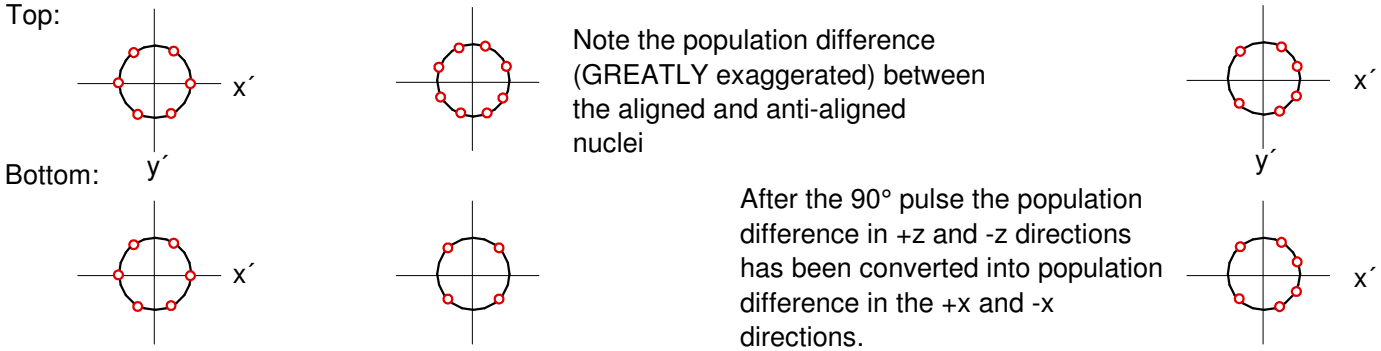
Detection of NMR Signals

The first generation of NMR spectrometers detected the NMR signals in much the same way as was done for the earlier spectroscopic methods such as IR and UV/VIS - the instrument scans through the frequency region of interest (or keeps the frequency constant and scans the magnetic field, a technically easier process used in the first spectrometers). When there is a frequency match (resonance: $\nu_{RF} = \nu_o$) the transitions are detected by the coils in the spectrometer probe, and, after signal processing, are plotted as an NMR spectrum.

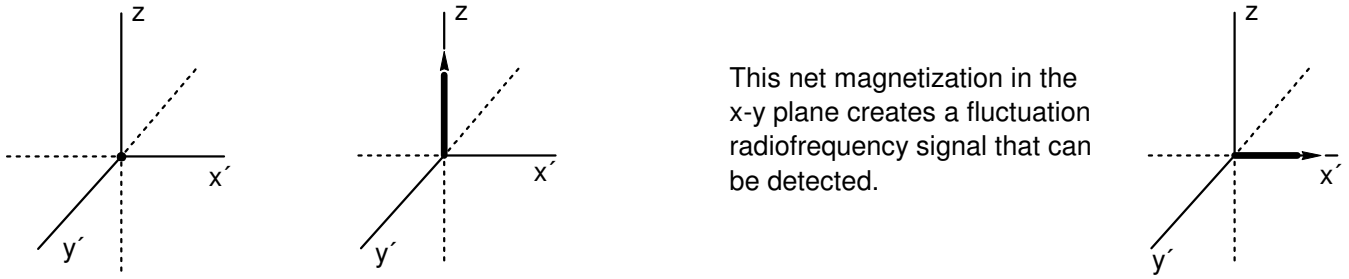
Advances in microwave electronics made possible a much more efficient way of detecting NMR signals in which frequencies are not scanned, but instead a very short powerful pulse is applied to the sample. The pulse is short enough that its frequency is not well defined to within a few thousand Hertz, so it interacts with all of the nuclei of one isotope in the sample. The pulse duration is accurately specified so that the precession of the nuclei around the axis of the pulse corresponds to a well defined angle (say 90 degrees).

Spin ½ nuclei in magnetic field B_0





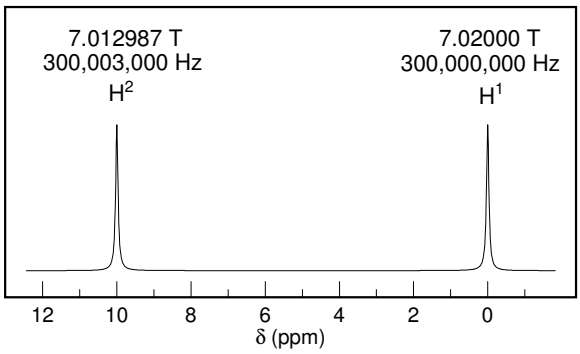
Net Magnetization Vector



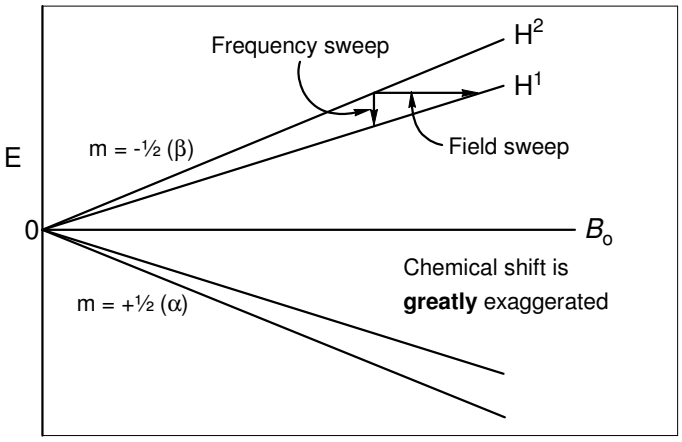
The pulse rotates the excess magnetization (resulting from the higher population of magnetic nuclei in the more stable orientation aligned with the magnetic field B_o) from the z-direction to the x-y plane. This magnetization vector rotates around the x-y plane at the Larmor precession frequency. The fluctuating magnetic field produced by these nuclei is detected by the spectrometer. Each set of nuclei with a distinct chemical shift in the sample has its own precession frequency (the chemical shift), and the spectrometer detects the sum of all of these oscillations (the Free Induction Decay, or FID). The FID is then mathematically manipulated (Fourier transformation) to detect the individual frequencies, which are plotted as a spectrum.

Chemical Shift

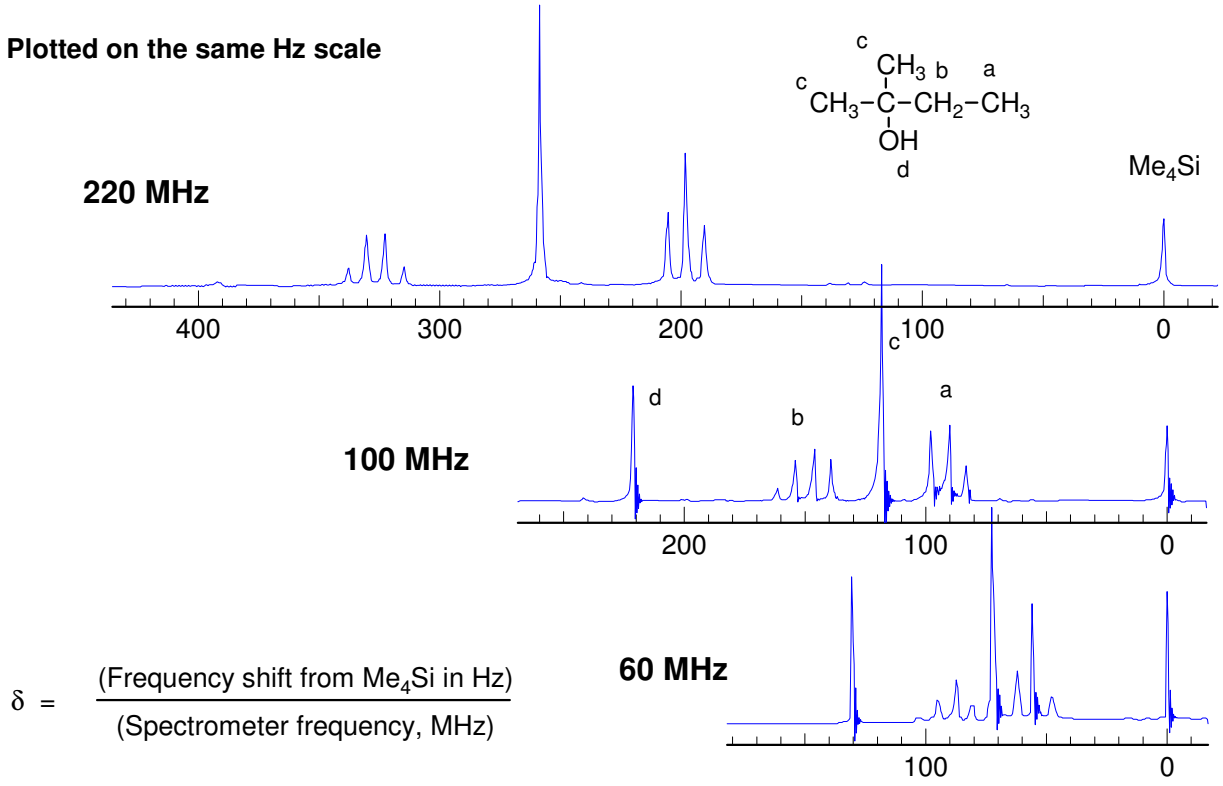
Circulation of electrons around the nucleus creates local magnetic fields which *shield* the nucleus from the external field B_o. The extent of shielding depends on the local chemical environment. Thus NMR signals show a *chemical shift*. The first NMR spectrometers used continuous wave detection, initially by using a magnetic field sweep to scan through the spectrum (a technically simpler process), later frequency sweep electronics were developed. All modern spectrometers use pulse techniques to detect NMR spectra.



Proton NMR spectrum at 7.02 T (300 MHz)

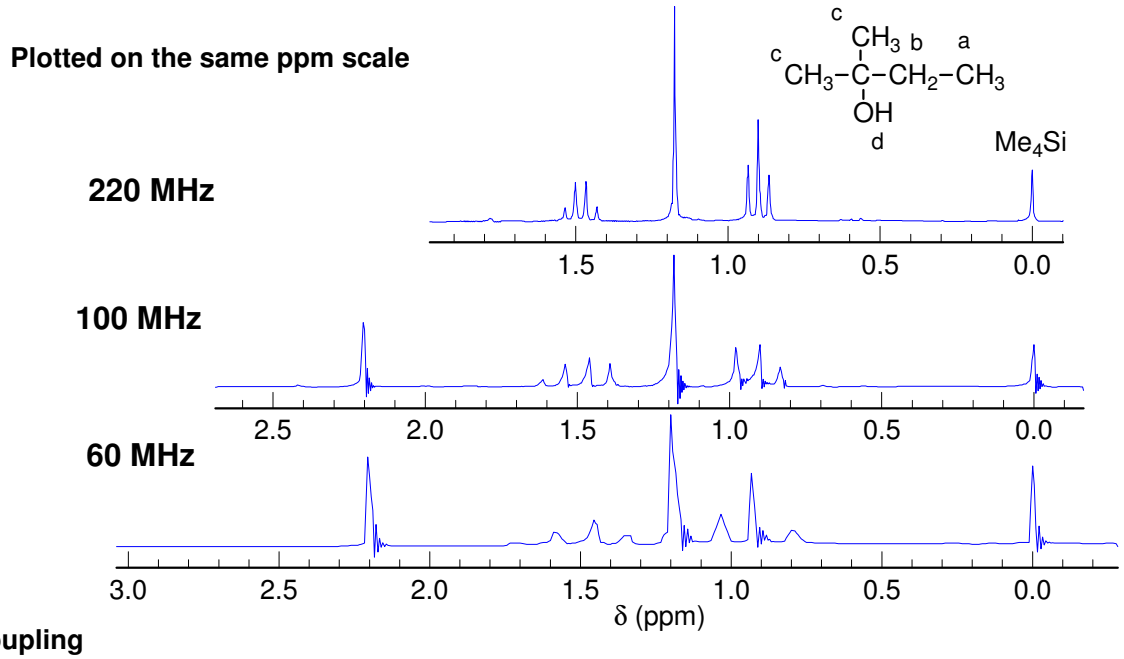


The Larmour precession frequency ν_o depends on the magnetic field strength. Thus at a magnet strength of 1.41 Tesla protons resonate at a frequency of 60 MHz, at 2.35 Tesla at 100 MHz, and so on. Although Hz are the fundamental energy unit of NMR spectroscopy, the use of Hz has the disadvantage that the position of a peak is dependent on the magnetic field strength. This point is illustrated by the spectra of 2-methyl-2-butanol shown below at several different field strengths, plotted at a constant Hz scale.



$$\delta = \frac{\text{(Frequency shift from } Me_4Si \text{ in Hz)}}{\text{(Spectrometer frequency, MHz)}}$$

For this reason, the distance between the reference signal (Me_4Si) and the position of a specific peak in the spectrum (the chemical shift) is not reported in Hz, but rather in dimensionless units of δ, which is the same on all spectrometers. Note that in the above spectra the multiplet separations (doublet, quartet) are the same at all fields, whereas in the spectra below the chemical shift separations are equal.



Coupling

Neighboring magnetic nuclei can also perturb the local magnetic field, so we observe *J-coupling*, which causes multiplet structure for NMR signals. *J* coupling is mutual ($J_{AX} = J_{XA}$). Coupling constants are independent of the magnetic field, and thus should always be reported in Hz.

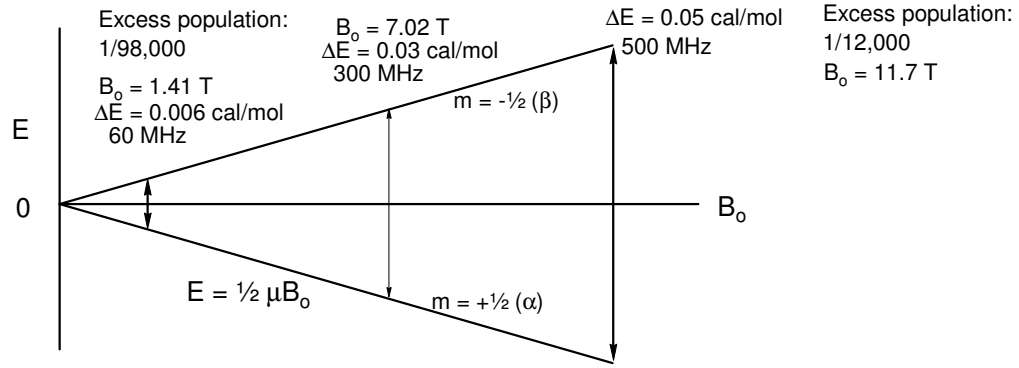
Multiplet structure resulting from several couplings to a given nucleus, however, often depends strongly on the chemical shifts between the nuclei, with larger chemical shifts usually leading to simpler spectra. Since chemical shifts (in energy units like Hz) increase with magnetic field strength, higher field magnets typically give much simpler and more easily interpreted NMR spectra.

Sensitivity

In sharp contrast to UV/VIS/IR spectroscopy, where essentially all molecules are in the ground state at room temperature, in NMR spectroscopy the excited states are thermally populated, with population difference between the spin states of only about one part in 10^5, so NMR signals are inherently very weak.

$$\frac{n^+}{n^-} = e^{-\Delta E/RT}$$ At 500 MHz and 298 K ΔE = -0.05 cal/mol, RT = 592 cal/mol, $n^+/n^- = 0.999916$

The energy separation between the two spin states of a spin ½ nucleus is directly proportional to the strength of the magnetic field ($\Delta E = \mu B_o$). This in turns affects the Boltzmann population differences of the α and β spin states. Thus stronger magnetic fields result in large increases in the strength of the NMR signal.

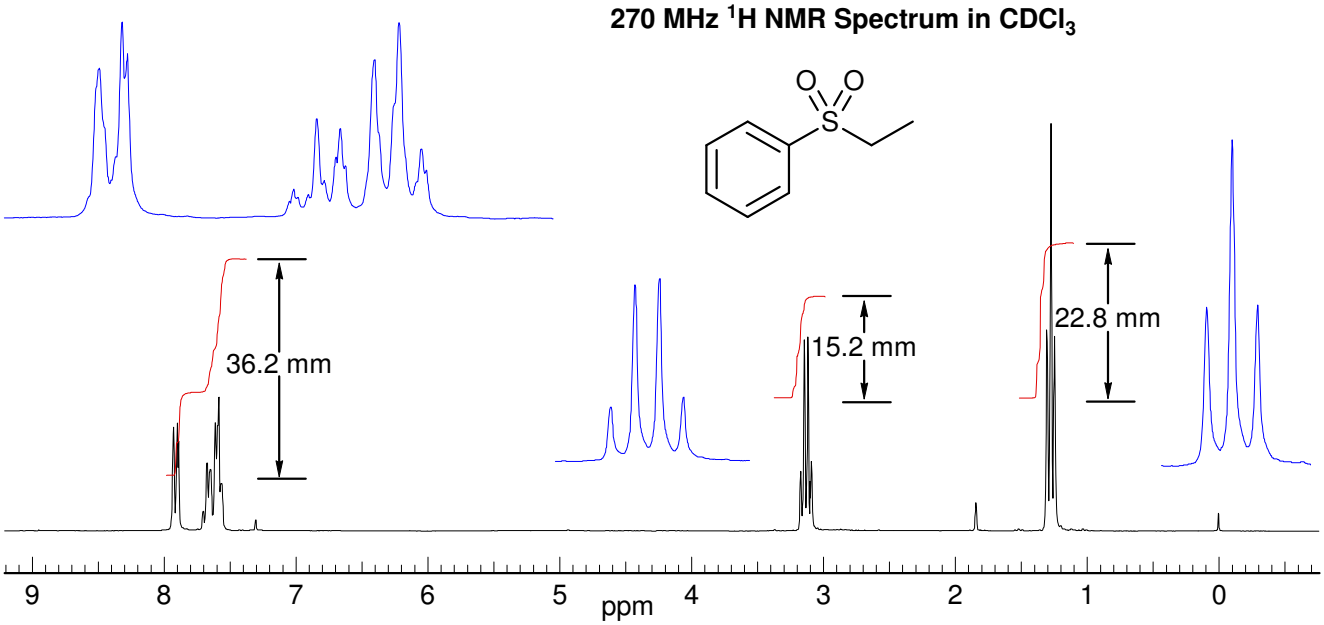


Relaxation

Relaxation of spin for I = 1/2 nuclei is slow (T_1 = 0.1 to 100 sec). This may further weaken NMR signals when the RF field is applied repeatedly (as it usually is), since the population of the spin states can become equalized if nuclei cannot fully relax back to their normal populations between pulses (*saturation*). See Section 8-TECH-1.

5.1 Integration of Proton NMR Spectra

NMR is unique among common spectroscopic methods in that signal intensities are directly proportional to the number of nuclei causing the signal (provided certain conditions are met). In other words, all absorption coefficients for a given nucleus are identical. This is why proton NMR spectra are routinely integrated, whereas IR and UV spectra are not. A typical integrated spectrum is shown below, together with an analysis.



