5.2 Chemical Shift

Fortunately for the chemist, all proton resonances do not occur at the same position. The Larmor precession frequency \( \nu_0 \) varies because the actual magnetic field \( B \) at the nucleus is always less than the external field \( B_0 \). 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 \( B_e \) is created, which opposes \( B_0 \). Thus \( B = B_0 - B_e \). 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 \( B_0 \), we use field independent units for chemical shifts: \( \delta \) 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).

\[
B = B_0 - B_e \quad \text{(magnetic field at nucleus)}
\]
\[
\nu_0 = \gamma B / 2\pi \quad \text{(Larmor precession frequency of H_A)}
\]

The Proton Chemical Shift Scale

Experimentally measured proton chemical shifts are referenced to the \(^1\text{H} \) signal of tetramethylsilane (Me\(_4\)Si). For NMR studies in aqueous solution, where Me\(_4\)Si is not sufficiently soluble, the reference signal usually used is DSS (Me\(_3\)Si-CH\(_2\)CH\(_2\)-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 alternative reference standard, DSA (Me\(_3\)Si-CH\(_2\)CH\(_2\)-NH\(_3\)^+CF\(_3\)CO\(_2\)-) has been suggested (Nowick Org. Lett. 2003, 5, 3511).

Proton chemical shifts cover a range of over 30 ppm, but the vast majority appear in the region \( \delta \) 0-10 ppm, where the origin is the chemical shift of tetramethylsilane.

\[
\delta = \frac{[\nu_0(\text{H}) - \nu_0(\text{TMS})]}{[\text{Spectrometer Frequency in MHz}]}
\]

In the original continuous wave (CW) method of measuring NMR spectra, they were scanned from left to right, increasing the magnetic field. 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. \( \delta \) units are defined as follows:

Chemical shifts of all nuclei should be reported using \( \delta \) values, with frequency and \( \delta \) increasing from right to left (many early papers on proton and multinuclear NMR used the opposite convention). 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 $\delta$ -2 for MeLi to $\delta$ 4 for MeF.

The $^1\text{H}$ 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). However, when there are strong resonance or other electronic interactions between substituents, or strong conformational effects then the predictions made by these calculations will be less accurate.

$$\Delta\delta$$

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Δδ 0.45</th>
<th>Δδ 0.45</th>
<th>Δδ -0.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zgem Me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zcis Br</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ztrans Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.25 (Base shift: CH₂=CH₂)  
0.45 (Zgem Me)  
0.45 (Zcis Br)  
-0.07 (Ztrans Ph)  
6.08 (δ Calculated)  
6.23 (δ Observed)

For aliphatic (sp³) 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 CH₃ (0.9), CH₂ (1.2) and C-H (1.55) protons, and then corrections are applied for all α and β substituents. The corrections for CH₃, CH₂ and CH protons are slightly different, and no corrections are applied for alkyl groups.

$$\Delta\delta$$

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Δδ 0.95</th>
<th>Δδ 2.20</th>
<th>Δδ 0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Ph for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Br for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Br for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.95 (δ Calculated)  
5.00 (δ Observed)

### Accuracy of Chemical Shift Calculations

Calculations using simple parameter lists such as in 9-HDATA-5.1 and 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:

$$\Delta\delta$$

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Δδ 2.55</th>
<th>Δδ 3.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cl for CH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-NO₂ for CH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.15 (δ Calculated)  
5.80 (δ Observed)  
**Δδ 1.35**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Δδ 7.36</th>
<th>Δδ 0.20</th>
<th>Δδ -0.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cl for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m-NO₂ for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m-NH₂ for CH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.82 (δ Calculated)  
6.62 (δ Observed)  
**Δδ 2.58**

 Reich, U. Wisc. Chem. 605 5-HMR-2.3
Cyclic Systems: Calculations are usually poor for cyclic systems. The base shift for a CH₂ 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. One of the reasons for this 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. Note especially that the protons on 3-membered rings of all kinds are strongly shifted to lower frequency from the acyclic value.

