Lecturenotes Chem 781 Part 3: Chemical Shift

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1   General

1.1   History and origin of chemical shift

Early NMR spectra were all taken of solids. Due to very small T_2 in solids those spectra had very broad lines and did not exhibit any fine structure.

However, in solution T_2 is normally rather long and sharp lines are observed. The first solution NMR ever taken was a ^{14}N NMR spectum of $^{14}NH_4(^{14}NO_3)$ saturated in H_2O ($I^{N-14} = 1$):

Result: Two lines were observed

=>   The two CHEMICALLY different N-atoms exhibit different lamor frequencies

$$\omega_{NH4} \ \neq \ \omega_{NO3}$$

Since $\omega = \gamma_{14N} B_0$ and γ_{14N} is a constant for each nucleus, the actual field has to be differ at the position of the two N-atoms in the molecule, i.e. each atom experiences a slightly different local field due to shielding from the surrounding electrons:

$$\omega = \omega_0 + \Omega = \ \gamma \ B_{loc} = \gamma \ (B_0 - B_{shielding}) = \gamma \ B_0 \ (1 - \sigma) \tag{3.1}$$

where σ is the shielding constant.

Important for the observed lamor frequency is the local field at the nucleus. The interaction of matter (electrons) with the magnetic field results in a change of the magnetic field inside the sample.


1.2   Macroscopic shielding:

A diamagnetic sample will decrease the magnetic field in the tube (paramagnetic compounds can cause an increase). This effect is equal throughout sample and just causes a constant shift for all nuclei.

As long only relative shifts are of interest the effect can be neglected.

However:

–   need for internal reference (TMS or lock solvent inside sample)

–   problem with external reference or unlocked samples

–   macroscopic paramagnetic susceptibility of compounds can be measured by NMR
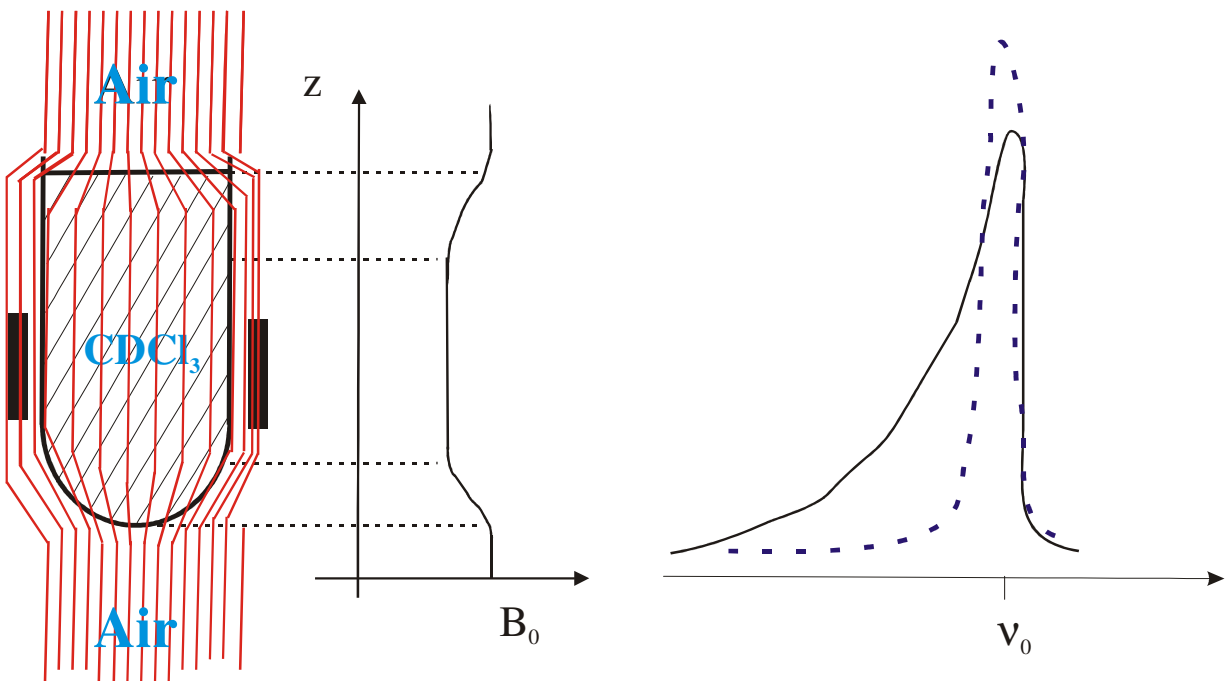
Left: A magnetic field is weaker inside a solvent compared to air **Middle:** Plot of field strength against the z-axis of sample

 Right: Spectrum with correct amount of solvent (**...**) and too little solvent (–). In the later sample near the solvent/air edge contributes

(Evan's method)

  –   Problems with too little solvent / misadjusted sample height (field changes at solvent/air interphase)

  –

1.3   Microscopic (local) shielding:

Interaction of B_0 field with matter takes place on a **microscopic** (molecular) scale:

The B_0 field is homogeneous on a *macroscopic* level, but it varies on a *microscopic* scale throughout the molecule depending on the distribution of electrons around the nucleus:

> **That is what makes NMR of interest to chemists (i.e. that is why you are in this lecture)**

Groups of equivalent nuclei will have same Lamor frequency (chemically equivalent). The intensity of the signal will be proportional to the number of nuclei in each group

=> Integration of signal

1.4   Measurement of chemical shift:

1.4.1   Definition

Shielding σ is defined with respect to the "naked" nucleus which is impractical to measure. Therefore frequencies are not reported as absolute values but relative to a reference compound: TMS (tetramethyl silane) for ^1H, ^{13}C and ^{29}Si NMR

This number is normally different from the off resonance frequency Ω (TMS not center of spectrum.