The vertical displacement of the integral gives the relative number of protons It is not possible to determine the absolute numbers without additional information (such as a molecular formula). In the example above, if we add up all of the integrals, we get 74.3. Dividing each integral by the smallest one (15.2) gives a ratio of 2.38/1.0/1.50 for the three signals. Multiplying by two gives 4.76/2.0/3.03, which is close to the integral numbers (5/2/3) expected for a pure compound. However, there is nothing in the spectrum that rules out 10/4/6 or higher multiples. If we have a molecular formula (in this case $C_8H_{10}O_2S$), dividing by the number of hydrogens gives 7.4 mm per H. We can then determine the number of protons corresponding to each multiplet by rounding to the nearest integer. It is generally possible to reliably distinguish signals with intensities of 1 to 10 or so, but it becomes progressively harder to make a correct assignment as the number of protons in a multiplet increases beyond 10, because of the inherent inaccuracies in the method.

The two parts of aromatic proton integral at δ 7.6 and 7.9 can be separately measured as a 2:3 ratio of ortho to meta+para protons.

If given the molecular formula ($C_8H_{10}O_2S$), we know there are 10H in molecule

Total area: 36.2 + 15.2 + 22.8 = 74.2 mm

Thus 7.4 mm per H

36.2 / 7.4 = 4.89 i.e. 5H
15.2 / 7.4 = 2.05 i.e. 2H
22.8 / 7.4 = 3.08 i.e. 3H

Accuracy of Proton NMR Integrations

The integration of NMR spectra can be carried out with high accuracy, but this is only possible if a number of sources of error are properly handled. On a modern spectrometer accuracy of ±5% can be achieved easily if relaxation issues are handled properly. To get errors of <1% a number of factors have to be considered and optimized.

1. **Signal to Noise**. The spectrum must have adequate signal to noise to support the level of accuracy required for the experiment.

2. **Saturation Effects**. NMR spectroscopy has a feature unique among spectroscopic methods, that *relaxation* processes are relatively slow (on the order of seconds or tenths of seconds), compared to milli, micro, and pico seconds for IR and UV. In other words, once the spectrometer has perturbed the equilibrium population of nuclei by scanning over the resonance frequency or pulsing the nuclei, it takes from 0.1 to 100s of seconds (typically several seconds) for them to return to their original populations (T_1 the spin-lattice relaxation time). If power settings are too high (for CW spectra) or pulse angle and repetition rates too high (for FT spectra) then spectra can become *saturated*, and integrations less accurate, because the relaxation rates of various protons in the sample are different. Saturation effects are particularly severe for small molecules in mobile solvents, because these typically have the longest T_1 relaxation times.

To get reliable integrations the NMR spectrum must be acquired in a way that saturation is avoided. It is not possible to tell whether a spectrum was run appropriately simply by inspection, it is up to the operator to take suitable precautions (such as putting in a 5-10 second *pulse delay* between scans) if optimal integrations are needed. Fortunately, even a proton spectrum taken without pulse delays will usually give reasonably good integrations (say within 10%). It is important to recognize that integration errors caused by saturation effects will depend on the relative relaxation rates of various protons in a molecule. Errors will be larger when different kinds of protons are being compared (such as aromatic CH to a methyl group), than when the protons are similar or identical in type (e.g. two methyl groups).

3. **Line Shape Considerations**. NMR signals in an ideally tuned instrument are Lorenzian in shape, so the intensity extends for some distance on both sides of the center of the peak. Integrations must be carried out over a sufficiently wide frequency range to capture enough of the peak for the desired level of accuracy. Thus, if the peak width at half height is 1 Hz, then an integration of ±2.3 Hz from the center of the peak is required to capture 90% of the area, ±5.5 Hz for 95%, ±11 Hz for 98% and ±18Hz for >99% of the area. This means that peaks that are closely spaced cannot be accurately integrated by the usual method, but may require line-shape simulations with a program like NUTS or WINDNMR to accurately measure relative peak areas.

4. **Digital Resolution**. A peak must be defined by an adequate number of points if an accurate integration is to be obtained. The errors introduced are surprisingly small, and reach 1% if a line with a width at half height of 1 Hz is sampled every 0.5 Hz.

5. **Isotopic Satellites**. All C-H signals have ^{13}C *satellites* located $\pm J_{C\text{-}H}/2$ from the center of the peak ($J_{C\text{-}H}$ is typically 115-135 Hz, although numbers over 250 Hz are known) Together these satellites make up 1.1% of the area of the central peak (0.55% each). They must be accounted for if integration at the >99% level of accuracy is desired. Larger errors are introduced if the satellites from a nearby very intense peak fall under the signal being integrated. The simplest method to correct this problem is by ^{13}C decoupling, which compresses the satellites into the central peak. A number of other elements have significant fractions of spin ½ nuclei at natural abundance, and these will also create satellites large enough to interfere with integrations. Most notable are $^{117/119}Sn$, ^{29}Si, ^{77}Se, ^{125}Te, ^{199}Hg. For more on satellites, see Section 7, Multinuclear NMR.

There is a bright side to ^{13}C satellites: they can be used as internal standards for the quantitation of very small amounts of isomers or contaminants, since their size relative to the central peak is accurately known.

6. **Spinning Sidebands**. These can appear at ± the spinning speed in Hz in spectra run on poorly tuned spectrometers and/or with samples in low-quality tubes. They draw intensity from the central peak. SSBs are rarely significant on modern spectrometers.

7. **Baseline Slant and Curvature**. Under some conditions spectra can show significant distortions of the baseline, which can interfere with obtaining high-quality integrations. Standard NMR work-up programs have routines for baseline adjustment.

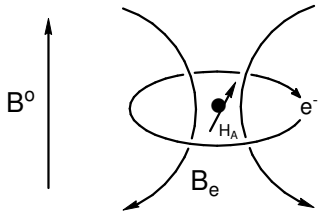
8. **Decoupling**. When decoupling is being used, as is routinely done for ^{13}C NMR spectra and occasionally for ^{1}H NMR spectra, peak intensities are distorted by Nuclear Overhauser Effects (NOE, see Sect. 8). Integrations of such spectra will not give accurate ratios of peak areas.

Peak Intensities. Under certain conditions, peak heights can also be a quite accurate method of quantitation. For example, if several singlets are being compared, and they all have *identical line widths*, and the spectra were measured such that there are *sufficient data points* to define the lineshape of each singlet, then peak heights may be useful, and under ideal conditions more accurate than integrations.

Determining Absolute Amounts by NMR Integration. Although NMR spectra in principle follow Beer's law, it is difficult (although not impossible) to make effective use of the *absolute* intensities of NMR spectra for quantitation (as is routinely done for UV, and sometimes IR). NMR integrations are always relative. Thus an *internal standard* must be used to determine reaction yields by NMR integration. A commonly used internal standard for proton NMR spectra is pentachloroethane -- it is a liquid, not too volatile, and appears in a region of the NMR spectrum (δ 6.11) where there are few signals. It is strongly recommended to avoid using volatile materials like CH_2Cl_2, $CHCl_3$, C_6H_6 and others, since it is very difficult to avoid some evaporation losses during the transfer process of the standard, leading to incorrect (high) concentrations of the substrate.

5.2 Chemical Shift

Fortunately for the chemist, all proton resonances do not occur at the same position. The Larmor precession frequency (ν_o) varies because the actual magnetic field *B* at the nucleus is always **less** than the external field B_o. The origin of this effect is the "superconducting" circulation of electrons in the molecule, which occurs in such a way that a local magnetic field $\mathbf{B}_e$ is created, which opposes B_o (B_e is proportional to B_o). Thus $B = B_o - B_e$. We therefore say that the nucleus is **shielded** from the external magnetic field. The extent of shielding is influenced by many structural features within the molecule, hence the name **chemical shift**. Since the extent of shielding is proportional to the external magnetic field B_o, we use **field independent** units for chemical shifts: δ values, whose units are ppm. Spin-spin splitting is not dependent on the external field, so we use energy units for coupling constants: Hz, or cycles per second (in mathematical formulas radians per second are the natural frequency units for both chemical shifts and couplings).



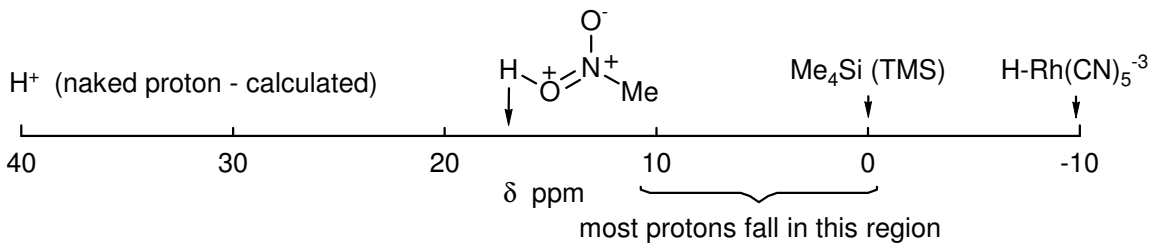
$B = B_o - B_e$ (magnetic field at nucleus)

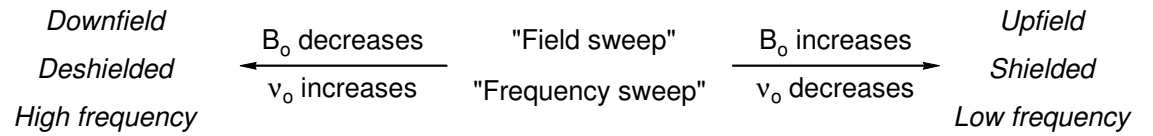
$\nu_o = \gamma B/2\pi$ (Larmor precession frequency of H_A - varies as B changes)

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 ($Me_3Si\text{-}CH_2CH_2\text{-}SO_3^-Na^+$, Tiers, *J. Org. Chem.* **1961**, *26*, 2097). For aqueous solution of cationic substrates (e.g., amino acids) where there may be interactions between the anionic reference compound and the substrates, an alternatice reference standard, DSA ($Me_3Si\text{-}CH_2CH_2\text{-}NH_3^+\ CF_3CO_2^-$, Nowick *Org. Lett.* **2003**, *5*, 3511) 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.



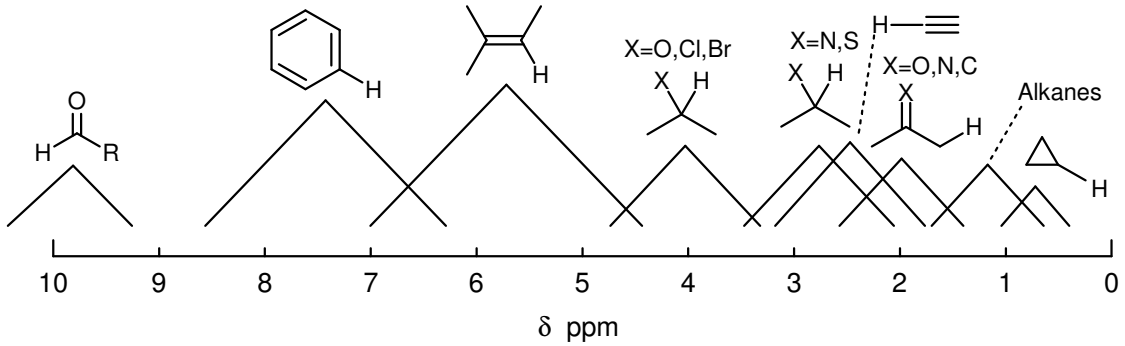


In the original continuous wave (CW) method of measuring NMR spectra, the magnetic field was scanned from left to right, from low to high values. We thus refer to signals on the right as upfield or shielded and signals to the left as downfield or deshielded. Later spectrometers gained the capability 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:

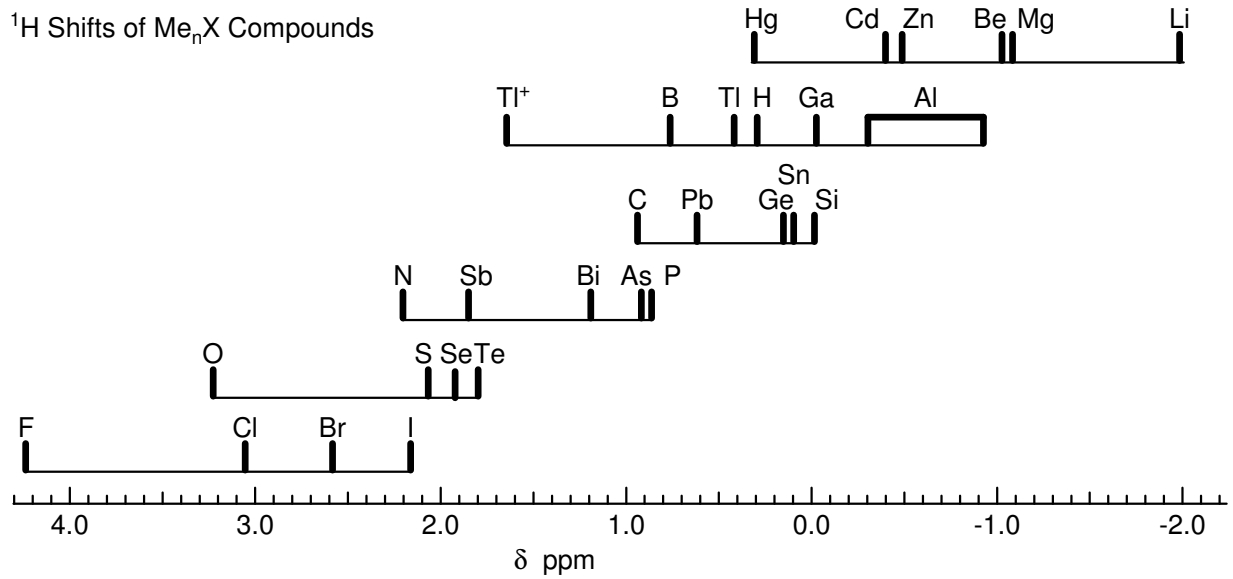
$$\delta = \frac{[\nu_o(H) - \nu_o(TMS)]}{[\text{Spectrometer Frequency in MHz}]}$$

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: $\delta = 10 - \tau$. Coupling constants are field independent, and should always be specified in Hz.

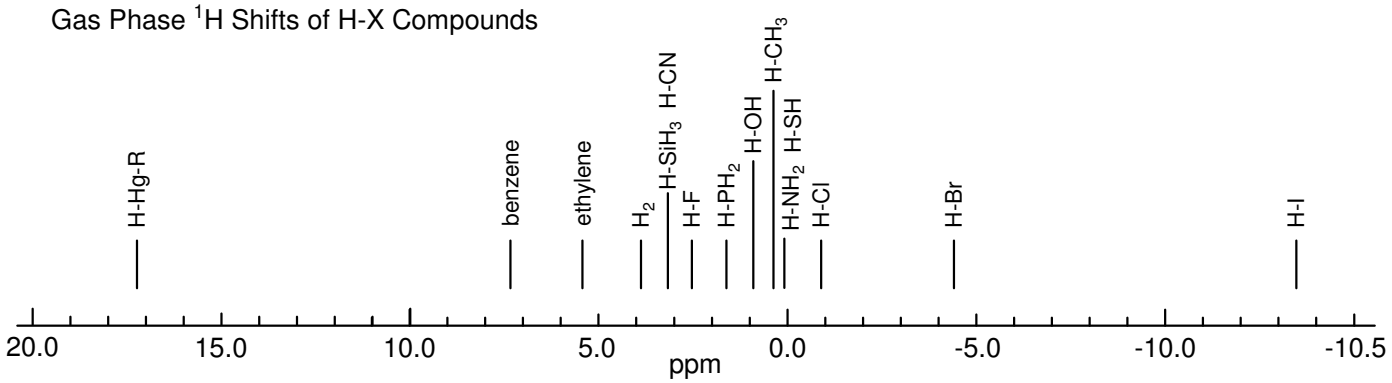
The chemical shifts of protons on carbon in organic molecules fall in several distinct regions, depending on the nature of adjacent carbon atoms, and the substituents on those carbons. The scale below should be used only as a rough guideline, since there are many examples that fall outside of the indicated 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.

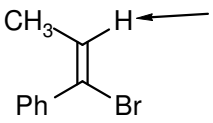


The ^{1}H chemical shifts of protons attached to heteroatoms (H-X) show a very wide chemical shift range, with no obvious correlation to the electronegativity of X or the acidity of HX.



Calculation of Proton Chemical Shifts

Parameters for the calculation of proton chemical shifts for many kinds of molecules have been tabulated (see Section 9, **Proton NMR Data**). All of these work in the same way. We establish the base chemical shift for a reference substance (e.g., ethylene for olefins, benzene for substituted aromatic compounds, methane for alkanes) and tabulate **Substituent Chemical Shift** values (Δδ) for the introduction of substituents into the reference molecules. Thus for a vinyl proton (C=C-H) there will be parameters for the introduction of substituents *cis*, *trans*, or *gem* to the hydrogen we are calculating, and this leads to reasonable estimations for most molecules, as in the example below (parameters from Section 9-HDATA-6.1). Here Δδ 0.15 is the difference between calculated and observed chemical shifts. However, when there are strong resonance or other electronic interactions between substituents (as in the β-aminoenone below, with Δδ 1.70), or strong conformational effects then the predictions made by these calculations will be less accurate. NOTE: the chemical shift increments were determined in weakly interacting solvents like CCl_4 and $CDCl_3$. They will work poorly for spectra taken in aromatic solvents like benzene or pyridine (see later section on aromatic solvent shifts).

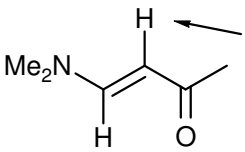


Calculate δ

5.25 (Base shift: CH_2=CH_2)
0.45 (Z_{gem} Me)
0.45 (Z_{cis} Br)
-0.07 (Z_{trans} Ph)

6.08 (δ Calculated)
6.23 (δ Observed)

Δδ 0.15



Obs: 5.47, Calc: 7.17

Δδ 1.70

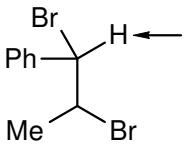
Calculate δ

5.25 (Base shift: CH_2=CH_2)
0.78 (Z_{gem} COMe)
-1.26 (Z_{cis} NMe_2)

4.77 (δ calculated)
5.05 (δ observed)

Δδ 0.28

For aliphatic (sp^3) C-H proton chemical shifts we can use the Curphy-Morrison table (Section 9-HDATA-5.1). In this system there are base shifts for CH_3 (0.9), CH_2 (1.2) and C-H (1.55) protons, and then corrections are applied for all α and β substituents. The corrections for CH_3, CH_3 and CH protons are slightly different, and no corrections are applied for alkyl groups.