Even more dramatic chemical shift effects are seen in polycyclic compounds. The calculated values for both cubane and dodecahedrane would be δ 1.55 (the base value for a methyne group), yet the actual values are several ppm to higher frequency.

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 shifts as large as 0.5 to 0.8 ppm when compared to less magnetically active solvents like chloroform or acetone. Since the standard solvent for chemical shift parameters like the Curphy-Morrison ones is CCl₄ or CDCl₃, 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.

Temperature dependence. Chemical shifts can vary with temperature because the chemical shifts of various conformations are different, and the populations of conformations change with temperature (the observed chemical shift is the weighted average of all the shifts of the individual conformations). Temperature can 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 altogether 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.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Dipolar Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃F</td>
<td>4.26</td>
</tr>
<tr>
<td>CH₃Cl</td>
<td>3.05</td>
</tr>
<tr>
<td>CH₃Br</td>
<td>2.69</td>
</tr>
<tr>
<td>CH₃I</td>
<td>2.19</td>
</tr>
<tr>
<td>CH₃CH₃</td>
<td>0.96</td>
</tr>
<tr>
<td>CH₄</td>
<td>0.2</td>
</tr>
<tr>
<td>CH₃SiMe₃</td>
<td>0.0</td>
</tr>
<tr>
<td>CH₃Li</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

Charge effects within $\pi$ systems are also reflected in proton chemical shift changes (approximately 10 ppm/unit negative charge).

Even without formal charges, resonance interactions can lead to substantial chemical shift changes due to $\pi$ 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.
2. **Lone Pair Interactions.** When lone pairs on nitrogen or oxygen are *anti* to C-H bonds, the proton is shifted upfield. 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.

![Electron donation to C-H bond](image1)

Little interaction

<table>
<thead>
<tr>
<th>C-M calculation: $\delta$ 5.60</th>
<th>C-M calculation: $\delta$ 7.85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed: $\delta$ 3.02</td>
<td>Observed: $\delta$ 4.96</td>
</tr>
</tbody>
</table>

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.

![Steric compression](image2)

The N-H distance is 2.25 Å

*Reich, U.Wisc. Chem. 605* 5-HMR-2.6
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, \(-\delta\)), 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 (\(-\delta\)) effects for protons placed above the ring, and deshielding (\(+\delta\)) 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 local magnetic field is higher here, so a higher frequency or lower external magnetic field is needed to achieve resonance. Signal is deshielded.

When the benzene ring is oriented with the ring parallel to the magnetic field, the electron circulation is much weaker. The shielding effects in these orientations do not cancel the deshielding effects in the other orientation.

The local magnetic field is lower here, so a lower frequency or a higher external field magnetic field is needed to achieve resonance. Signal is shielded.

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:

Alkene

Carbonyl

Sulfoxide\(^3\)

Alkyne

Nitro\(^4\)

C-C Single Bond

Cyclohexane Ax-Eq

Cyclopropane\(^2\)

Epoxide\(^1\)

**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.

\[
\begin{array}{c}
\text{H} & 5.76 \\
\text{H} & 5.87 \\
\text{H} & 7.27 \\
\Delta\delta = 1.40 \text{ ppm}
\end{array}
\quad \begin{array}{c}
\text{H} & 1.64 \\
\text{CH}_3 & 2.36 \\
\Delta\delta = 0.72 \text{ ppm}
\end{array}
\quad \begin{array}{c}
\text{H} & 5.77 \\
\text{H} & 7.38 \\
\Delta\delta = 1.66 \text{ ppm}
\end{array}
\]

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

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

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

*Reich, U.Wisc. Chem. 605* 5-HMR-2.8
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 (+\(\delta\))

If ring is perpendicular, get upfield shifts (-\(\delta\))

<table>
<thead>
<tr>
<th>Structure</th>
<th>(\delta) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>5.46</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>5.31</td>
</tr>
<tr>
<td>H cis to Ph</td>
<td>downfield</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure</th>
<th>(\delta) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>5.22</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>5.48</td>
</tr>
<tr>
<td>H cis to Ph</td>
<td>upfield</td>
</tr>
</tbody>
</table>

TET-70-4783

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.