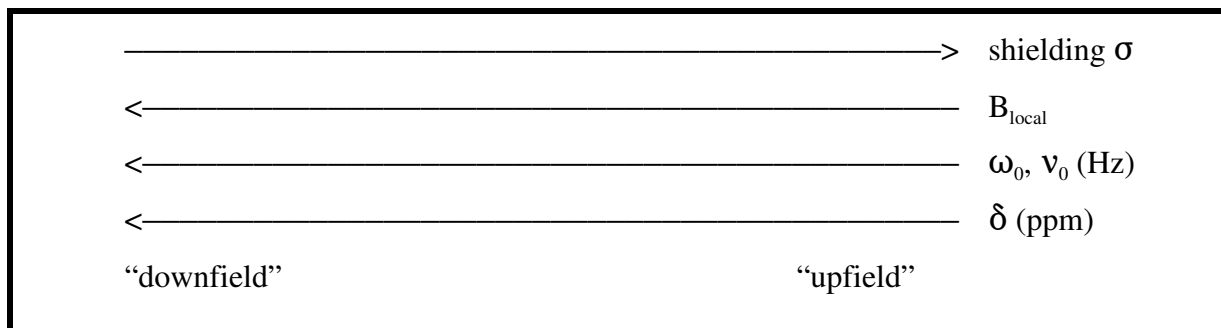Also, the frequency of a nucleus will depend on magnetic field:

$$\Delta\nu_0 = \nu_0 - \nu_0^{TMS} = \gamma B_0/(2\pi)\,(\sigma^{TMS} - \sigma) \tag{3.2}$$

it is therefore convenient to express the chemical shift as a fraction of the main field:

$$\boxed{\delta = \frac{\nu_0 - \nu_0^{TMS}}{\nu_0^{TMS}}} \tag{3.3}$$

δ is normally a very small number and is therefore expressed in ppm (10^{-6}). δ is **independent** of the magnetic field.

Higher values of δ correspond to lower shielding and thus higher local field B_0^{loc} and higher frequency ω_0. The axis is normally plotted with δ increasing from *right to left*.

————————————————————————————>	shielding σ
<————————————————————————————	B_{local}
<————————————————————————————	ω_0, ν_0 (Hz)
<————————————————————————————	δ (ppm)
"downfield" "upfield"	

Note that for historic reasons a shift to the left (high δ) is called downfield and a shift to the right(low δ) is called upfield. This results from the times when excitation was performed using low power irradiation at constant frequency, and the field was changed to move different signals through resonance condition, and it is the *additional* field which was referred to.

Various reference compounds are used for different nuclei (see also table of nuclei).

Note that sometimes different standards are in use for the same nucleus, so make sure to check when comparing data from literature !!!

^1H, ^{13}C, ^{29}Si	TMS (insoluble in water, DSS is used in water samples)
^{15}N	NH_3(liq) (tyically biochemists) CH_3NO_2 (often used by organic chemists)
^{31}P	H_3PO_4 80%

1.4.2 Indirect reference:

Often chemical shifts of solvent signals are tabulated and can be used as indirect reference, so no TMS has to be added to ^1H and ^{13}C spectra. Many lock solvent shifts are stored in the spectrometer computer, allowing a correct scaling to be available once the sample is locked using the shift of the deuterium signal of the lock solvent (note that ^2D and ^1H have the same chemical shifts).

Careful: $\delta(H_2O)$ depends on the temperature: 4.78 ppm at 298 K, 5.018 ppm at 278 K. If your instrument is locked on D_2O and you change the sample temperature, the lock system will keep the instrument locked at the predefined frequency for D_2O, and all other signals will appear to shift.

1.4.3 Absolute frequency referencing:

If no reference compound is available tabulated frequencies can be used to calibrate the chemical shift against the proton frequency of TMS. These Ξ values have been either measured once using standard compounds or were calculated using the ratio γ_H / γ_X and are typically listed

as values for a TMS ^{1}H frequency of 100.00000 MHz. Thus an internal reference (solvent signal) can be used to calibrate the spectrum of a different nucleus in the sample without the need for a reference for that nucleus to be present in the sample.