Calculate δ

1.55 (Base shift: tertiary CH)
0.95 (α-Ph for CH)
2.20 (α-Br for CH)
0.25 (β-Br for CH)

4.95 (δ Calculated)
5.00 (δ Observed)

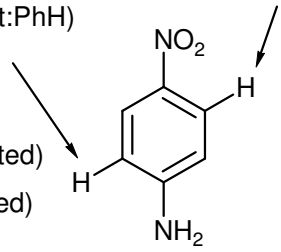
Δδ 0.05

Calculate δ

7.36 (Base shift:PhH)
0.20 (m-NO_2)
-0.71 (o-NH_2)

6.82 (δ Calculated)
6.62 (δ Observed)

Δδ 0.20



Calculate δ

7.36 (Base shift:PhH)
0.87 (o-NO_2)
-0.22 (m-NH_2)

8.01 (δ Calculated)
7.93 (δ Observed)

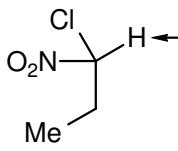
Δδ 0.08

Accuracy of Chemical Shift Calculations

Calculations using simple parameter lists such as in Section 9-HDATA-5.1 and Section 9-HDATA-6.1 will typically give results accurate to within 0.5 ppm, but there are exceptions:

Multiple Substituents: The more parameters you are adding together, and the larger they are, the less accurate the calculation is likely to be. This is especially true for electronegative substituents like O, N and Cl if they are applied several times to the same proton as the examples below. This is perfectly reasonable, since electron withdrawal from the C-H group becomes progressively more difficult as the C-H group becomes more electron deficient.

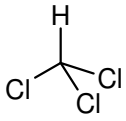
Calculate δ



1.55 (Base shift: tertiary CH)
2.55 (α-Cl for CH)
3.05 (α-NO_2 for CH)

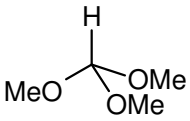
7.15 (δ Calculated)
5.80 (δ Observed)

Δδ 1.35



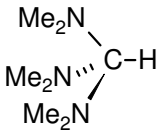
Obs: δ 7.26, Calc: 9.2

Δδ 1.94



Obs: δ 4.97, Calc: 8.9

Δδ 3.93



Obs: δ 3.02, Calc: δ 5.60

Δδ 2.58

Cyclic Systems: Calculations are usually poor for cyclic systems, or otherwise conformationally constrained compounds. The base shift for a CH_2 group in an alkane is 1.2 ppm, and this would be the calculated value of any methylene group in a cycloalkane. The actual shift for methylenes in cycloalkanes varies by 1.7 ppm, from δ 0.2 for cyclopropane to δ 1.9 for cyclobutane, although if you ignore cyclopropane and cyclobutane, the range is only 0.5 ppm. One of the reasons is that in cyclic compounds conformational mobility is greatly restricted, so that less rotational averaging of various chemical shift anisotropic effects occurs. At low temperatures the axial and equatorial hydrogens of cyclohexane differ by 0.5 ppm, the average shift at room temperature is 1.44, close to the standard value of 1.2. Note especially that the protons on 3-membered rings of all kinds are strongly shifted to lower frequency from the acyclic value.

Standard CH_2

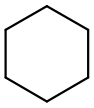
$-CH_2-$

δ 1.20

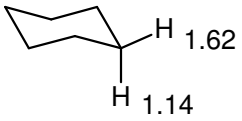
0.22

1.94

1.51



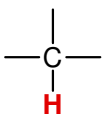
1.44



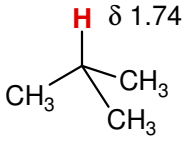
-103 °C

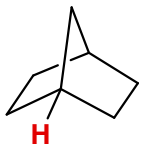
Even more dramatic chemical shift effects are seen in polycyclic compounds. The Curphy-Morrison calculated values for all of the compounds below would be δ 1.55 (the base value for a methyne group), yet the actual values vary by several ppm. Not sur[risingly, cubane and dodecahedrane are especially far from the typical values.

Standard CH

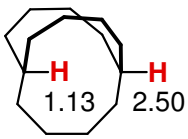


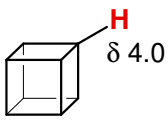
δ 1.55

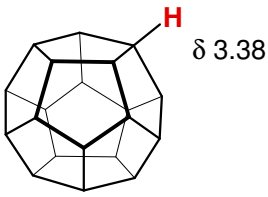




2.19







Reproducibility of Proton Chemical Shifts

It is important to understand that the chemical shift of a given proton is not an invariant property of a molecule (like a melting point or boiling point), but will change depending on the molecular environment. The variability is especially large for NH and OH protons (several ppm), but even for CH protons reported shifts vary by a few tenths of a ppm. This is in part due to changes in measurement conditions, but additional variability in chemical shift is present in old NMR data (CW spectra) since spectrometer calibrations and spectrum referencing were not nearly as accurate as they are today. Nevertheless, if conditions are rigorously controlled, very high reproducibility of chemical shifts can be achieved. Databases of precise chemical shifts for many biomolecules have been created which facilitate simultaneous detection by NMR in aqueous solution.

Solvent effects. The aromatic solvents benzene and pyridine cause changes in chemical shifts as large as 0.5 to 0.8 ppm compared to less magnetically active solvents like chloroform or acetone. Since the standard solvent for chemical shift parameters like the Curphy-Morrison ones is CCl_4 or $CDCl_3$, expect less accurate calculations for spectra taken in aromatic solvents.

Concentration dependence. Chemical shifts of C-H protons can vary with concentration, especially if intermolecular hydrogen bonding can occur, as for many amines, alcohols and carboxylic acids. The chemical shifts of protons on oxygen (OH) and nitrogen (NH), which are often directly involved in hydrogen bonding are especially strongly dependent (several ppm) on concentration, solvent and temperature. Aromatic molecules can also show significant concentration dependence because of the aromatic solvent effect mentioned above.

Temperature dependence. For molecules that are conformationally flexible, the populations of conformations change with temperature. Since the chemical shifts of various conformations are different, the chemical shifts will vary with temperature (the observed chemical shift is the weighted average of the shifts of the individual conformations). Temperature will also affect the degree of intermolecular hydrogen bonding or other types of aggregation, and this provides an additional source of shift changes.

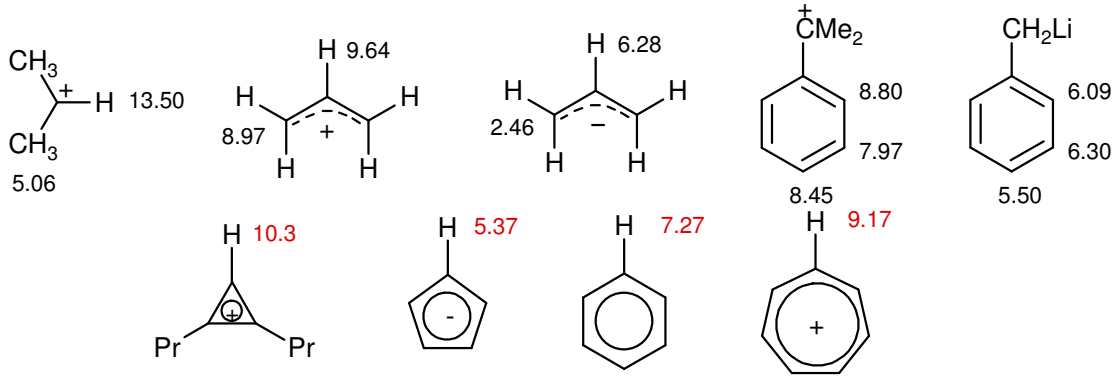
Paramagnetic impurities (unpaired electrons, transition metals with unpaired spins) can cause very large shifts (tens and hundreds of ppm) as well as large amounts of line broadening. Must avoid these alltogether if you want to get high quality NMR spectra.

Proton Chemical Shift Effects

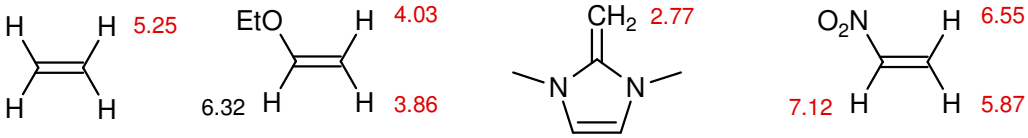
1. **Electronegativity**. Proton shifts move downfield when electronegative substituents are attached to the same or an adjacent carbon (see Curphy-Morrison chemical shift table). Alkyl groups behave as if they were weakly electron withdrawing, although this is probably an anisotropy effect.

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

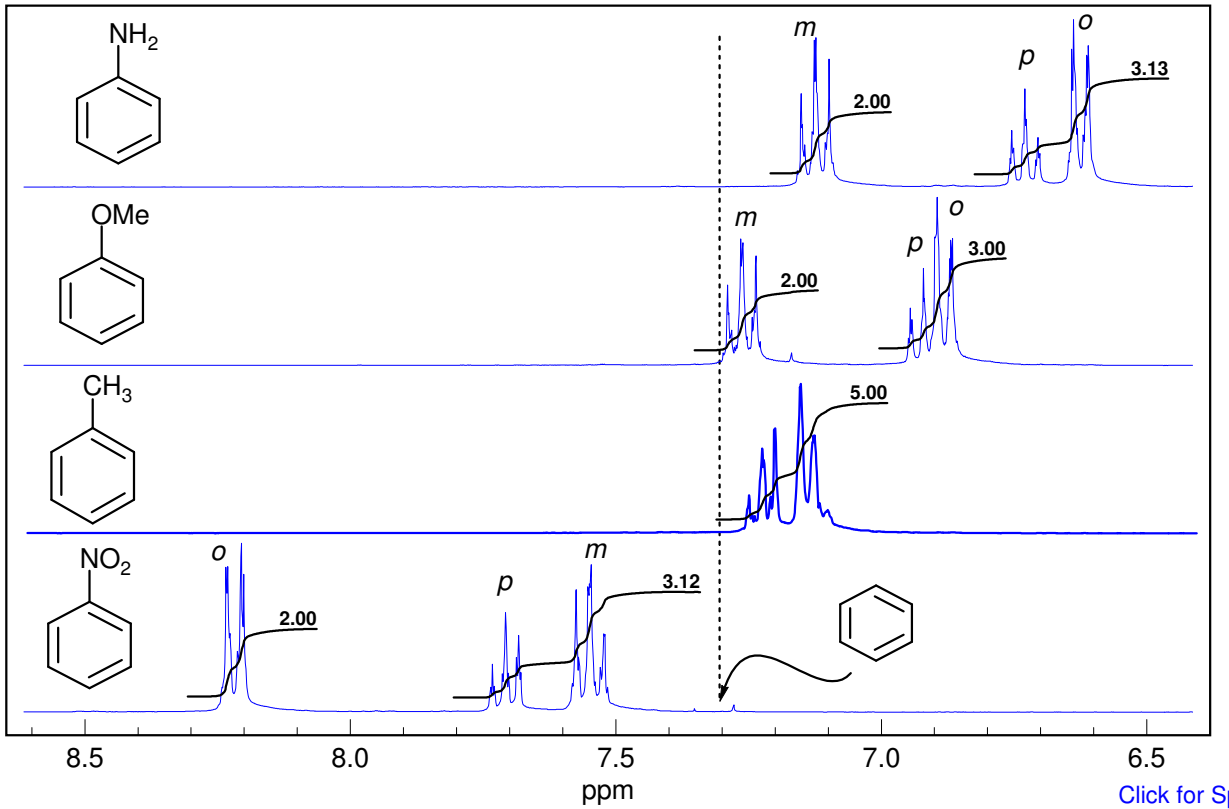
The chemical shifts of protons attached to sp^2 hybridized carbons also reflect charges within the π system (approximately 10 ppm/unit negative or positive charge).



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



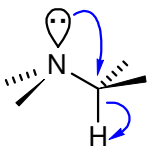
This is especially useful in the interpretation of the NMR chemical shift of protons in aromatic systems. The protons ortho and para to electron donating and electron withdrawing substituents show distinct upfield and downfield shifts.

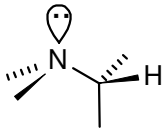


Click for Spectra

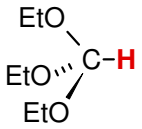
2. **Lone Pair Interactions**. When lone pairs on nitrogen or oxygen are *anti* to a C-H bond, the proton is shifted upfield (n --> σ* interactions). There is thus a strong conformational dependence of chemical shifts of protons α to heteroatoms. This interaction is one of the reasons that Curphy-Morrison chemical shift calculations work poorly when multiple O or N substituents are attached to one carbon. 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. For example, the Θ = 180 ° compound shows IR absorption at 2450 cm^{-1}, as well as at 2690-2800 cm^{-1}.

Electron donation to C-H bond gives a -δ (upfield) shift effect



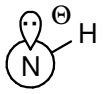


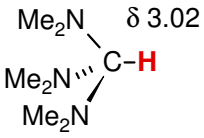
Little interaction

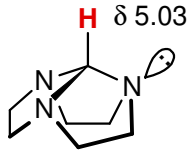


C-M calculation: δ 7.85
Observed: δ 4.96

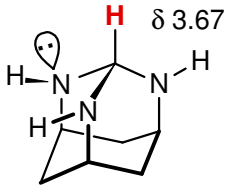
Curphy-Morrison calculation would give δ 5.60 for all of these:



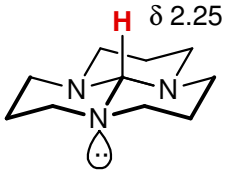




Θ = 0 °
Weisman *TL* **1980**, 3635

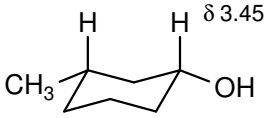


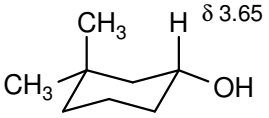
Θ = 60 °
Stetter *Ber* **1973**, 2523

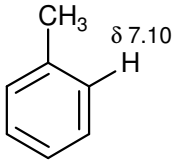


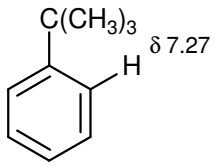
Θ = 180 °
Weisman *TL* **1980**, 3635

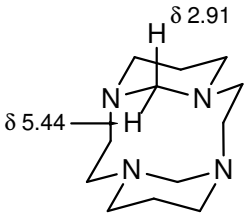
3. **Steric Compression**. When molecular features cause a proton to be forced close to other protons, or to various functional groups, the proton will in general be deshielded (dispersion interactions). Shifts of this type are hard to distinguish from magnetic anisotropy interactions.



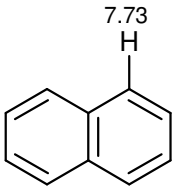


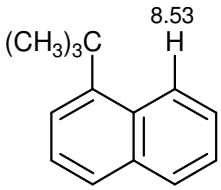


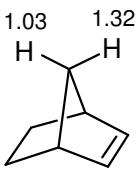




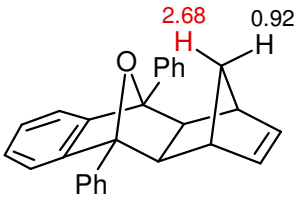
The N-H distance is 2.25 A





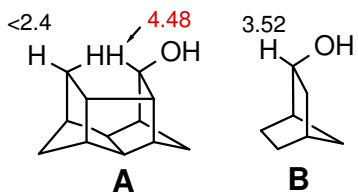


JACS **1968**, 3724



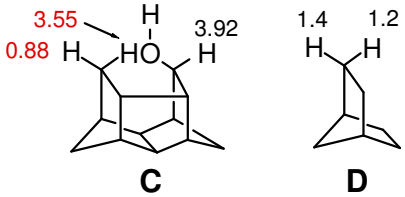
JOC **1967**, 1304

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.



A **B**

JACS **1965**, 5247

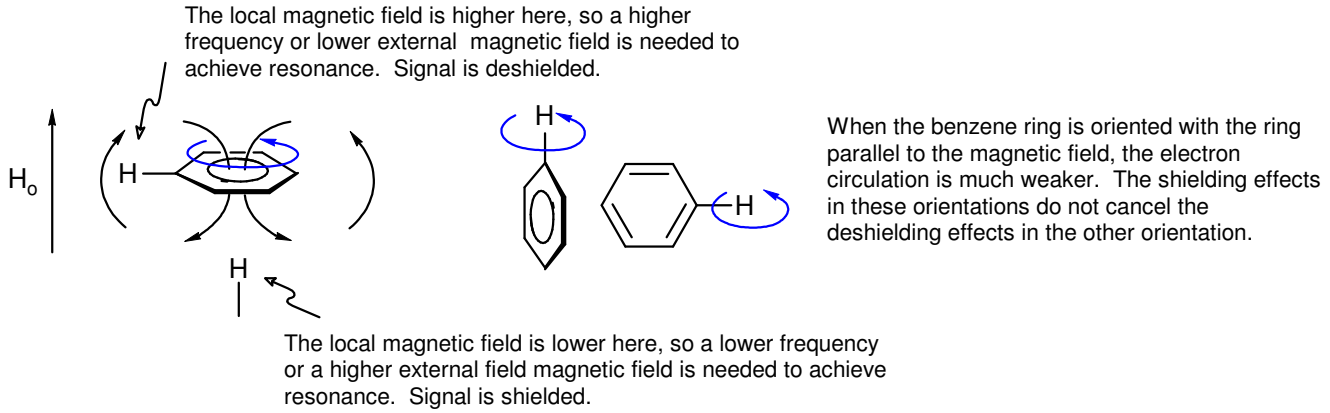


C **D**

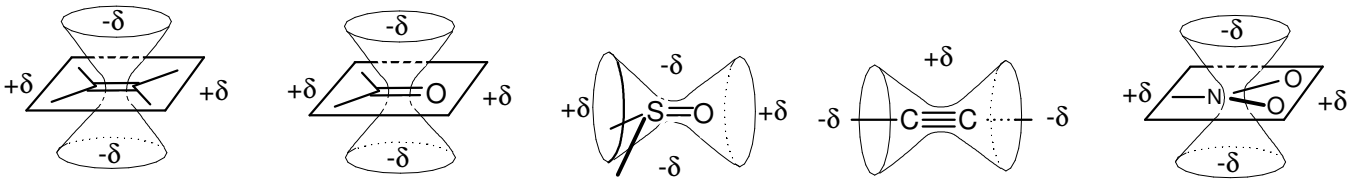
JACS **1965**, 5247

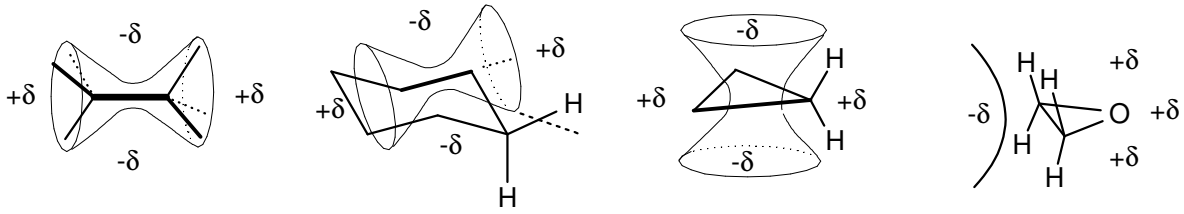
4. **Magnetic Anisotropy**. Whereas the local circulation of electrons around H_A is a shielding effect (i.e., to the *right* in the NMR spectrum, -δ), there can be both shielding and deshielding effects on H_A from electron motion in other parts of the molecule. We refer to such interactions as **magnetic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

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:





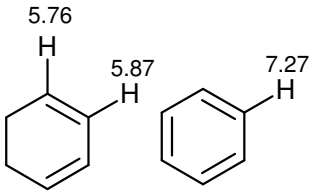
1. H. C. Brown, A. Suzuki *J. Am. Chem. Soc.* **1967**, *89*, 1933. L. A. Paquette, G. Kretschmer, *J. Am. Chem. Soc.* **1979**, *101*, 4655.