<table>
<thead>
<tr>
<th>Structure</th>
<th>(\delta) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>0.7</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>1.1</td>
</tr>
</tbody>
</table>

HO

JOC-82-3943

Reich, U.Wisc. Chem. 605

5-HMR-2.9

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 method of data analysis 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.

For a related method using 1-phenyltrifluoroethanol, see Org. Lett. 2003, 5, 1745.
**Aromatic Solvent Induced Shifts (ASIS).** Polar molecules have substantially different chemical shifts in aromatic solvents (benzene, pyridine, C₆F₆) than in less magnetically interactive solvents like CCl₄, CDCl₃, acetone-d₆ and CD₃CN. A typical result of going from CDCl₃ to benzene is shown in the spectra of butyrophenone below. The shifts are large enough that chemical shift calculations are seriously in error when applied to spectra taken in benzene.

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 deshielding 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).

\[ \Delta \delta (\text{CCl}_4 \text{ vs. } \text{C}_6\text{D}_6): \]
\[
\begin{align*}
\text{CH}_3\text{C}=\text{N} &\quad -0.95 \\
\text{O} &\quad -0.35
\end{align*}
\]

Effect of dipole moment:
\[
\begin{array}{c|c|c}
\text{MeSnCl}_3 & -1.43 & 3.6 \\
\text{MeSnI}_3 & -1.02 & 2.6 \\
\text{MeCCl}_3 & -0.59 & 1.5 \\
\text{Me}_4\text{Sn} & -0.09 & 0
\end{array}
\]

Δδ (benzene):
\[
\begin{align*}
\text{C}_6\text{D}_6 &\quad -0.47 \text{ ppm} \\
\text{CDCl}_3 &\quad 300 \text{ MHz}
\end{align*}
\]

Source: Amanda Jones 02-09


Reich, U.Wisc. Chem. 605

5-HMR-2.11
When $^1$H NMR spectra are complicated by accidental superposition of coupled protons, as in the spectrum of eugenol below, then switching to benzene as solvent (or even just adding a few drops of C$_6$D$_6$ to the sample) will often move signals enough that more interpretable 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$_6$D$_6$ is essentially first order.

Effect of benzene to simplify a closely 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 versus the terminal protons in conjugated dienes (which are affected by the anisotropy of both \( \pi \) systems). It also explains the downfield shifts of allylic protons.

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

There is, however, one major exception. In norbornene itself, the proton shifts are in the opposite direction than seen in the 7-substituted norbornenes above. Both the proton assignment and the absence of a \(-\delta\) region above the double bond are supported by high level \textit{ab initio} MO chemical shift calculations (\textit{J. Am. Chem. Soc.} \textbf{1998}, \textit{120}, 11510). Thus the anisotropy of 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.

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.

\[
\begin{array}{c}
\text{J. Org. Chem. 1992, 57, 1970} \\
\end{array}
\]

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

\[
\begin{array}{c}
\text{Magn. Res. Chem. 1989, 27, 796} \\
\end{array}
\]

In one of these stereoisomers, one of the aromatic protons is close to the carbonyl, and is shifted downfield by 1.3 ppm, whereas in the other isomer the carbonyl is remote, and the chemical shift is normal.
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 (δ 8.20 for the same isomer) the proton has a β-interaction with one carboxylate function, and a γ-interaction with the other:

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

**Anisotropy of Nitro groups.** The NO₂ groups may have 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 between the NO₂ 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.
**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 $\pi$ system.