Example: *You measure a ^{15}N NMR signal ν_0 = 50.68306615 MHz and want to know the chemical shift against NH$_3$(liq). The frequency of TMS in the proton spectrum is 500.1300000 MHz. Using a Ξ value of 10.13291444 for ^{15}N-NH$_3$(liq) one can calculate the frequency of liq. NH$_3$ at that spectrometer (note that the number in the handout is using MeNO$_2$):*

$$\nu_0^{NH3} = 500.13 \cdot \Xi / 100.000 = 50.67774499 \text{ MHz}$$

$$and \quad \delta = \nu_0 - \nu_0^{NH3} / \nu_0^{NH3} = 105 \cdot 10^{-6} = 105 \text{ ppm relative to NH}_3\text{(liq.)}$$

1.4.4 Internal versus External reference

Ideally the reference compound should be within the same sample as the compound measured. In some cases that will not always be practical (For example adding 80% H$_3$PO$_4$). In those cases the reference compound can be inserted in a capillary inside the sample or the reference spectrum can be acquired separately just prior or just after the sample of interest. But one has to be aware that for accurate results the difference in bulk solvent susceptibility between the two samples (**1.2**) needs to be taken into account. Thus this method should only be used when not deuterated solvent is used and use of other internal reference is impractical.

2   Structure dependence of magnetic shielding:

The shielding constant σ can be broken down into three contributions:

$$\sigma = \sigma^{dia}_{local} + \sigma^{para}_{local} + \sigma_{remote}$$

σ^{dia}_{local} :   diamagnetic induction of local spherical electron density. Depends only on the ground state electron density.

σ^{para}_{local} :   Contribution of electron orbital angular momentum. The term can be regarded as a correction for deviation from spherical symmetry and includes excited electronic states. It is Negligible for ^{1}H (high energy 1s - 2p gap) , but dominant for most other nuclei with p- or d- electrons. The effect is opposite in sign to σ^{dia}_{local}, and acts deshielding. Hence the name paramagnetic, but note that ***this has nothing to***

do unpaired electrons

σ_{remote} :   effect of other atoms or groups ("ring currents", dipolar effect), solvent effects.
Small in most nuclei, but often dominant for protons

2.1   Diamagnetic shielding contribution:

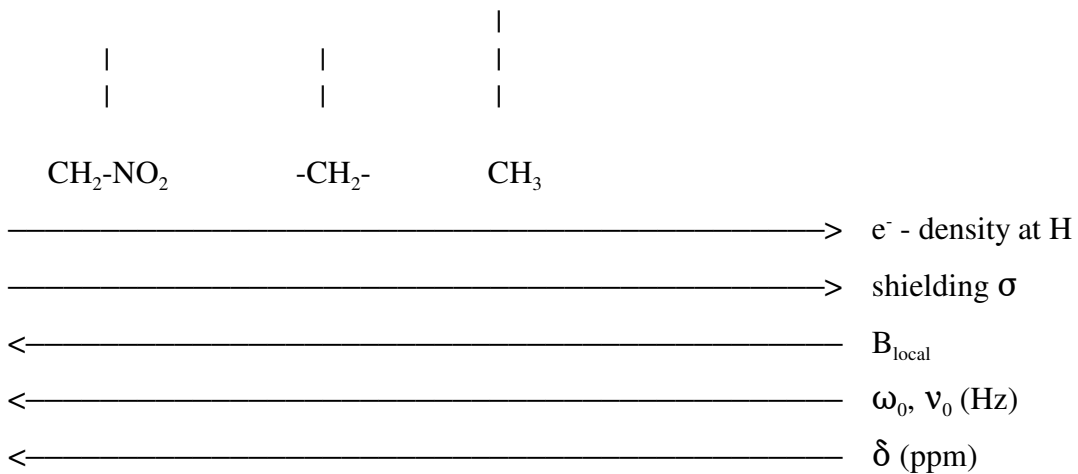Consider proton (^1H): Directly adjacent electrons are in s orbital (1s):
Spherical charge distribution: The main field B_0 will induce a diamagnetic ring current of the electrons in the orbital such that the induced field B_{dia} is opposing the main field (induction law) causing a shielding of B_0
The shielding depends on the electron density in the orbital: A higher electron density will result in higher shielding.
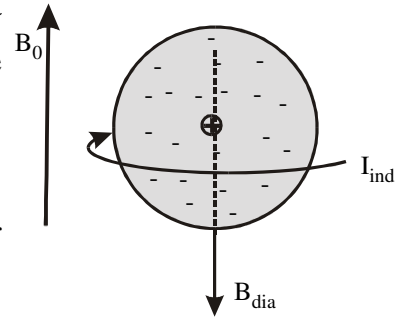
Hydrogen has only one electron, and shielding is relatively small, resulting in a fairly small chemical shift range. Heavier nuclei have more electrons, so shielding (and chemical shift ranges) are typically larger. But the electron distribution deviates more from spherical and σ^{para}_{local} becomes more important.