2. C. D. Poulter et al. *J. Am. Chem. Soc.* **1972**, *94*, 2291.

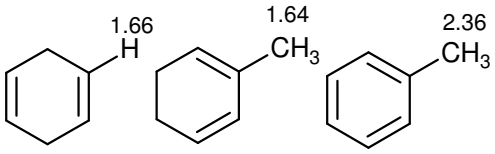
3. The Thiosulfinyl Group Serves as a Stereogenic Center and Shows Diamagnetic Anisotropy Similar to That of the Sulfinyl Group: Tanaka, S.; Sugihara, Y.; Sakamoto, A.; Ishii, A.; Nakayama, J.; *J. Am. Chem. Soc.*, **2003**, *125*, 9024.

4. Magnetic Anisotropy of the Nitro Group by NMR I. Yamaguchi, *Mol. Phys.* **1963** , *6*, 103

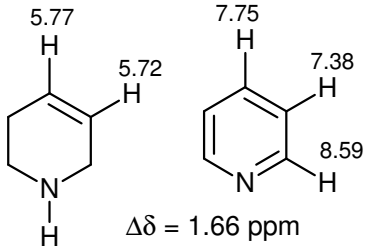
Aromatic Chemical Shifts. The ring current in Huckel aromatic systems, i.e., those with 4n + 2 π electrons (2, 6, 10, 14, 18 ...) causes downfield shifts in the plane of aromatic ring.



Δδ = 1.40 ppm

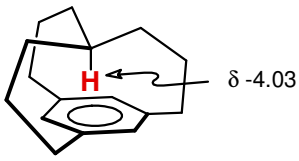


Δδ = 0.72 ppm

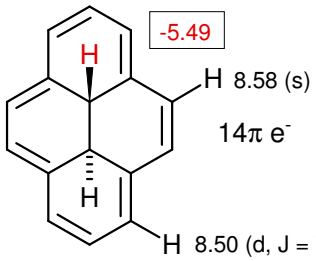


Δδ = 1.66 ppm

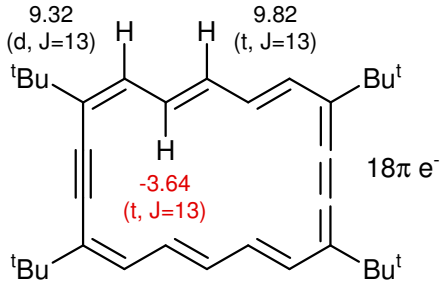
When protons are above or below the plane (or in the middle) of the aromatic ring then upfield shift effects are observed.



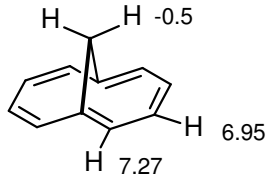
Pascall *JACS* **1987**, 6878



Boekelheide *JACS* **1970**, 3511

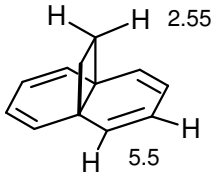


Nakagawa *TL* **1973**, 4743



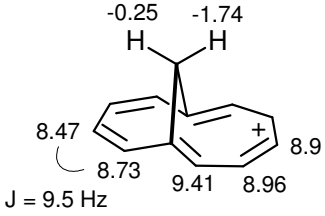
10π e- Aromatic

Vogel *AC* **1964**, 145, 784

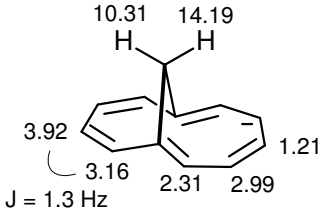


Nonaromatic

Vogel *TL* **1966**, 655



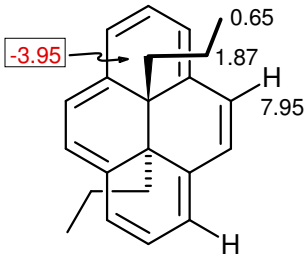
10π e- (aromatic)



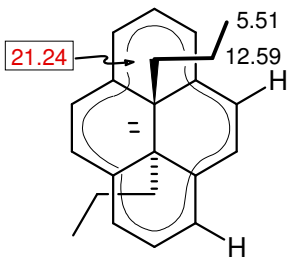
12π e- (antiaromatic)

Staley *JACS* **1973**, 3384

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.

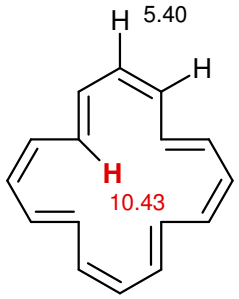


14π e- (aromatic)

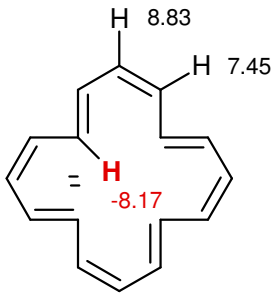


16π e- (antiaromatic)

Boekelheide *JACS* **1969**, 4931



16π e- (antiaromatic)

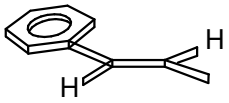


18π e- (aromatic)

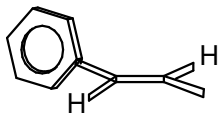
Oth *TL* **1968**, 6265

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.

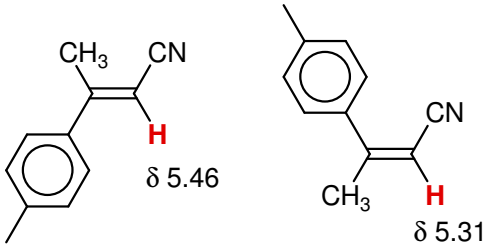
Chemical Shift Effects of Phenyl Groups. The effects of a phenyl substituent are highly dependent on conformation. For example, for styrenes the chemical shift effect of the phenyl is downfield when the phenyl is in the plane of the double bond, but upfield when the rotamer with the phenyl group perpendicular is the more stable one:



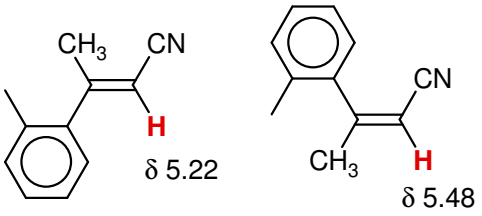
If ring is flat, get downfield shifts (+δ)



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



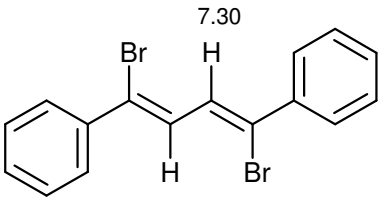
H cis to Ph is downfield

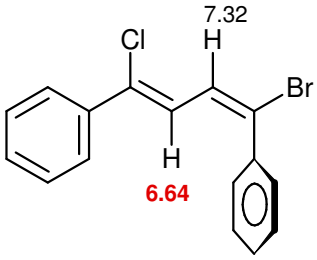


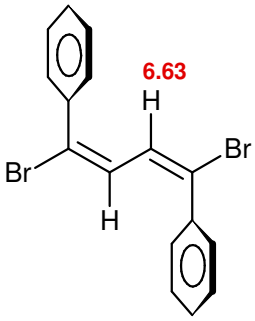
H cis to Ph is upfield - the ortho-methyl substituent presumably rotates the Ph group out of the C=C plane.

TET **1970**, 4783

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

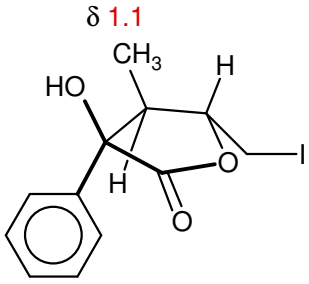


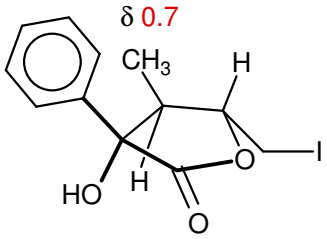




Reich *J. Org. Chem.* **1975**, *40*, 2248

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.

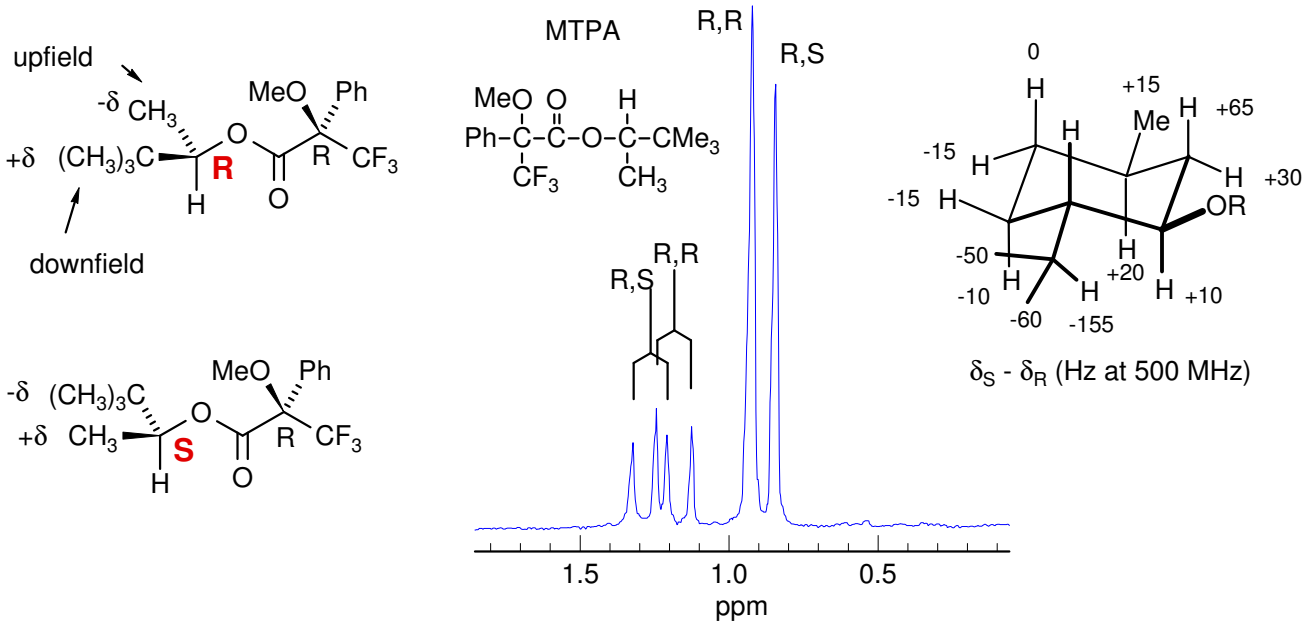




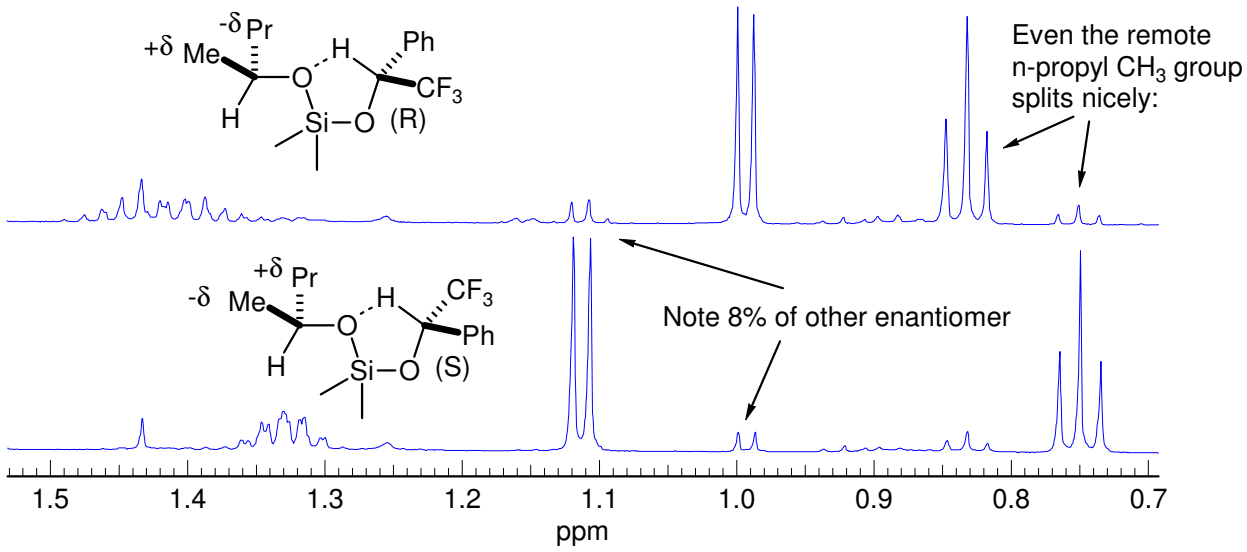
JOC **1982**, 3943

Determination of Enantiomer Ratios and Absolute Configuration with Mosher Esters. Esters of 2-phenyl-2-methoxy-3,3,3-trifluoropropionic acid (Mosher esters, or MTPA esters) with secondary alcohol show characteristic chemical shift effects in the alcohol portion which can be used to measure enantiomeric purity and assign the absolute configuration of the alcohol. It is necessary to assign key protons, and to make both the R- and S-Mosher ester to arrive at an unambiguous determination (Dale, J. S.; Mosher, H. S. *J. Am. Chem. Soc.*, **1973**, *95*, 512; Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.*, **1991**, *113*, 4092).

This method works because the principal conformation of MTPA esters is the extended one shown. The anisotropy of the phenyl group then causes upfield shifts of the protons behind the plane of the paper, downfield shifts for those in front. A typical procedure is to do a complete analysis of all assignable protons of the R and S esters, and calculate the difference between the chemical shifts of the two diastereomers. Note that the t-Bu group is upfield in the R,S ddistaereomer, whereas the Me group is upfield in the R, R isomer.

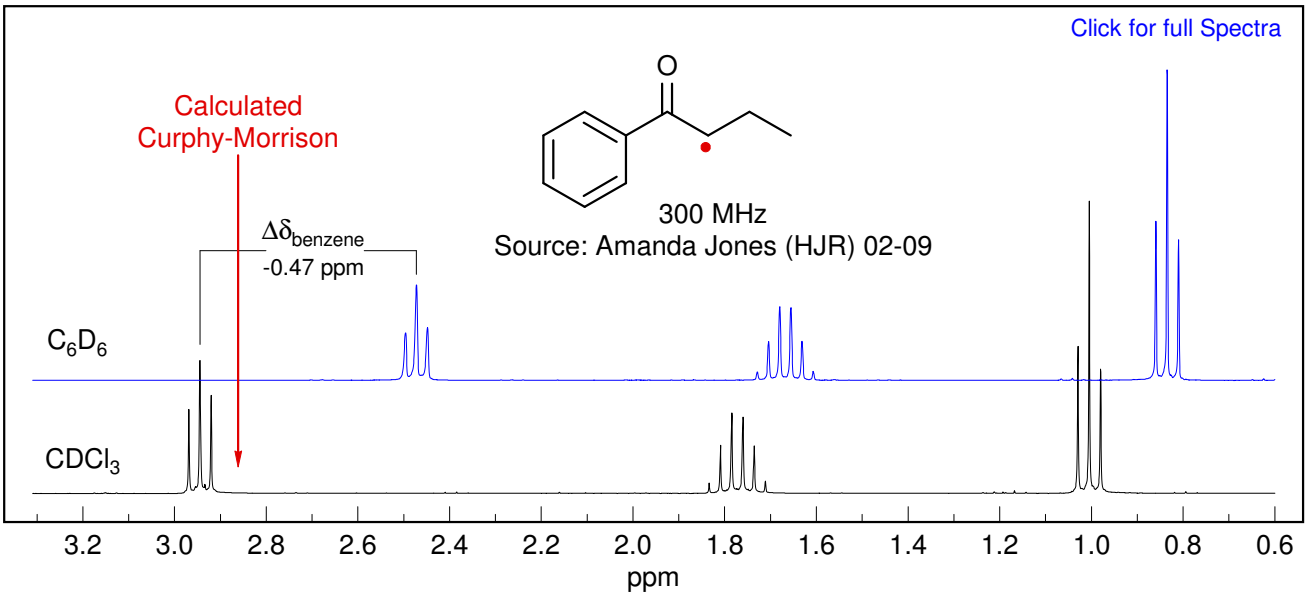


For a related method using 1-phenyltrifluoroethanol, see *Org. Lett.* **2003**, *5*, 1745.



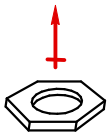
"Chiral Reagents for the Determination of Enantiomeric Excess and Absolute Configuration Using NMR Spectroscopy." Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256-70. " The Assignment of Absolute Configuration by NMR," Seco, J. M.; Quinoa, R.; Ricardo, R. *Chem. Rev.* **2004**, *104*, 17. Parker, D. "NMR Determination of Enatiomeric Purity" *Chem. Rev.* **1991**, *91*, 1441

Aromatic Solvent Induced Shifts (ASIS). Polar molecules have substantially different chemical shifts in aromatic solvents (benzene, pyridine, C_6F_6) than in less magnetically interactive solvents like CCl_4, $CDCl_3$, CCl_2D_2, acetone-d_6 and CD_3CN. A typical result of going from $CDCl_3$ to benzene is shown in the spectra of butyrophenone below. The shifts are large enough that chemical shift calculations can be seriously in error when applied to molecules whose spectra were taken in benzene (P. Laszlo *Progr. NMR Spectrosc.* **1967**, *3*, 231).