\[
\begin{array}{ccc}
\delta 8.64 & \delta 10.27 & \text{CH}_3-\text{CH}_3 \\
\text{Δδ} 1.63 \text{ ppm} & & \text{δ} 0.90 \\
& & \text{CH}_2=\text{CH}_2 \\
& & \text{δ} 5.25 \\
& & \text{HC≡CH} \\
& & \text{δ} 2.88 \\
\end{array}
\]

\[
\begin{array}{ccc}
\delta 8.64 & \delta 10.27 & \text{H} \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{Δδ} 1.63 \text{ ppm} & & \text{JOC-84-1323} \\
\end{array}
\]

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

\[
\begin{array}{ccc}
\delta 0.98 & \delta 0.96 & \text{H} \\
\text{t, J}=11.5 \text{ Hz} & & \text{δ} 1.24 \\
\end{array}
\]

\[
\begin{array}{ccc}
\delta 9.7 & \text{Δδ} 1.0 \text{ ppm} & \text{ACIE-75-264} \\
\end{array}
\]

**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.

\[
\begin{array}{ccc}
\text{δ} 8.64 & \delta X & \text{X} \\
\text{δ} 9.15 & \text{F} & \text{δ} 0.56 \\
\text{δ} 9.6 & \text{Cl} & \text{δ} 1.16 \\
\text{δ} 9.83 & \text{Br} & \text{δ} 1.39 \\
\text{δ} 9.9 & \text{I} & \text{δ} 1.46 \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{δ} 8.64 & \text{δ} X & \text{MRC-89-13} \\
\text{δ} 9.15 & \text{Tet-69-4339} \\
\end{array}
\]
**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. 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 $\delta_{e}-\delta_{a}$ values:

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$</td>
<td>0.52</td>
<td>0.52</td>
<td>0.52</td>
</tr>
<tr>
<td>NH</td>
<td>0.48</td>
<td>0.12</td>
<td>0.45</td>
</tr>
<tr>
<td>NH$_2^+$</td>
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<td>0.16</td>
<td>0.34</td>
</tr>
<tr>
<td>O</td>
<td>0.50</td>
<td>-0.07</td>
<td>0.32</td>
</tr>
<tr>
<td>S</td>
<td>-0.19</td>
<td>0.38</td>
<td>0.50</td>
</tr>
<tr>
<td>SO$_2$</td>
<td>&lt;0.10</td>
<td>0.17</td>
<td>0.45</td>
</tr>
</tbody>
</table>

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

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 CH$_2$OH proton in syn and anti isomers of aldol products ($\delta_{\text{syn}} > \delta_{\text{anti}}$) that can be used to assign configuration, although such assignments should be viewed is 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 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.
**Anisotropy of Cyclopropanes.** The principal magnetic anisotropy of cyclopropane groups appears to involve shielding above the ring and deshielding in the plane of the ring, a ring current effect a little like that of a benzene ring.

\[
\begin{align*}
\delta_{\text{shielding}} &> \delta_{\text{deshielding}} \\
\delta_{\text{shielding}} &\approx 3.57 \\
\delta_{\text{deshielding}} &\approx 4.24
\end{align*}
\]

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.

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**Stereochemical Relations in Cyclopentanes.** Because coupling constants are not very reliable for determining stereochemical relationships in 5-membered rings, chemical shift effects have been utilized more extensively than in cyclohexanes. It has been observed that in tetrahydrofurans the diasterotopic chemical shift effect of a C-3 CH₂ 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. More specifically, protons with cis-vicinal substituents are generally shifted to lower δ values (upfield) than those with cis hydrogens.

\[
\begin{align*}
\Delta\delta_{\text{ca 1.0}} &< \Delta\delta_{< 0.3} \\
\Delta\delta_{> 0.5} &< \Delta\delta_{< 0.2}
\end{align*}
\]

Anisotropy of Cyclopropanes. The principal magnetic anisotropy of cyclopropane groups appears to involve shielding above the ring and deshielding in the plane of the ring, a ring current effect a little like that of a benzene ring.
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 strong 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$_2$O, 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$_2$Cl$_2$, CCl$_4$) since the formed DOH is in the drop of water floating at the top of the sample where it is not detected. In water miscible solvents (acetone, DMSO, acetonitrile, pyridine, THF) the OH and NH signals are largely converted to OD and ND, but the DOH formed remains in solution and will be detected in the water region.