Example: schematic ^1H spectrum of CH_3-CH_2-CH2-NO2:

```
                              |
        |            |        |
        |            |        |

    CH2-NO2       -CH2-      CH3
    ─────────────────────────────────────────> e⁻ - density at H
    ─────────────────────────────────────────> shielding σ
    <───────────────────────────────────       B_local
    <───────────────────────────────────       ω₀, ν₀ (Hz)
    <───────────────────────────────────       δ (ppm)
```

Exact calculation of electron density is very complex, but many empirical correlations exist:

electro negativity of substituent:

	CH_3F	CH_3Cl	CH_3Br	CH_3I	CH_3-H
$\delta(^1H)$	4.13	2.84	2.45	1.98	0.13
E (X)	4.0	3.0	2.8	2.5	2.1

number of electron withdrawing ligands:

	CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$	CCl_4
$\delta(^1H)$	0.13	2.84	5.32	7.25	-
$\delta(^{13}C)$	-2.1	25.6	54.4	77.7	96.7

=> the electron density on neighbored carbon is directly related to electron density on hydrogen

But note that for heavy substituent atoms the shear number of additional electrons can more than compensate for electronegativity effects (***heavy atom effect***):

		CH_3X	CH_2X_2	CHX_3	CX_4
δ_C	X = F	71.6	111.2	118.8	119.4
	X = Cl	25.6	54.4	77.7	96.7
	X = Br	9.6	21.6	12.3	-28.6
	X = I	-24	-53.8	-139.7	-292.2

anions are normally highly shielded, cations highly deshielded:

    metal hydrides M-H CH_3-Li $(CH_3)_2C^+$-H

        -2 - -25   - 1.3   + 5.06

2.2 "Paramagnetic" (de)shielding contribution

This term accounts for non spherical symmetry in case of most non-hydrogen atoms, where p- or d- orbitals are involved in the bonding. Its magnitude describes the influence of orbital angular momentum of the surrounding electrons in a non spherical environment. Usually this contribution

is opposite in sign to the diamagnetic shielding term above. For hydrogen nuclei this contribution is usually negligible because only s- orbitals are present in hydrogen. But for most other nuclei it plays an important role and is particular important if double/triple bonds are present.
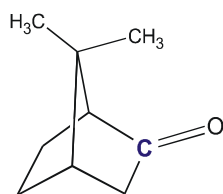
In a rough approximation, the paramagnetic shielding of nucleus *i* depends on the energy gap ΔE between the ground state and the lowest excited state, the average radius of the 2p electrons (r_{2p}) and a bond order tem Q_j.

$$\sigma_i^{para} \approx \frac{\mu_0 \mu_B^2}{2\pi \Delta E} \frac{1}{r_{2p}^3} \sum_{i \neq j} Q_j$$

In the case of doubly bound substituents the paramagnetic shielding term causes a deshielding heavy atom effect:

Example of group 6 substituents:

	CO_2	CS_2	CSe_2
$\delta_C =$	124.2	192.8	209.9

δ_{CO} = 215.6 ppm	δ_{CO} = 269.0 ppm
$\Delta E_{n-\pi^*}$ = 401.5 kJ/mol	$\Delta E_{n-\pi^*}$ = 234.5 kJ/mol
$\lambda^{n-\pi^*}$ = 292 nm	$\lambda^{n-\pi^*}$ = 492 nm
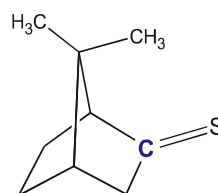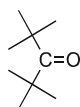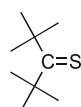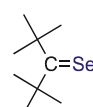
| $\delta_{C=X}$ /ppm	218.0	279.8	291.4

Correlation of electronic excitation ΔE and decreased shielding of carbonyl, thio- and seleno-carbonyl compounds

2.3   Shielding by remotely induced fields:

Magnetic fields induced from electrons on neighboring atoms (groups of atoms) will also effect the field at the local nucleus. This effect can be additive or subtractive, depending of the relative location of the group with respect to the main field:

$\theta = 90°$	$\theta = 180°$
$B_{loc} (H) > B_0$	$B_{loc} (H) < B_0$
$\Delta \sigma < 0$	$\Delta \sigma > 0$
$\Delta \delta > 0$	$\Delta \delta < 0$
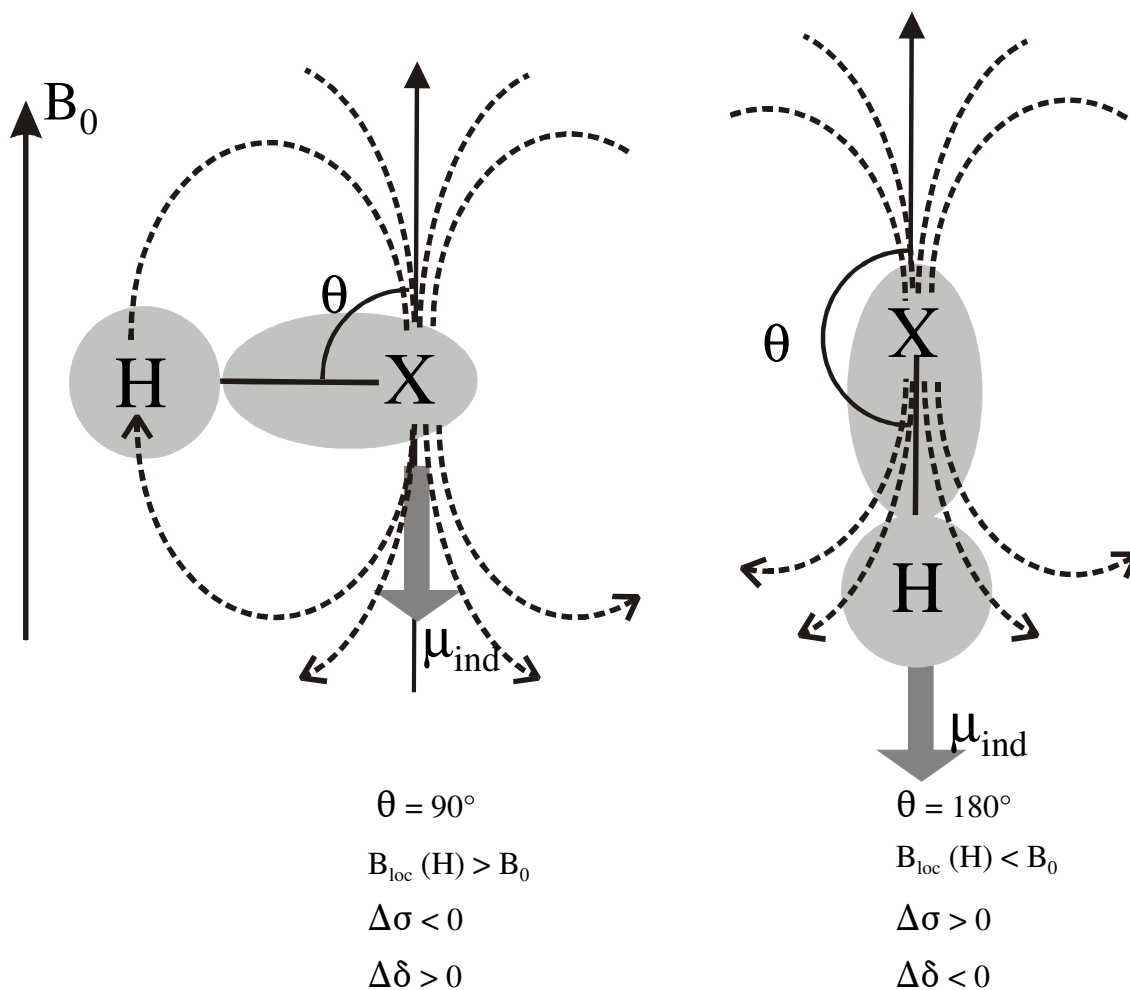
In a solid crystal, the chemical shift will depend on the orientation of the crystal in a magnetic field. In a powder a broad line pattern representing all orientations of individual micro crystals will be observed (chemical shift anisotropy).

In solution, many orientations are interconverted by fast molecular tumbling, and the time average contribution of the orientations along x,y,z is observed:

$$\Delta\sigma = \frac{1}{4\pi B_0} \sum_{i=x,y,z} \mu_{ind}^i \frac{1-3\cos^2\theta_i}{R_{HX}} \quad \textbf{(3.4)}$$

If μ_{ind} was equal for each orientation (isotropic, spherical group), the average effect in solution would be zero. However, bonds are not spherical, thus the effect of one of the orientations will dominate and result in a shift.

Most bonds show strongest μ_{ind} with the bond $\perp$ to B_0 (axial symmetry)

$$\Delta\sigma_{iso} = \frac{1}{3}\left(\frac{\mu_\parallel - \mu_\perp}{B_0}\right)\frac{1-3\cos^2\theta}{4\pi R_{HX}} \quad \textbf{(3.5)}$$

Note that the above anisotropy of the shielding constant dos not only apply to σ^{remote}, but in similar fashion to σ^{para}. It is just most easily visualized for σ^{remote}.

2.3.1 Single bond (relative small effect)

example: axial versus equatorial protons: $\delta H^{ax} < \delta H^{eq}$
($+\sigma$ indicates increased shielding, $-\sigma$ deshielding)
The effect is small in σ-bonds, and often overshadowed by other contributions. But in many cases, tenative assignments of axial vs. equatorial can be made based on shift.
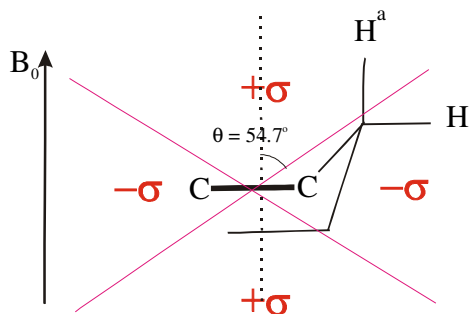
2.3.2 Anisotropic effect of π-bonds:

C=C double bond $\delta H_{olefin} = 5\text{-}7$ ppm
aldehydes $\delta H_{CHO} = 9\text{-}11$ ppm
      (combined effect of anisotropy of CO and electron withdrawing effect)
but note alkynes: $\delta H_{C\equiv H} = 1.8$ ppm ($\equiv$C-H in shielding part of cone)
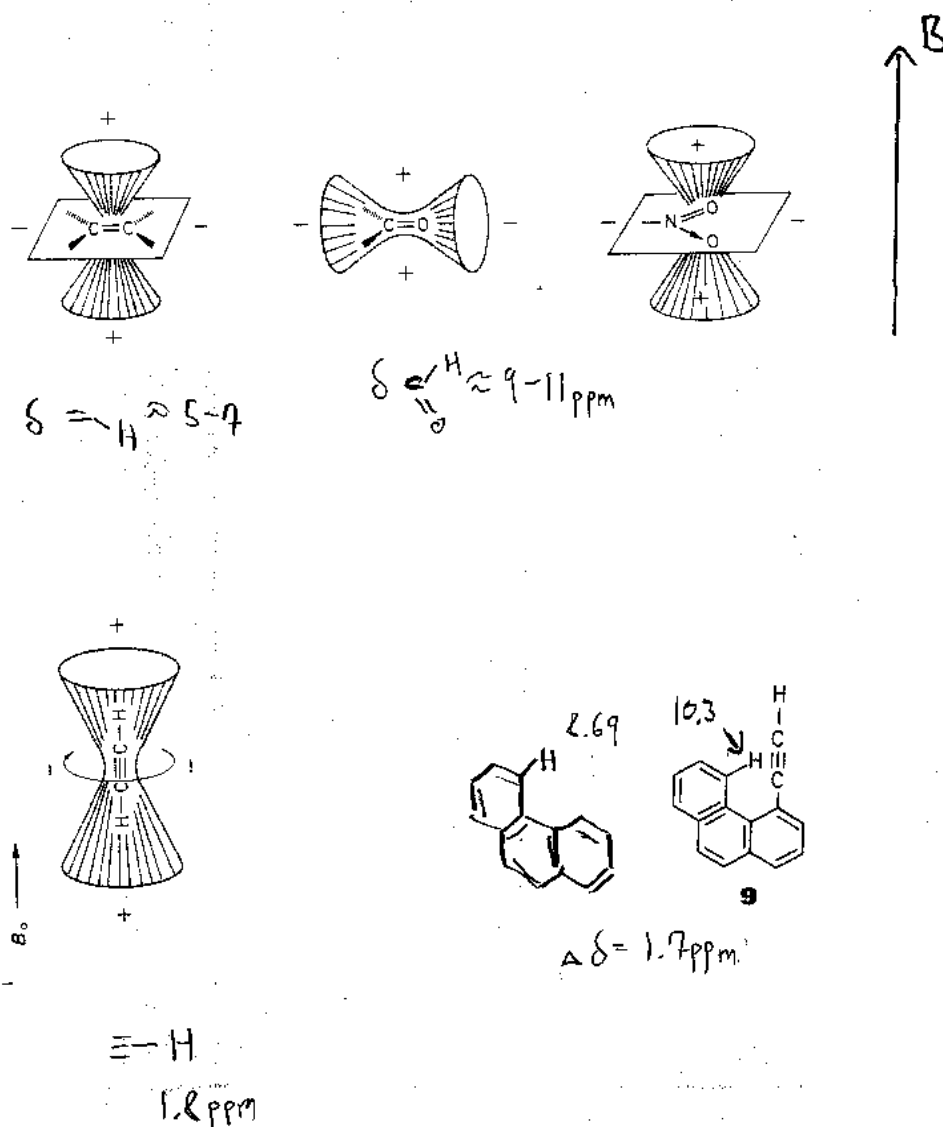   see figure of substituted phenanthrene
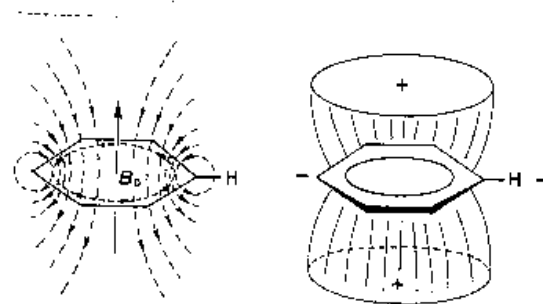
2.3.3   Ring Currents

Ring currents are particular strong cases of anisotropy of double bond:

aromatic rings ($4n + 2\,e^-$):   protons outside ring strongly deshielded (7 - 9 ppm), inside of ring strongly shielded (annulenes)
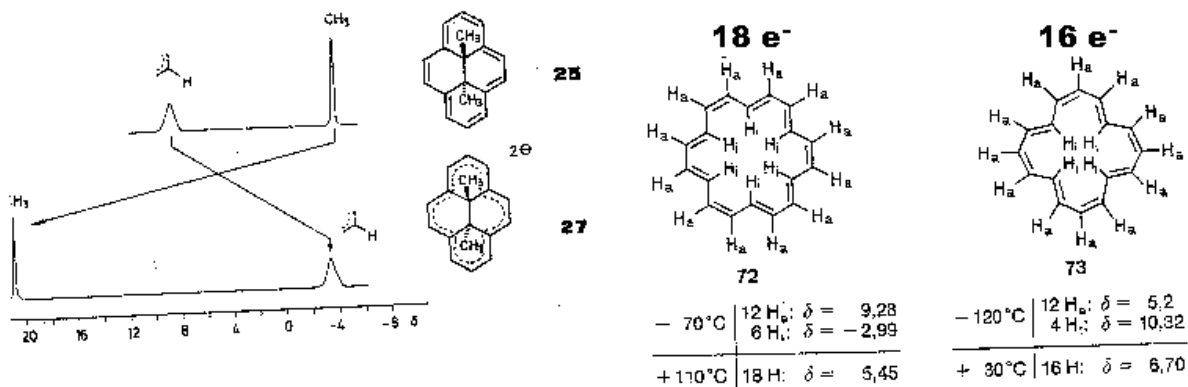
anti-aromatics ($4n\,e^-$)**:**   reversed "ring current": shielded outside, deshielded inside