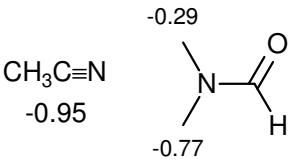
The origin of these chemical shift effects is believed to be a partial orientation of the solvent by the dipole moment of the solute. For benzene, the shifts can be rationalized on the basis of a weak and transient complexation of the electron-rich π-cloud of the aromatic ring with the positive end of the molecular dipole, such that the protons spend additional time in the shielding (-δ) region above and below the benzene ring. There is a strong correlation between the dipole moment and the size of the solvent shift. With occasional exceptions, the benzene shifts are upfield (-δ).

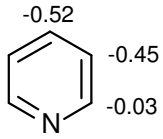
Δδ (CCl_4 vs. C_6D_6):

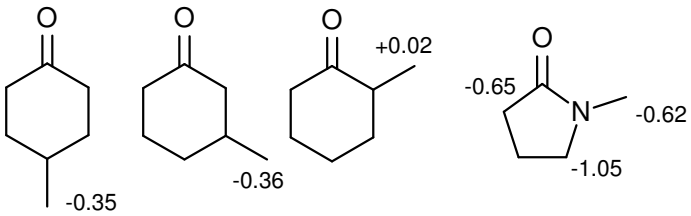


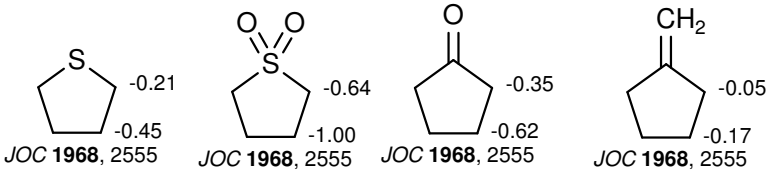
Effect of dipole moment on ASIS:

	Δδ	μ
$MeSnCl_3$	-1.43	3.6
$MeSnI_3$	-1.02	2.6
$MeCCl_3$	-0.59	1.5
Me_4Sn	-0.09	0

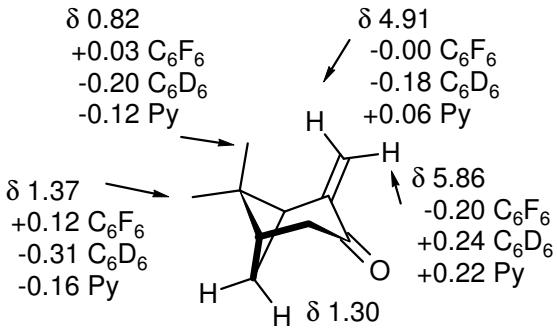




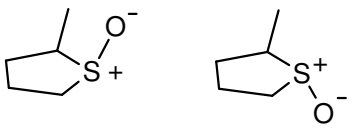




JOC **1968**, 2555 *JOC* **1968**, 2555 *JOC* **1968**, 2555 *JOC* **1968**, 2555



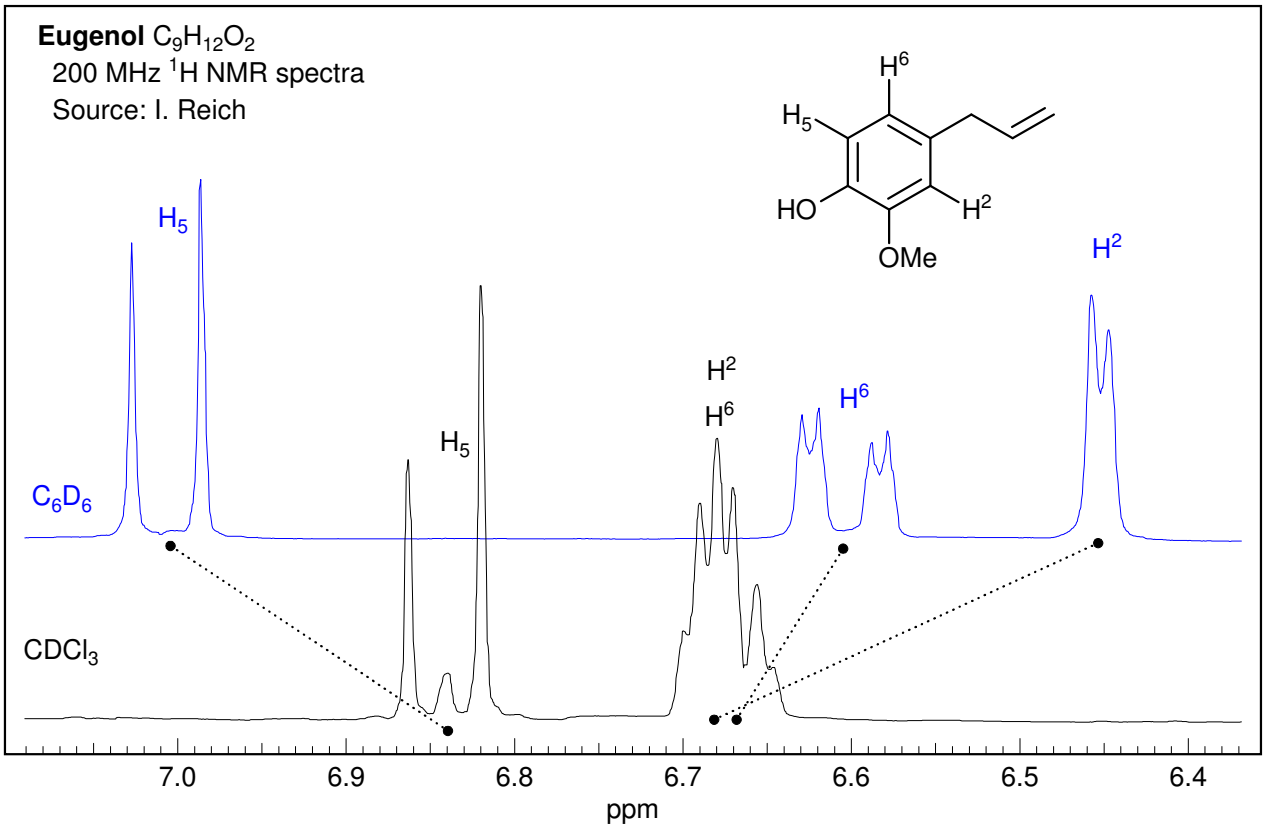
K. Tori *Tetrahedron Lett.* **1975**, 2199.



δ_{Me} ($CDCl_3$)	1.40	1.23
δ_{Me} (C_6D_6)	1.18	0.74
Δ δ	-0.22	-0.49

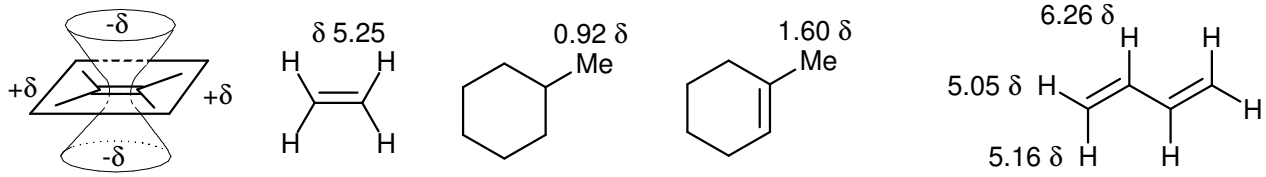
JOC **1970**, 3655

When ^{1}H NMR spectra are complicated by accidental superposition of coupled protons, as in the spectrum of eugenol in $CDCl_3$ below, then switching to benzene as solvent (or even just adding a few drops of C_6D_6 to the sample) will often move signals enough that more interpretable (first order) spectra result. In the $CDCl_3$ spectrum of eugenol H^2 and H^6 are nearly superimposed, leading to a complex ABX pattern of the Solution 2 type. The spectrum in C_6D_6 is essentially first order.

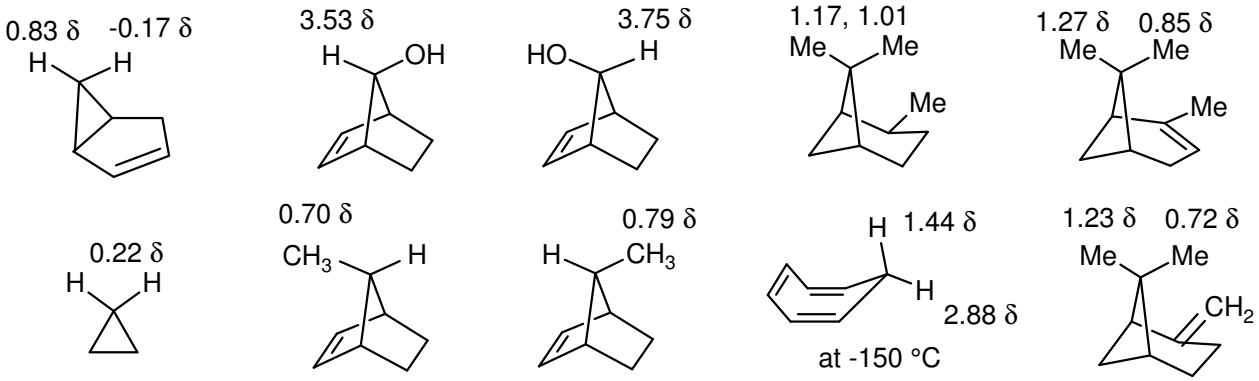


Effect of benzene to simplify a strongly coupled NMR spectrum.

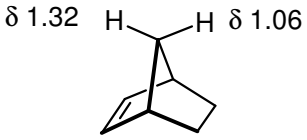
Anisotropy of Double Bonds. The magnetic anisotropy of C-C double bonds has generally been assumed to be similar to that of aromatic rings, with a deshielding region in the plane of double bond. This explains both the downfield shifts of vinyl protons, and the larger downfield shifts of the internal (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.



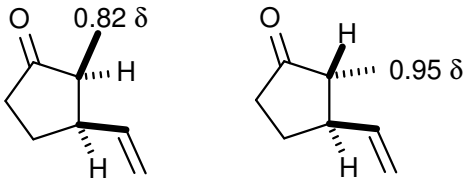
The shielding region above and below the plane of the double bond is more controversial. A number of examples show the expected upfield shifts of protons above double bonds.



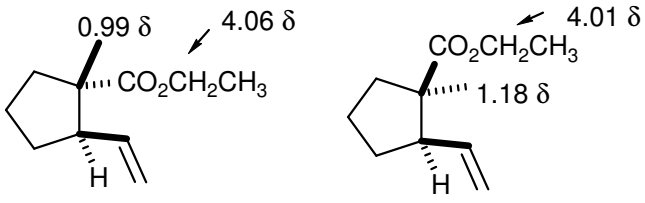
There is, however, one major exception. In norbornene itself, the proton shifts are in the opposite direction than seen in the 7-substituted norbornenes above (*J. Am. Chem. Soc.* **1968**, *90*, 3721). Both the proton assignment and the absence of a -δ region above the double bond are supported by high level *ab initio* MO chemical shift calculations (*J. Am. Chem. Soc.* **1998**, *120*, 11510). Thus the deshielding region above double bonds shown in the figure must be viewed with some skepticism.



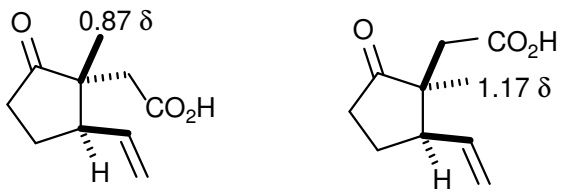
For this reason, assignment of stereochemistry in cyclopentanes based on an assumed anisotropy of double bonds, as in the examples below, should be used with caution. Possibly the shifts are the result of C-C single bond anisotropy of the C-vinyl bond.



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



Chem. Commun. **1988**, 760

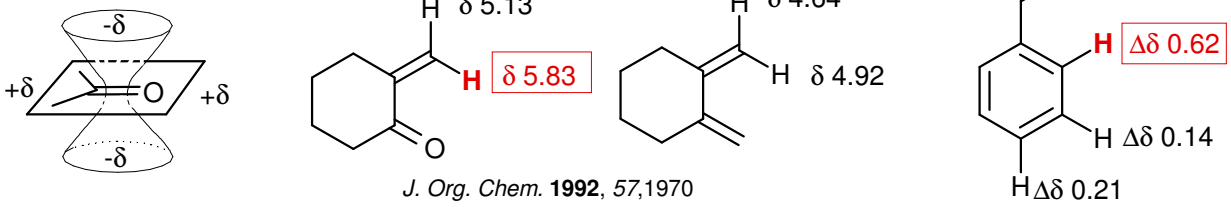


Vollhardt *J. Am. Chem. Soc.* **1980**, *108*, 5253.

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

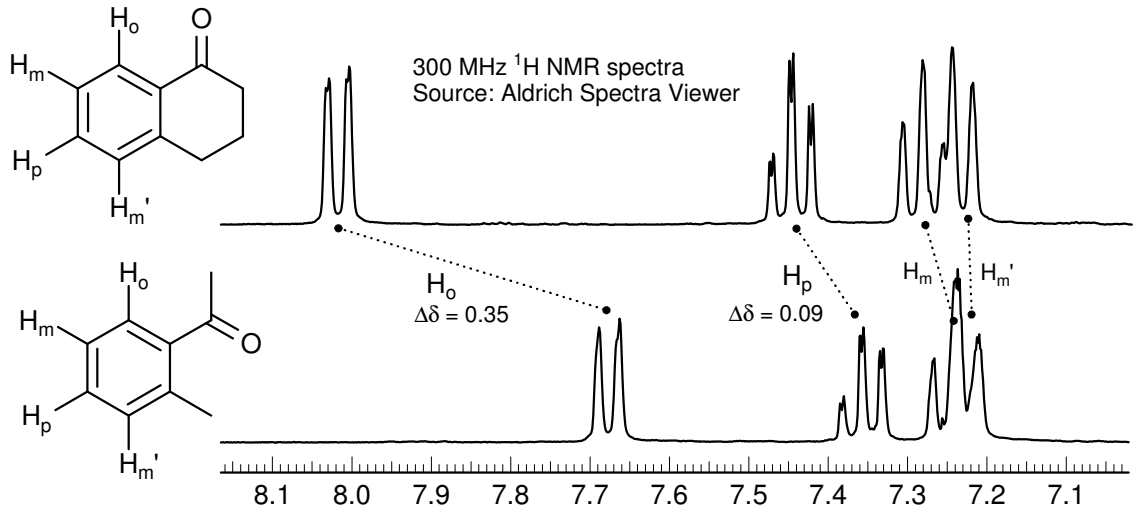
Anisotropy of Carbonyl Groups. The magnetic anisotropy of C=O has a strongly deshielding (+δ) region in the plane of carbonyl group. This accounts for numerous chemical shift effects in aryl ketones, α,β-unsaturated carbonyl compounds, and conformationally rigid ketones, and is reliable enough to be used for structure assignments.

The effect is seen both when the proton is β to the carbonyl group, as in the enones and acetophenones below, or when there is a γ-relationship.

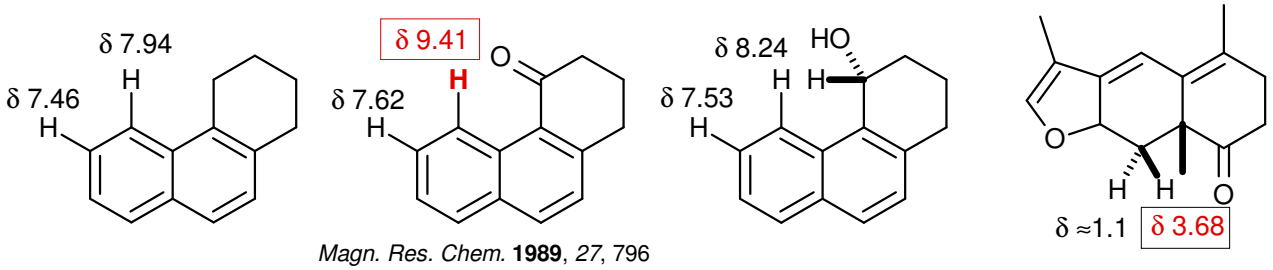


J. Org. Chem. **1992**, *57*,1970

The tetralone below shows a strongly downfield shifted ortho-proton, to δ 8.0. The ortho-methyl acetophenone, on the other hand shows as smaller downfiled shift (δ 7.7), probably due to some rotation of the carbonyl group out of the plane, as well a preference for the conformation shown, with the smaller C=O group cis to the ortho-CH_3 group. Acetophenone ortho proton appears at δ 7.9.

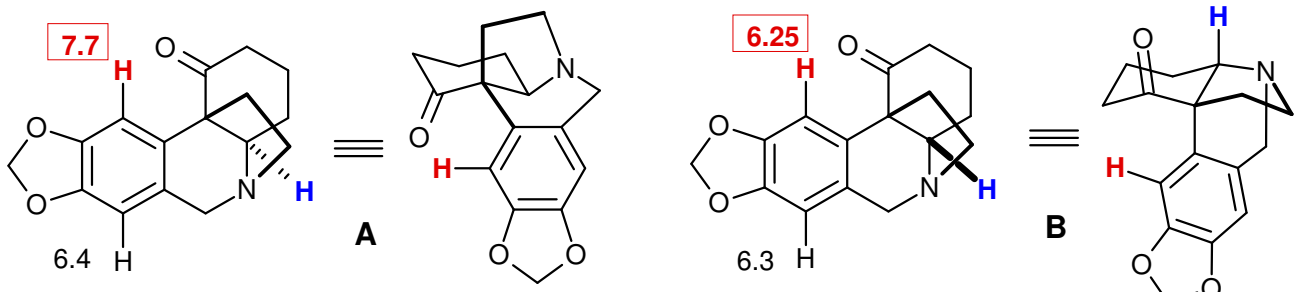


In the compounds below, the proton is γ to the carbonyl and close to same plane, leading to quite large downfield shifts:



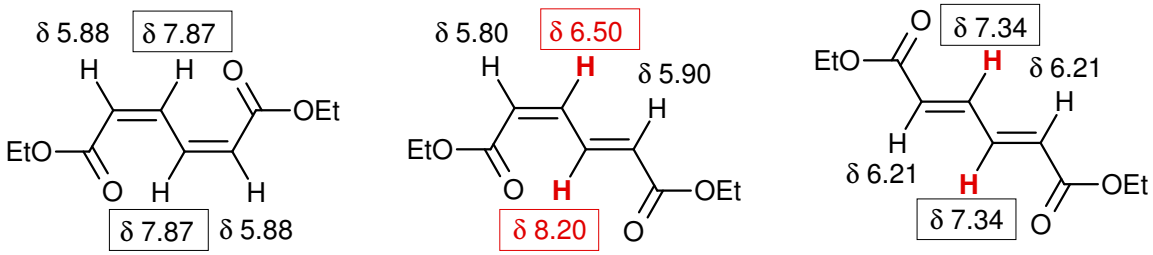
Magn. Res. Chem. **1989**, *27*, 796

In the stereoisomer **A** below, one of the aromatic protons is close to the carbonyl, and is shifted downfield by 1.3 ppm, whereas in isomer **B** the carbonyl is remote, and the chemical shift is normal.