Alcohol OH Protons. In dilute solution of alcohols in non hydrogen-bonding solvents (CCl$_4$, CDCl$_3$, C$_6$D$_5$) the OH signal generally appears at δ 1-2. At higher concentrations the signal moves downfield, e.g. the OH signal of ethanol comes at δ 1.0 in a 0.5% solution in CCl$_4$, and at δ 5.13 in the pure liquid.
**Dynamic Exchange.** Under ideal conditions OH groups of alcohols can show sharp signals with full coupling to neighboring protons, as in the spectrum of neat ethanol above, and in the spectrum of 1-phenyl-4,4-dimethyl-1-pentyn-3-ol below.

300 MHz $^1$H NMR spectrum in CDCl$_3$
Source: Olafs Daugulis/Vedejs

More typically, signals for OH protons are subject to 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. The rates of exchange are a complex function of temperature, solvent, concentration and 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.

300 MHz $^1$H NMR spectrum in DMSO-d$_6$
Source: Aldrich NMR Library

In the remarkable spectrum 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.

500 MHz $^1$H NMR spectrum of sucrose (2:1 acetone-d$_6$/H$_2$O at -20°C)

*Reich, U.Wisc. Chem. 605* 5-HMR-2.20
Phenols. The OH signals of phenols are generally well downfield of those of alcohols, appearing at $\delta$ 5-7 in CDCl$_3$, and $\delta$ 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.

\[
\begin{align*}
\text{300 MHz }{}^1\text{H NMR spectrum in DMSO-d$_6$} \\
\text{Source: Aldrich NMR Library}
\end{align*}
\]

$\beta$-Dicarbonyl Compounds. Especially dramatic shifts are observed for the strongly intramolecularly H-bonded enol forms of $\beta$-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 (CDCl$_2$/CDF$_3$) at 128 K appears at $\delta$ 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 N-H Protons.** NH$_2$ protons of primary alkyl amines typically appear as a somewhat broadened signal at $\delta$ 1-2 in CDCl$_3$. The broadening is in part due rapid intermolecular exchange, and in part because of 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 ($\delta$ 2.82) shows no sign of coupling to the NH$_2$ protons.

300 MHz $^1$H NMR spectrum in CDCl$_3$
Source: Aldrich NMR Library

The N-H signals of ammonium salts are strongly downfield shifted, typically appearing at $\delta$ 4-7 in CDCl$_3$ and $\delta$ 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 coupling (1:1:1 triplet, $J_{HN} \approx 70$ Hz).

300 MHz $^1$H NMR spectrum in CDCl$_3$
Source: Aldrich NMR Library

**Aniline NH Protons.** The NH protons of anilines are typically at $\delta$ 3.5-4.5 in CDCl$_3$ solution, moving downfield by 1-2 ppm in DMSO solution. o-Nitroanilines (ca $\delta$ 5-6) and heterocyclic amines such 2-aminopyridines ($\delta$ 4.5) have signals downfield of this range.

300 MHz $^1$H NMR spectrum in CDCl$_3$
Source: Aldrich NMR Library

**Amide NH Protons.** Amide NH signals typically appear around $\delta$ 7, as in the example of N-acetylethlenediamine above. 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 example, where the CH$_2$ bonded to the amide nitrogen is a sharp quartet. The coupling to neighboring protons is not resolved in the NH signal because of broadening from coupling to $^{14}$N.
Thiol S-H Protons. S-H protons of alkyl thiols typically appear between \( \delta \) 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.

Aryl thiol S-H signals are further downfield, typically \( \delta \) 3.5-4.5, as a result of normal ring-current 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 somewhat further upfield (around \( \delta \) 0 for SeH and \( \delta \) -3 to -5 to TeH.)