cyclopropane ring: ring current like benzene, but weaker (no π system). Ring protons are in shielded part of the cone ($\delta = 0.22$ ppm)
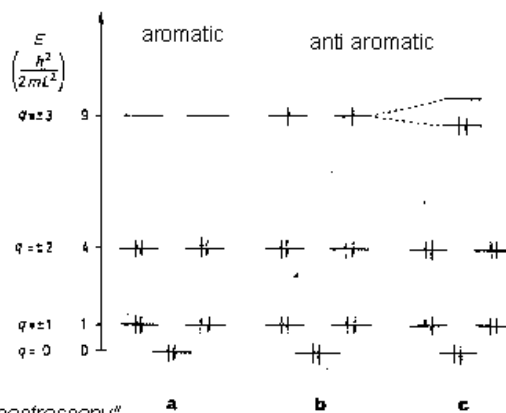
Ring current model for aromatic systems

18 e⁻

72

$-70°C$	12 H$_a$:	$\delta =$	9,28
	6 H$_i$:	$\delta =$	$-2,99$
$+110°C$	18 H:	$\delta =$	5,45

16 e⁻

73

$-120°C$	12 H$_a$:	$\delta =$	5,2
	4 H$_i$:	$\delta =$	10,32
$+30°C$	16 H:	$\delta =$	6,70

Energy levels for aromatic and anti aromatic systems

Figures from H. Günther, "NMR Spectroscopy"

2.3.4 Exchanging Protons: (OH, NH): Hydrogen Bonding

δ for OH and NH signals can vary very much depending on their hydrogen bonding. In general, stronger H-bonding will cause more deshielding (larger δ)

example $\delta^H(H_2O)$ in different solvents:

solvent	$\delta(H_2O)$
H_2O	4.78
DMSO	3.3
acetone	2.5
$CDCl_3$	1.4
C_6D_6	0.3

The reason for that shift is that the hydrogen bond is a highly polar bond with the positive part on the hydrogen end. That is at first counterintuitive when looking at the hydrogen as

-       See example of H^N vs H^α chemical shift range in proteins
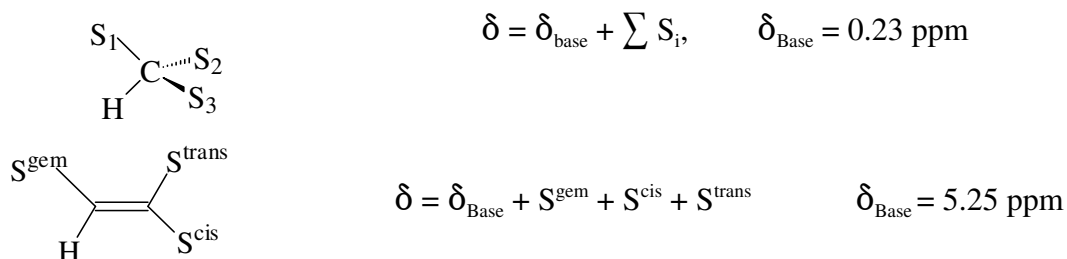
intra or *inter*molecular: *inter*molecular H-bonds cause concentration- and temperature dependent shifts => in proteins solvent exposed amide hydrogens can be identified by temperature dependent shift

Also: exchanging protons are very sensitive to charge (acidity -> electron density):

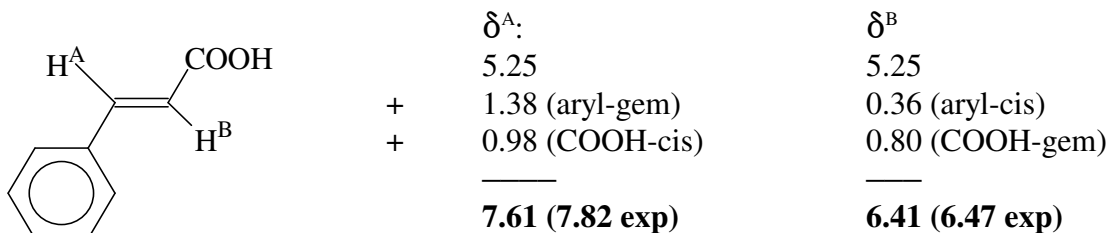|	R-OH	Ph-OH	C-OH $\overset{\parallel}{O}$	>NH	O=C-NH-, >NH$_2^+$
δ/ppm	2-3	5-6	12-14	≈ 3	≈ 8

3   Empirical Methods:

Due to the multitude of contributions to the chemical shielding, calculation of accurate chemical shifts from *ab initio* is often not feasible. Therefore empirical methods based on experimental data are important. Often, chemical shifts can be calculated as a sum of contributions from substituents which are tabulated for may common groups. The shift of the unsubstituted fragment is used As base:

$$\delta = \delta_{base} + \sum S_i, \qquad \delta_{Base} = 0.23 \text{ ppm}$$

$$\delta = \delta_{Base} + S^{gem} + S^{cis} + S^{trans} \qquad \delta_{Base} = 5.25 \text{ ppm}$$

See Handout for tables with substituent increments.