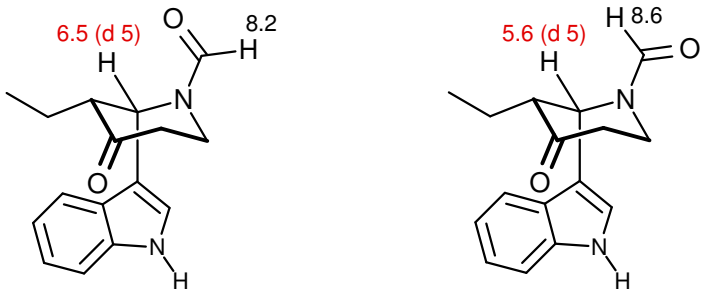


J. Am. Chem. Soc. **1967**, *89*, 3600

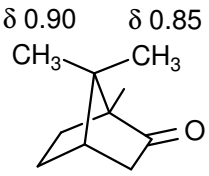
These α,β-unsaturated esters show a shift range of 1.7 ppm resulting from the various β- and γ-carbonyl interactions. In the most upfield shift (δ 6.50 for the E,Z-isomer) there are no close interactions, whereas the most downfield proton (δ 8.20 for the same isomer) has a β-interaction with one carboxylate function, and a γ-interaction with the other:



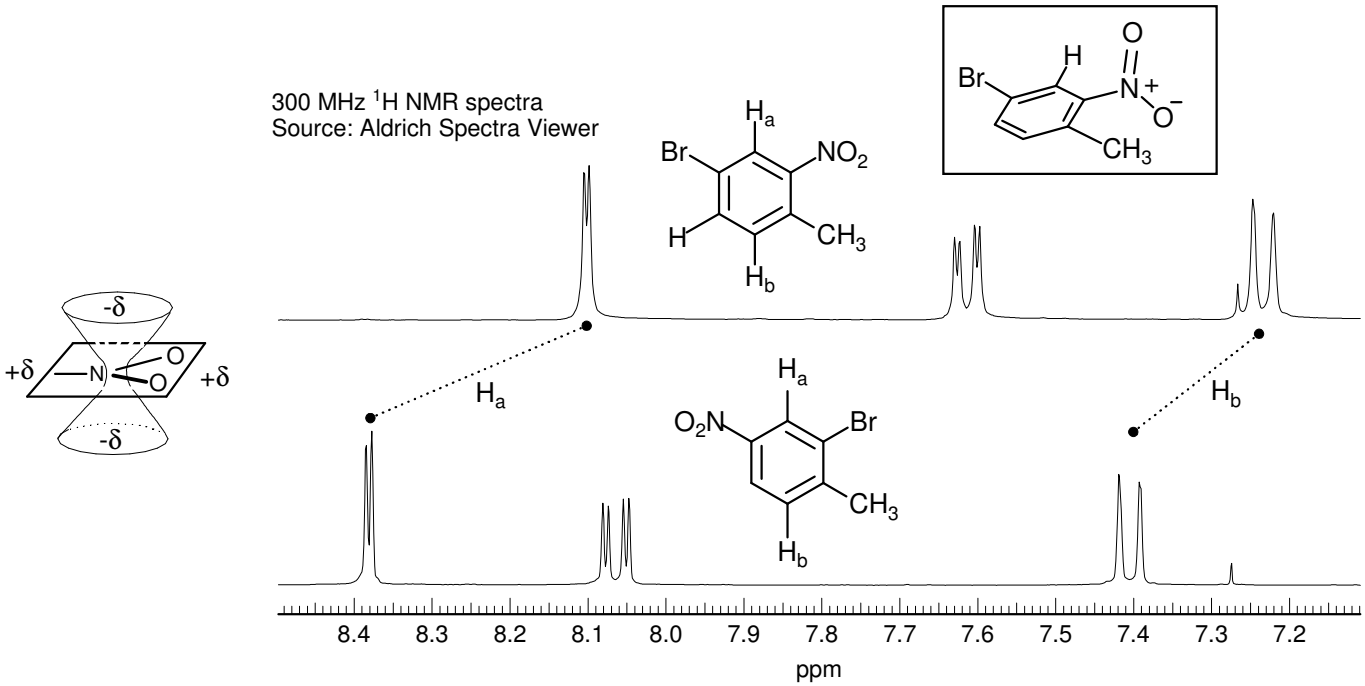
Amides also show these chemical shift effects. Thus, for the two rotamers of the formamide below, the α-N proton is 0.9 ppm downfield in the isomer with this proton close to the formyl oxygen (Buchi, G.; Gould, S. J.; Naf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492)



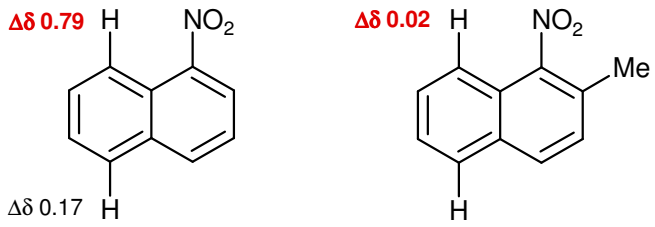
There is some evidence that there is a shielding (-δ) region above the plane of the carbonyl group:



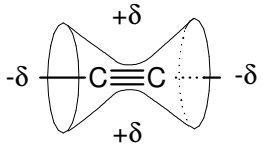
Anisotropy of Nitro groups. The NO_2 group may have a a small anisotropic effect similar to that of C=O groups, with a deshielding (+δ) region in the plane of carbonyl group. The *ortho* protons of nitrobenzenes are strongly downfield, in part due to this interaction. For example the proton H_a between the NO_2 and Br groups (the small downfield doublet) has a very similar electronic environment in the two compounds whose spectra are shown below. The upper one has this proton upfield in part because the ortho-methyl group turns the nitro group out of the plane. Of course, turning the nitro group also causes reduced resonance interactions, which causes a shift in the same direction, as seen from the change in the proton ortho to the Me group (H_b).



A similar chemical shift effect in a naphthalene is illustrated below:



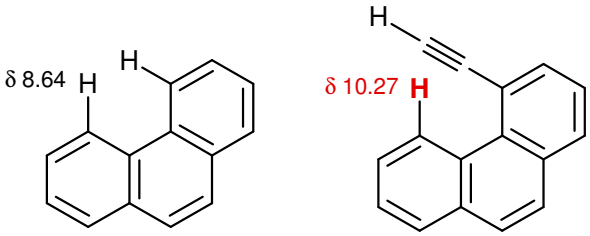
Anisotropy of Acetylenes. The magnetic anisotropy of C≡C bonds seems to be well-defined. Both the unusual upfield shift of C≡C-H signals, and the downfield shifts of protons situated next to a triple bond as in the examples below support a strong diamagnetic affect of electron circulation around the triple bond π system. .



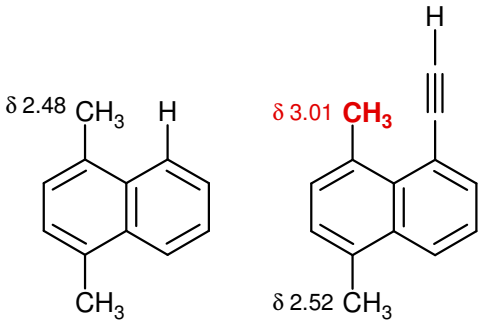
CH_3-CH_3 δ 0.90

CH_2=CH_2 δ 5.25

HC≡CH δ 2.88

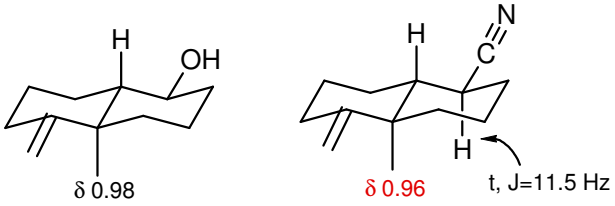


Δδ 1.63 ppm
JOC **1984**, 1323

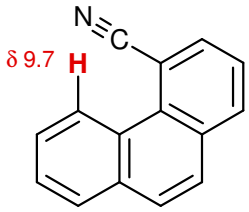


Δδ 0.49 ppm
JOC **1984**, 1323

Anisotropy of Nitriles. The cyano group presumably has the same anisotropy as the alkynyl group, as shown by the examples below.

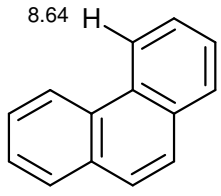


Ed Piers, J. Wai, private commun

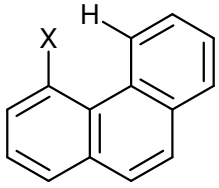


Δδ 1.0 ppm
ACIE **1975**, 264

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 and affect the chemical shifts.



ASV

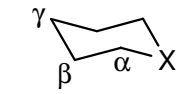


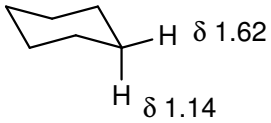
MRC **1989**, 13
Tet **1969**, 4339

X	δ	Δδ
F	9.15	0.56
Cl	9.6	1.16
Br	9.83	1.39
I	9.9	1.46

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.

Axial and Equatorial Cyclohexane Shifts. In cyclohexane itself, as well as in most substituted and heterocyclic 6-membered rings the axial protons are upfield of the equatorial ones. Unfortunately, there are a few exceptions, and so this chemical shift effect must be used with caution. Below some δ_e-δ_a values:

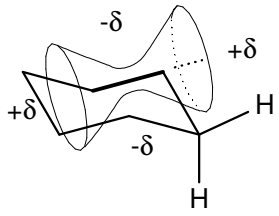




At -103 °C (Garbisch, *J. Am. Chem. Soc.* **1968**, *90*, 6543)

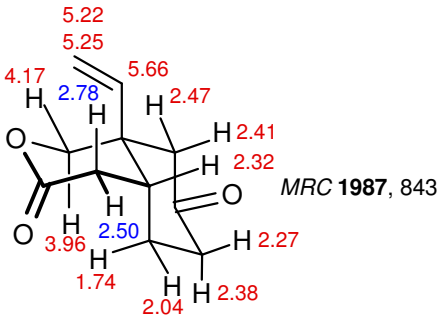
δ_e-δ_a

X	α	β	γ
CH_2	0.52	0.52	0.52
NH	0.48	0.12	0.45
NH_2^+	0.47	0.16	0.34
O	0.50	-0.07	0.32
S	-0.19	0.38	0.50
SO_2	<0.10	0.17	0.45



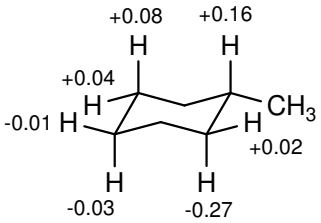
One explanation for this shift effect is based on the anisotropy cones shown in the figure, where the equatorial protons reside in the deshielding (+-δ) region of the C-C anisotropy, and the axial in the -δ region. An alternative explanation, or additional contributing effect, is based on the supposition that a C-H bond is a stronger σ donor than a C-C bond, which leads to increased electron density in the axial protons (anti to two C-H bonds), hence -δ. The variation in $^1J_{CH}$ has also been interpreted in these terms.

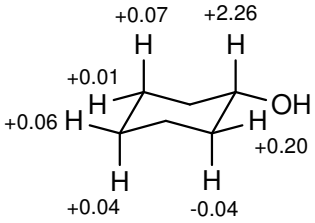
A more complicated bicyclic ring system shows several shifts that are consistent with the chemical shift effect $\delta_{eq} > \delta_{ax}$, and one exceptions:

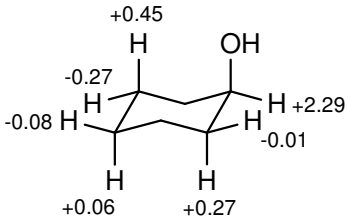


MRC **1987**, 843

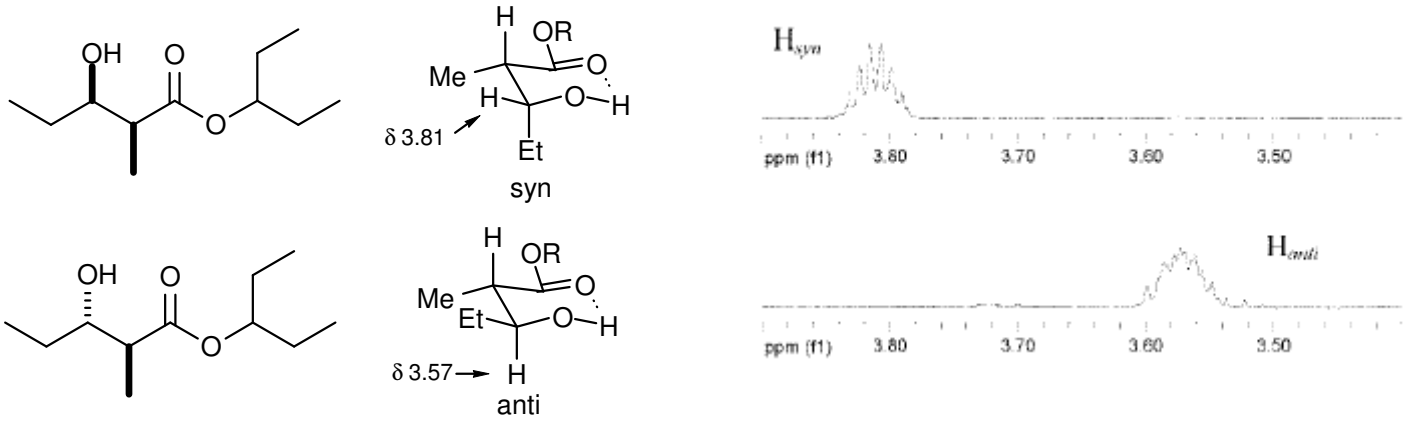
Substituent effects on cyclohexanes (Anteunis *Tetrahedron Lett.* **1975**, 687):



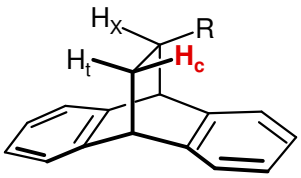




Assignment of syn and anti Aldol Adducts. A similar type of single bond anisotropy has been used to rationalize the empirical observation of a systematic variation in the chemical shift of the CHOH proton in syn and anti isomers of aldol products ($\delta_{syn} > \delta_{anti}$) that can be used to assign configuration, although such assignments should be viewed as less definitive than other methods, because of the usual problem with interpreting small chemical shift differences (Kalaitzakis, D.; Smonou, I.; *J. Org. Chem.* **2008**, *73*, 3919-3921). The argument is that in the favored conformation of the hydrogen bonded anti isomer the carbinol proton is in a pseudo-axial orientation subject to similar anisotropy effects as an axial cyclohexane proton, whereas in the syn isomer the proton is pseudo-equatorial.



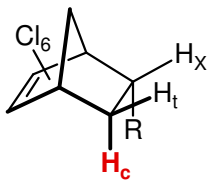
Cis-Substituent effect in Rigid Rings. Chemical shifts in rigid bicyclic or polycyclic systems can provide some insights into general chemical shift effects, although care must be utilized because there are typically a number of effects operating simultaneously. One example is the tendency for eclipsed or nearly-eclipsed cis-vicinal substituents to cause upfield shifts relative to the trans proton (and also relative to the compound with hydrogen replacing the substituent). In the dibenzobicyclo[2.2.2]octadiene system **A** the proton which is eclipsed (or nearly so) with the R substituent is always upfield of the one trans to it, and upfield of the unsubstituted compound as well. For the hexachloro bicyclo[2.2.2]heptane **B** this is also seen, although here the inherent shift difference is not known since the compound with R = H has not been reported.



A

R	δ_c	δ_t	δ_X
H	1.68	1.68	1.68
OAc	1.41	2.25	4.90
OH	1.18	2.19	3.94
OTs	1.50	2.08	4.88
NH_2	0.97	2.14	3.11
SPh	1.44	2.28	3.52

JOC **1966**, 581

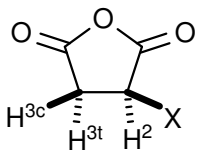


B

R	δ_c	δ_t	δ_X
H			
CN	2.15	2.93	3.40
CO_2H	2.43	2.55	3.62
C_6H_5	2.38	2.83	3.87
Cl	2.22	3.08	4.72
OH	1.90	2.78	4.63
OAc	1.90	2.95	5.50

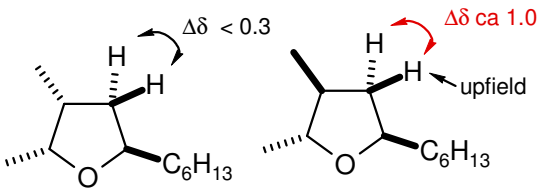
JACS **1963**, 516

The upfield shift of *cis* substituents compared to *trans* is also seen in a series of succinic anhydrides:

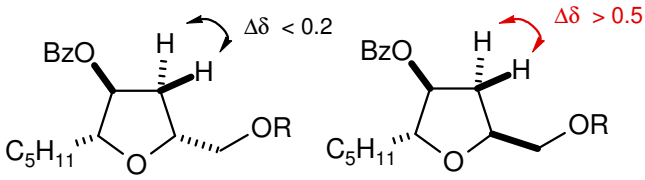


X	δ_{3c}	δ_{3t}	J_{trans}	J_{cis}	
H	2.94	2.94	5.2	10.7	
Me	2.65	3.18	6.9	10.0	ASV
AcO	3.03	3.39	6.3	9.6	ASV
AcS	2.97	3.48	6.9	10.7	ASV
HOCHN	2.87	3.26	6.2	9.9	ASV
$CF_3(O=)CHN$	3.00	3.31	6.2	9.9	ASV
Ph	3.09	3.43	6.6	10.3	ASV

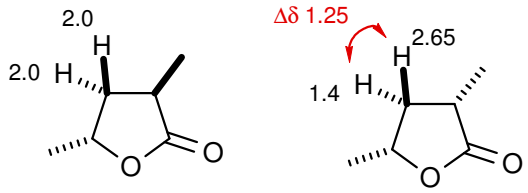
Stereochemical Relations in Cyclopentanes. Because coupling constants are not very reliable for determining stereochemical relationships in 5-membered rings, chemical shift effects such as the one discussed above have been utilized more extensively than in cyclohexanes. It has been observed that in cyclopentanes, γ-butyrolactones (Ollis *JCS-PT1* **1975**, 1480) and tetrahydrofurans the diasterotopic chemical shift effect of a ring CH_2 group is consistently larger when flanking substituents are *cis* to each other (when the anisotropic effects of the C-C or C-O bonds are additive) compared to when they are trans (both protons see the effect). More specifically, protons with cis-vicinal substituents are generally shifted to lower δ values (upfield) than those with cis hydrogens.



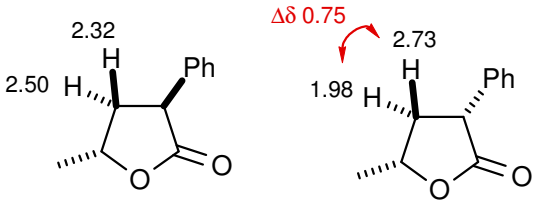
JACS **1992**, 7318



JACS **1984**, 2641

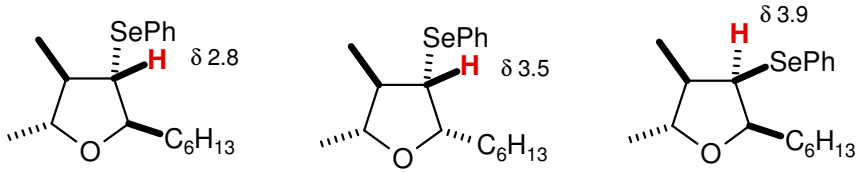


JCS P1 **1975**, 1470



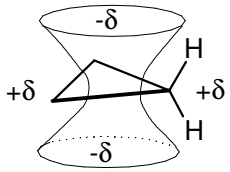
JCS P1 **1975**, 1470

Similarly, the chemical shift of a proton will be a function of the number of cis-alkyl substituents on the ring. To use such chemical shifts it is necessary to have several members of a series for comparison.

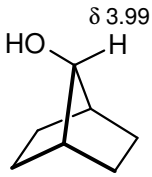


JACS **1992**, 7318
(see also *TET* **1986**, 3013)

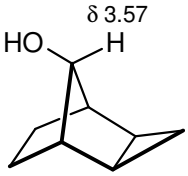
Anisotropy of Cyclopropanes. The principal magnetic anisotropy of cyclopropane groups appears to be shielding above the ring and deshielding in the plane of the ring, a ring current effect a little like that of benzene.



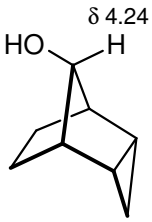
JACS **1972**, 2291
TET 1998, 337



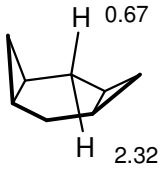
TET **1998**, 337



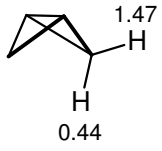
TET, **1966**, 2007



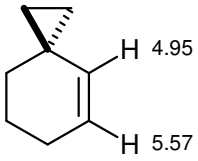
TET **1966**, 2007



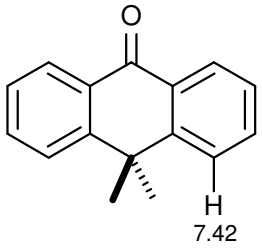
JACS **1972**, 2291

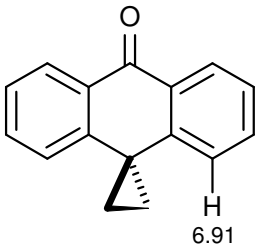


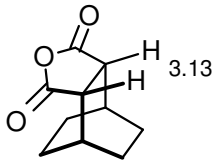
JACS **1966**, 5272



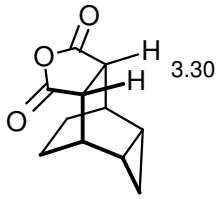
JOC **1967**, 939







JACS **1965**, 386



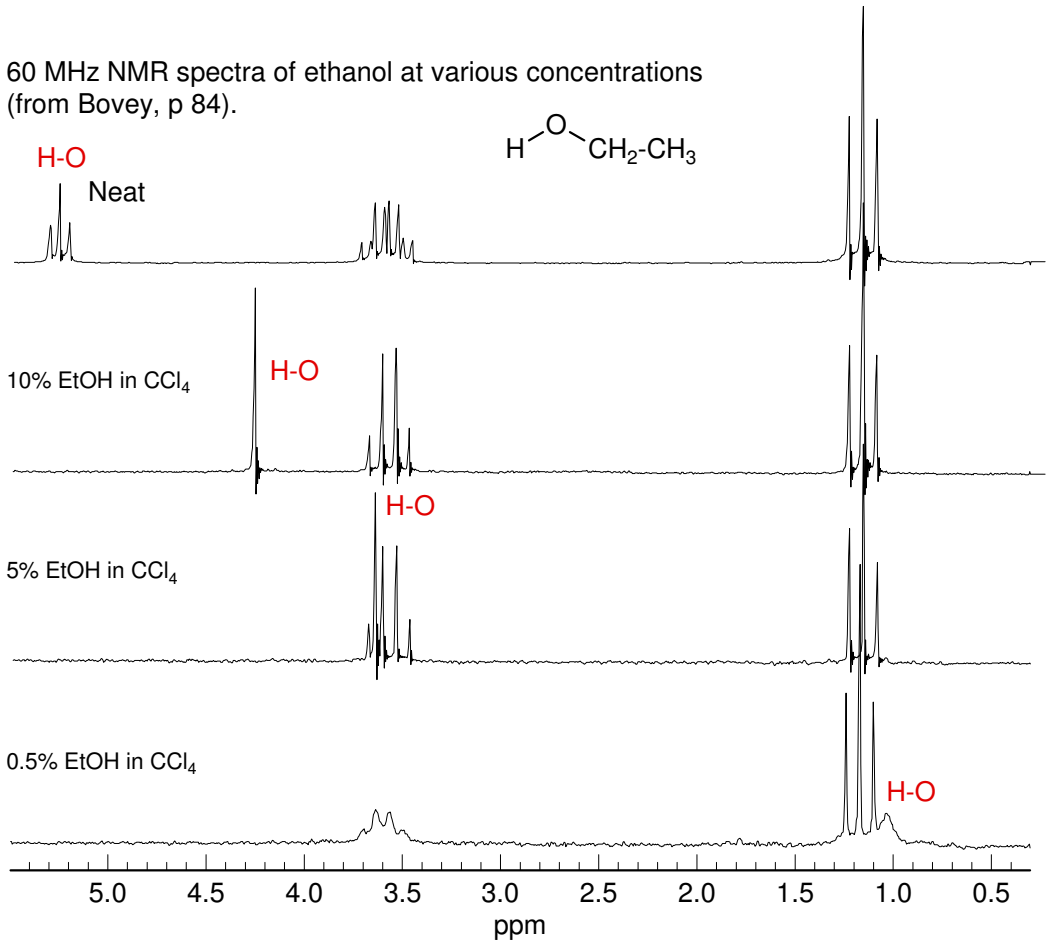
JACS **1965**, 386

5. Hydrogen Bonding Effects on Chemical Shifts - OH, NH and SH Protons. The chemical shifts of OH and NH protons vary over a wide range depending on details of sample preparation and substrate structure. 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.

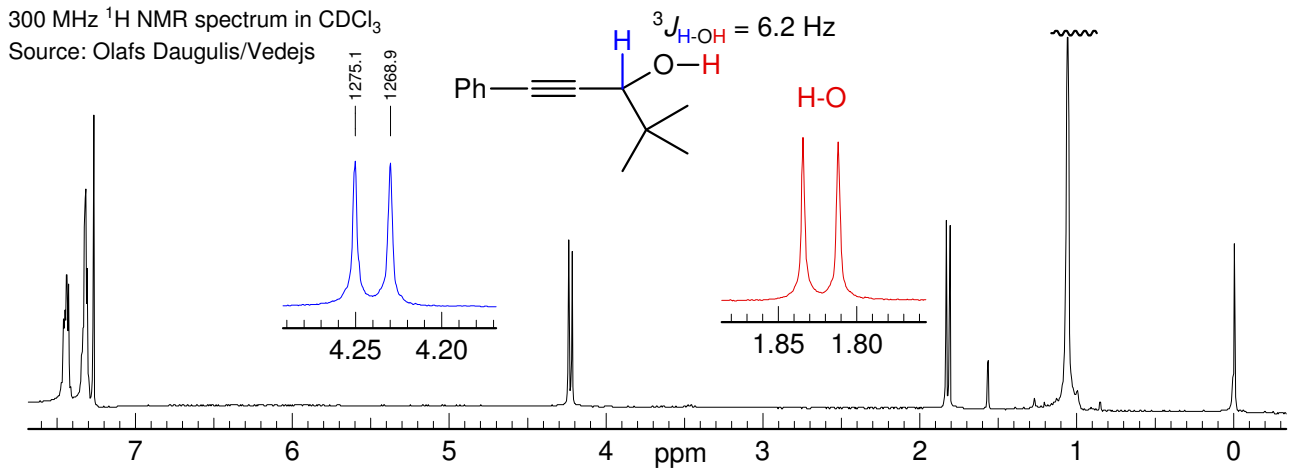
There is a general tendency for the more acidic OH and NH protons to move further downfield. This effect is in part a consequence of the stronger H-bonding propensity of acidic protons, and in part an inherent chemical shift effect. Thus carboxylic amides and sulfonamides NH protons are shifted well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

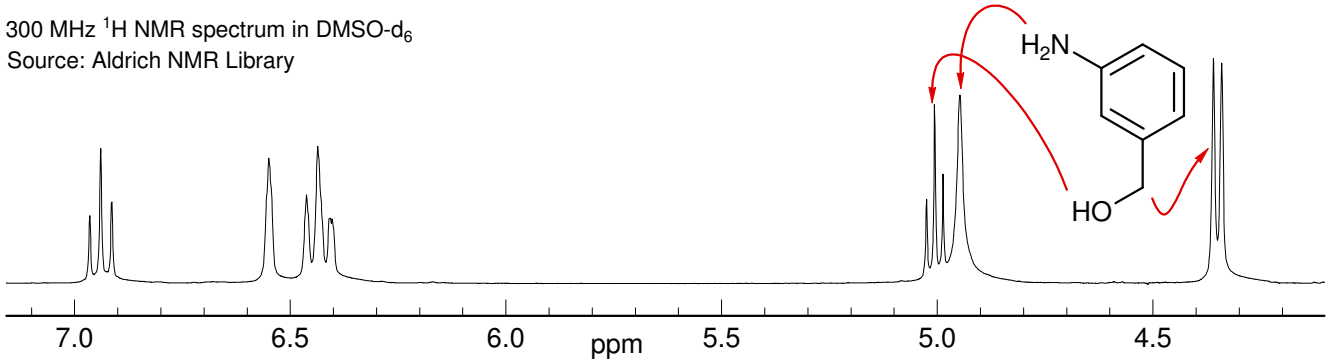
Hydroxyl OH Protons. In dilute solution of alcohols in non hydrogen-bonding solvents (CCl_4, $CDCl_3$, C_6D_5) the OH signal generally appears at δ 1-2 At higher concentrations the signal moves downfield as a result of increased fraction of H-bonded alcohols, e.g. the OH signal of ethanol comes at δ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



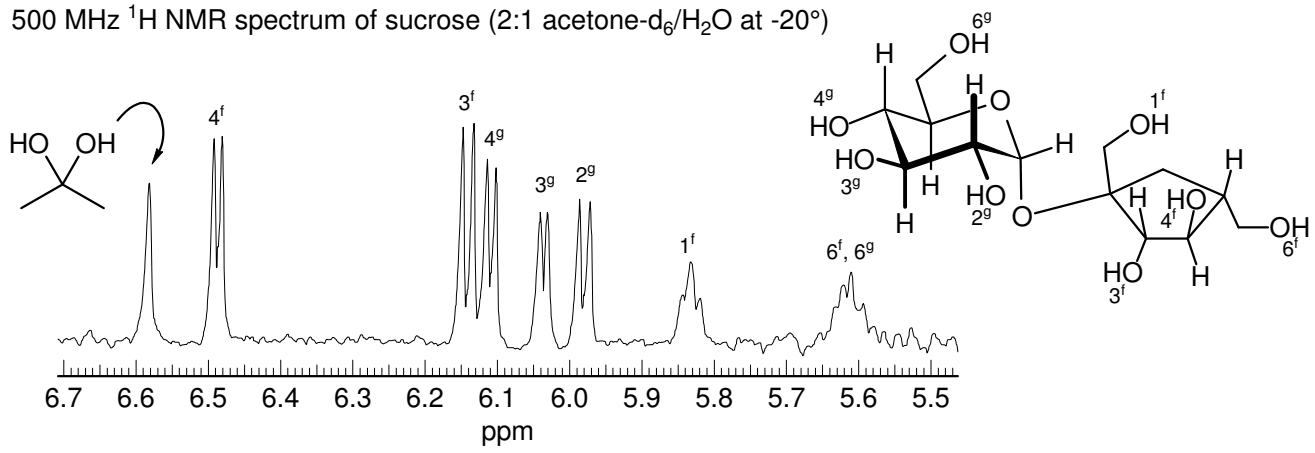
Dynamic Exchange. Under ideal conditions OH groups of alcohols can show sharp signals with full coupling to neighboring protons even at room temperature, as in the spectrum of neat ethanol above, and in the spectrum of 1-phenyl-4,4-dimethyl-1-pentyn-3-ol below.



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. 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. In contrast, solvents like DMSO and acetone form strong hydrogen bonds to the OH group. This has the effect of slowing down the 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.

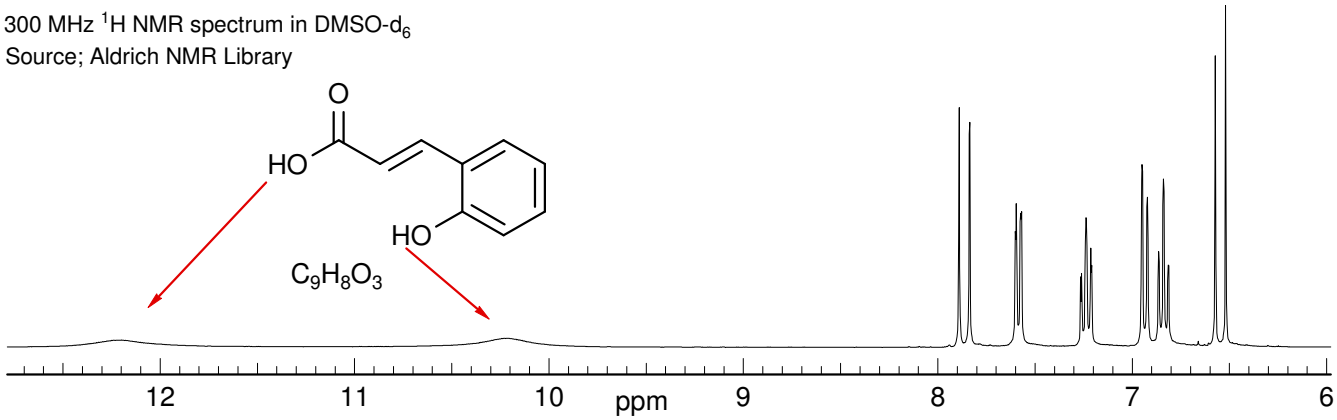


In the remarkable NMR spectrum of the OH region of sucrose below (Adams, Lerner *J. Am. Chem. Soc.* **1992**, *114*, 4828) all of the OH signals and their coupling are resolved in aqueous acetone solvent.

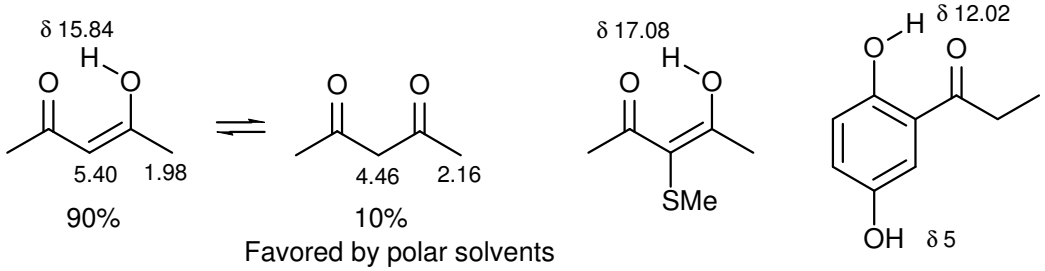


Phenols. The OH signals of phenols are generally well downfield of those of alcohols, appearing at δ 5-7 in $CDCl_3$, and δ 9-11 in DMSO. The higher acidity of phenols results in faster exchange rates, so that polyphenolic compounds will usually show only one OH signal.

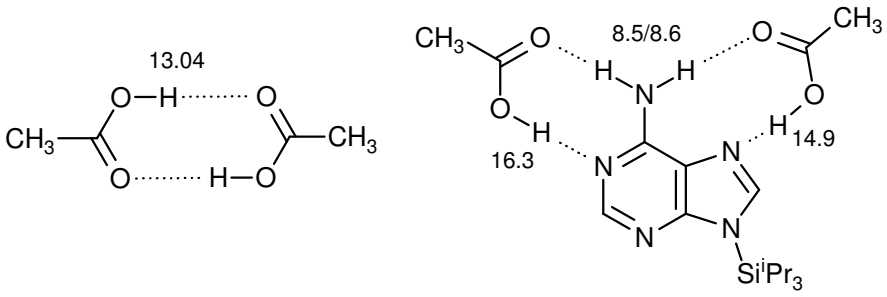
In DMSO solution, even the exchange between carboxylic acid protons and other OH groups can be slowed enough to allow individual observation, as in the spectrum of 2-hydroxycinnamic acid below.



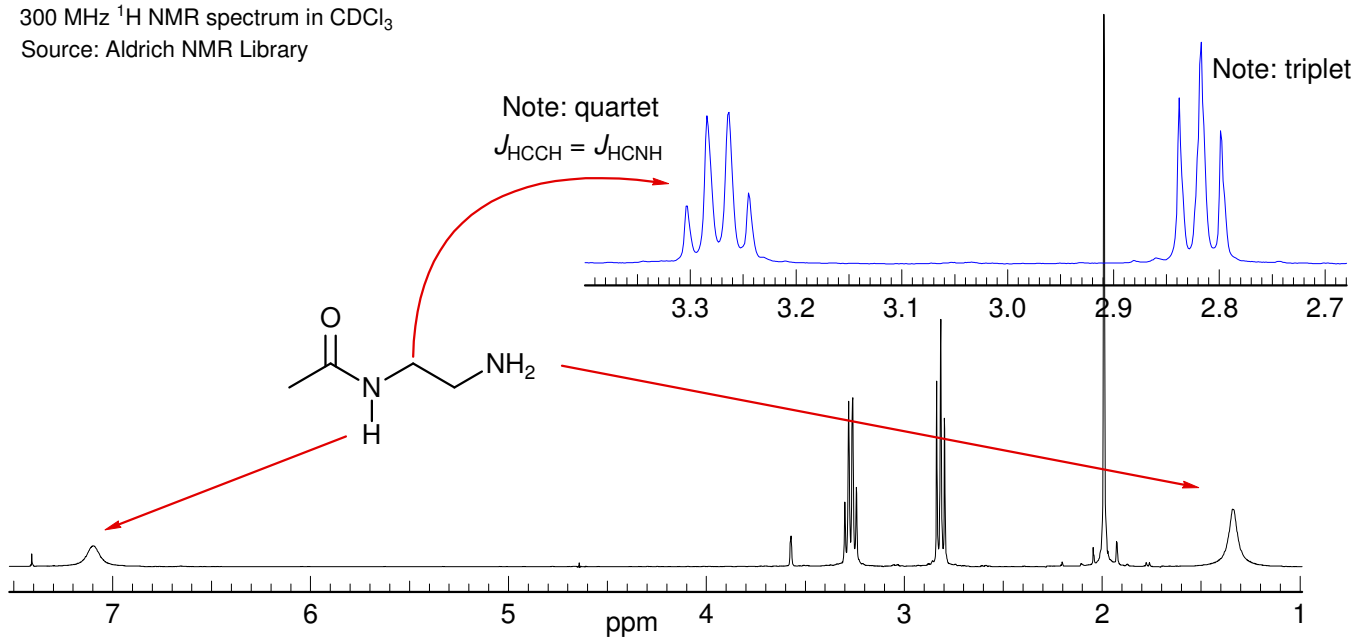
β-Dicarbonyl Compounds. Especially dramatic shifts are observed for the strongly intramolecularly H-bonded enol forms of β-dicarbonyl compounds, o-ketophenols and related structures.



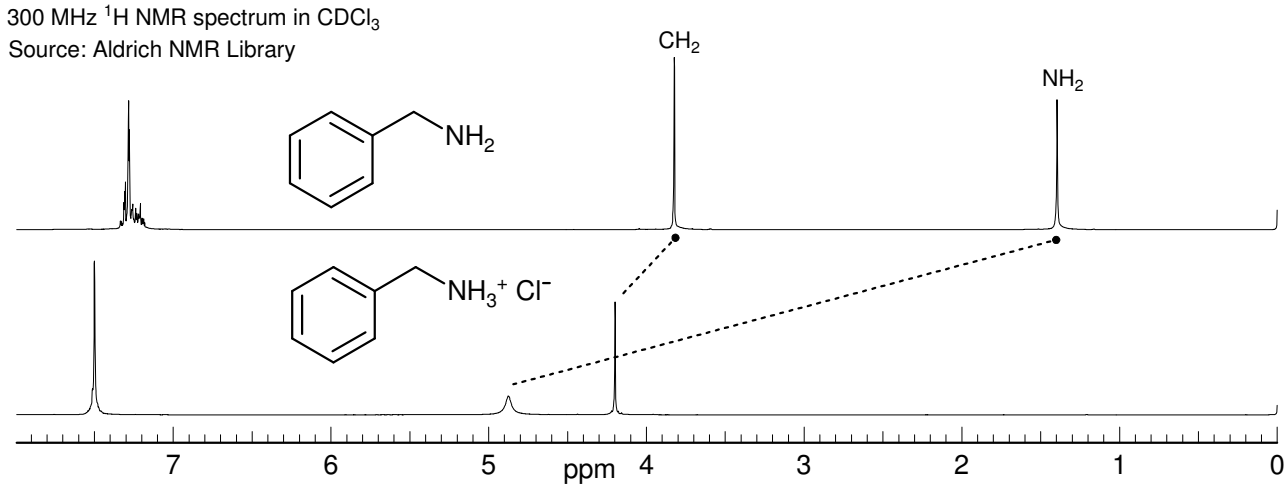
Carboxylic Acids. Most carboxylic acids are strongly hydrogen bonded in non-polar solvents, and the OH protons are correspondingly downfield shifted. Acetic acid dimer in Freon solvent ($CDClF_2/CDF_3$) at 128 K appears at δ 13.04, and the OH signals of acetic acid hydrogen bonded to a protected adenosine under conditions of slow exchange appear at even lower field (Basilio, E. M.; Limbach, H. H.; Weisz, K. *J. Am. Chem. Soc.* **2004**, *126*, 2135).



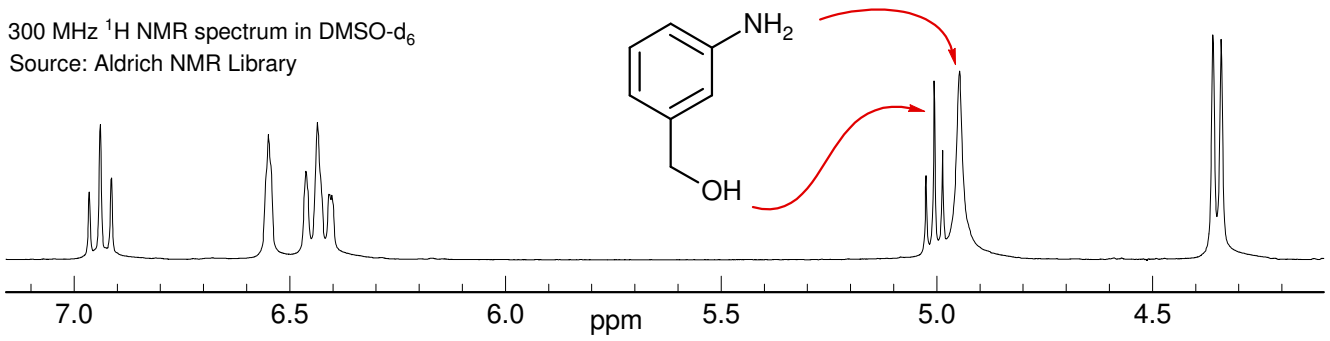
Amine and Amide N-H Protons. NH_2 protons of primary alkyl amines typically appear as a somewhat broadened signal at δ 1-2 in $CDCl_3$. The broadening has several sources: partially averaged coupling to neighboring protons, intermolecular exchange with other NH or OH protons, and partially coalesced 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 equivalant).



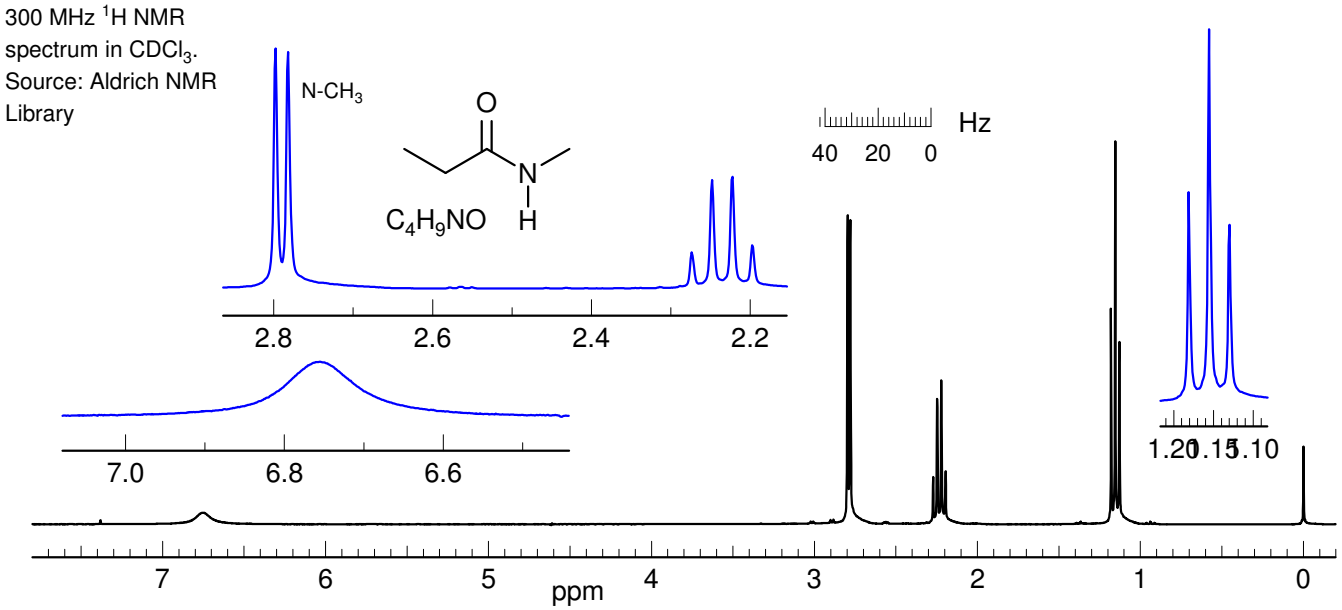
The N-H signals of ammonium salts are strongly downfield shifted, typically appearing at δ 4-7 in $CDCl_3$ and δ 8-9 in DMSO. If spectra are taken in strongly acidic solvents (e.g. trifluoroacetic acid), where intermolecular exchange is slowed, the signals are sometimes very broad, and can show poorly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



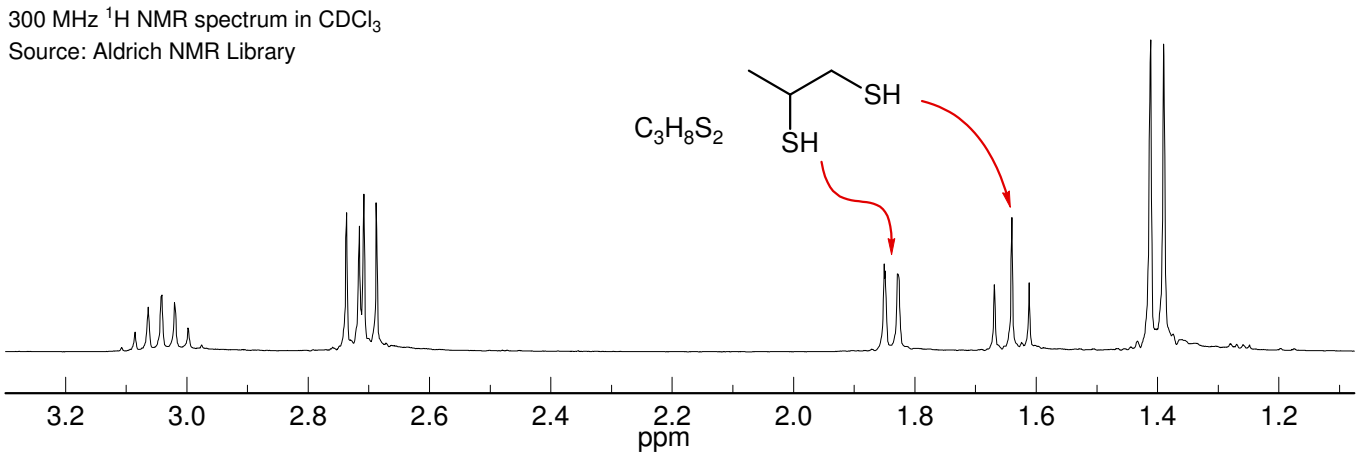
Aniline NH Protons. The NH protons of anilines are typically at δ 3.5-4.5 in $CDCl_3$ solution, moving downfield by 1-2 ppm in DMSO solution. o-Nitroanilines (ca δ 5-6) and heterocyclic amines such 2-aminopyridines (δ 4.5) have signals downfield of this range.

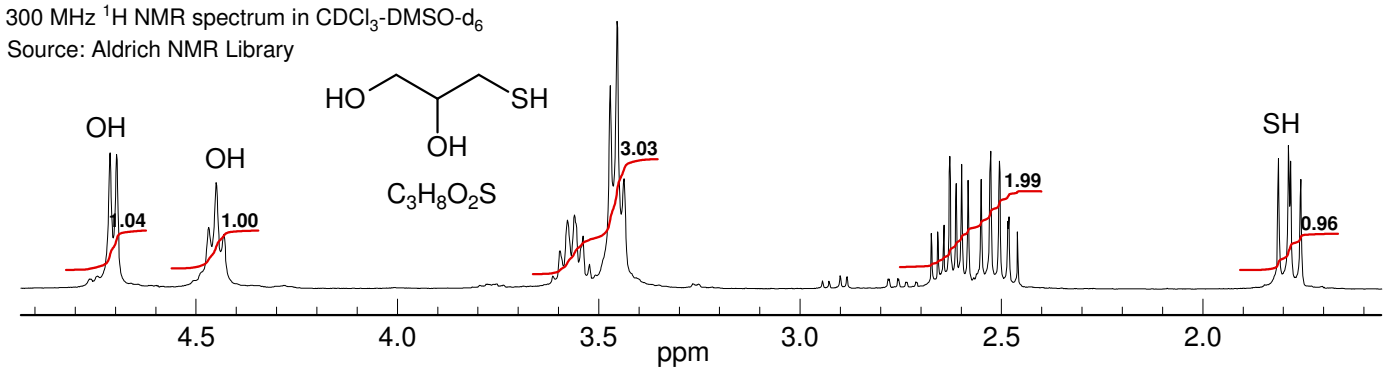


Amide NH Protons. Amide NH signals typically appear around δ 7, as in the example of N-acetylethylenediamine above and N-methylpropionamide below. They are generally in slow exchange with other NH and OH signals. Thus, neighboring protons will show coupling to the NH proton, as in the examples, where 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 in the NH signal.

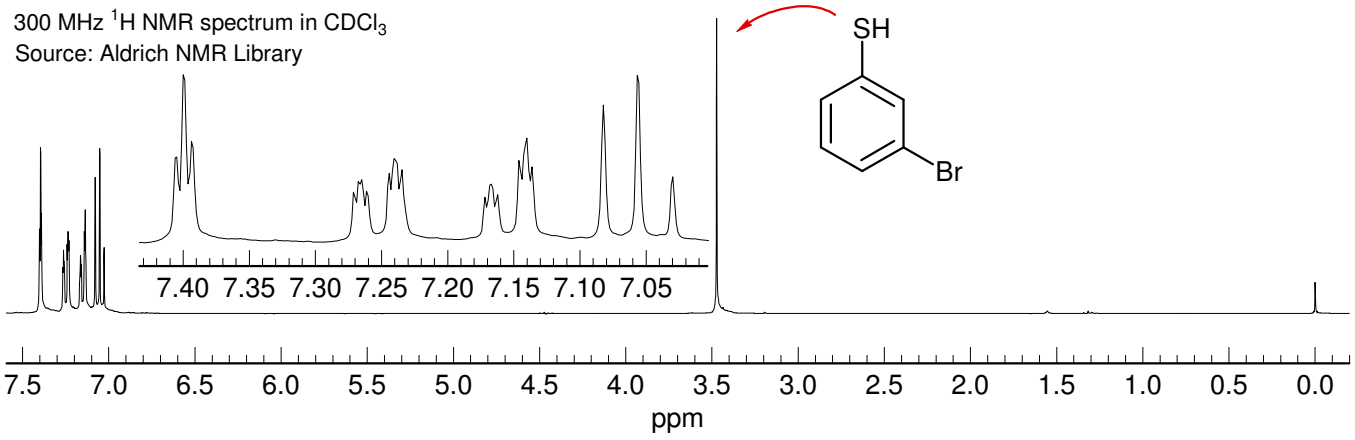


Thiol S-H Protons. S-H protons of alkyl thiols typically appear between δ 1.2 and 2.0 in $CDCl_3$. The position is not strongly affected by hydrogen bonding solvents like acetone or DMSO, since SH protons are only weakly hydrogen bonded. Coupling to nearby protons is usually seen, although broadened or fully averaged signals are not uncommon, especially in molecules containing OH protons (or in impure samples).

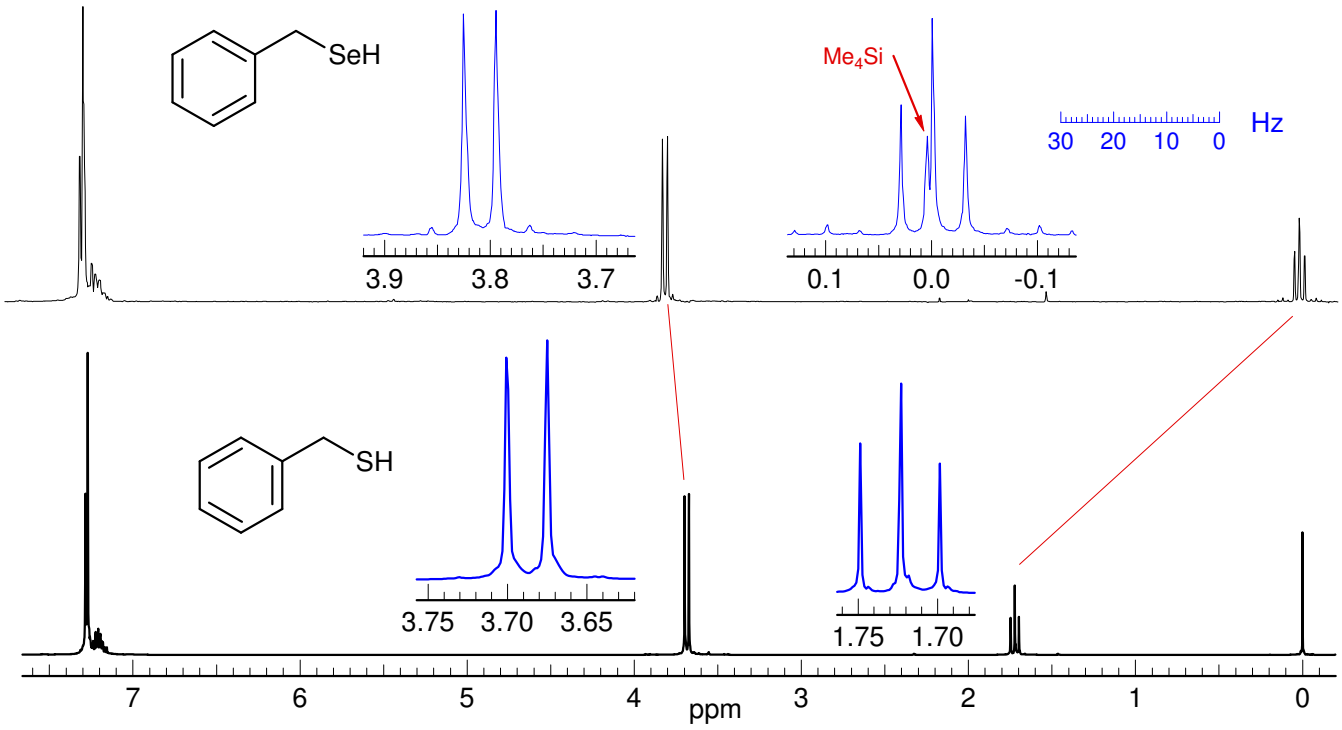




Aryl thiol S-H signals are further downfield, typically δ 3.5-4.5, as a result of normal ring-currrent effects, and the greater electron withdrawing effect of aryl vs alkyl groups.



Selenol and tellurol protons (SeH and TeH) behave like thiol protons, but appear further upfield -- around δ 0 for SeH and δ -3 to -5 for TeH. Below a comparison of the NMR spectra of benzylselenol and benzylthiol. Note that both the Se-H and S-H protons are coupled to the CH_2 group (AX_2 pattern).



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