Example:

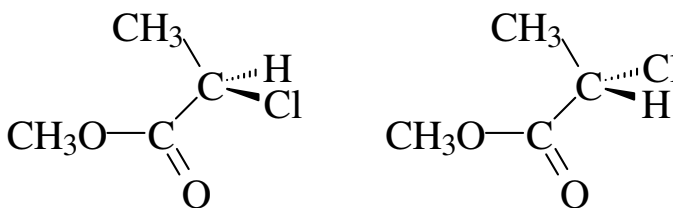|	δ^A:	δ^B
	5.25	5.25
+	1.38 (aryl-gem)	0.36 (aryl-cis)
+	0.98 (COOH-cis)	0.80 (COOH-gem)
	————	———
	7.61 (7.82 exp)	**6.41 (6.47 exp)**

4 Equivalent and non equivalent nuclei (symmetry):

If two nuclei can be interconverted by a symmetry operation (mirror, rotation, translation) they are equivalent and will have the same chemical shift
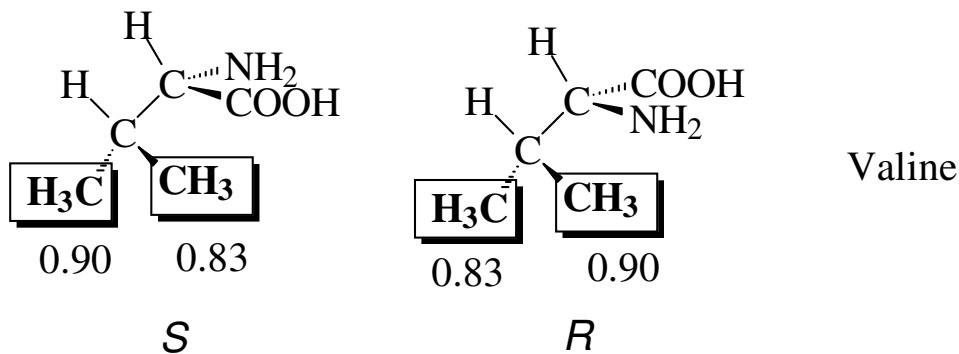
4.1 Enantiomers

Enantiomers always have identical NMR spectra since they can be interconverted into each other by a symmetry operation (mirror image) =>*but see recent publications on*

calculated asymmetries on molecular level due to weak force parity violation <=

4.2 Diastereotopic protons:

Valine

Chiral centers can cause neighboring pairs of protons or other groups to be inequivalent. The chemical shift difference will decrease with distance from chiral center.

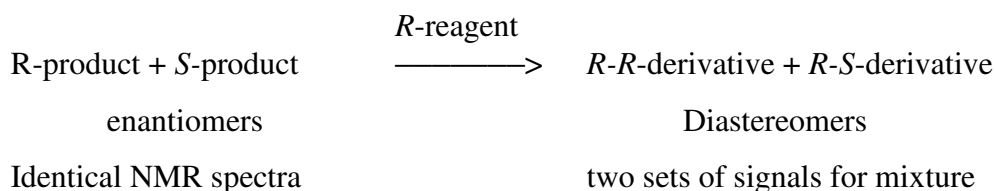$$\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III}$$
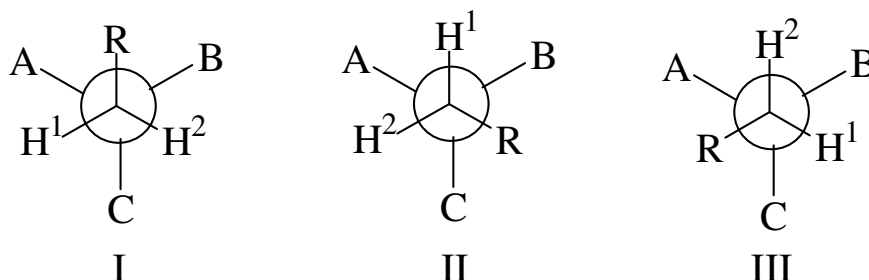
This will still hold true for the time average shift in the case of fast rotation of the group in question, even if the three conformations I, II and III above are equally populated because $H^1[I] \neq H^2[II]$ etc. However, the chemical shift difference will be smaller than in rigid (ring) systems. Note however methyl groups (R = H): Here fast rotation will result in the same average shift for all protons since $H^1[I] = H^2[II]$ in this case => methyl protons almost always equivalent
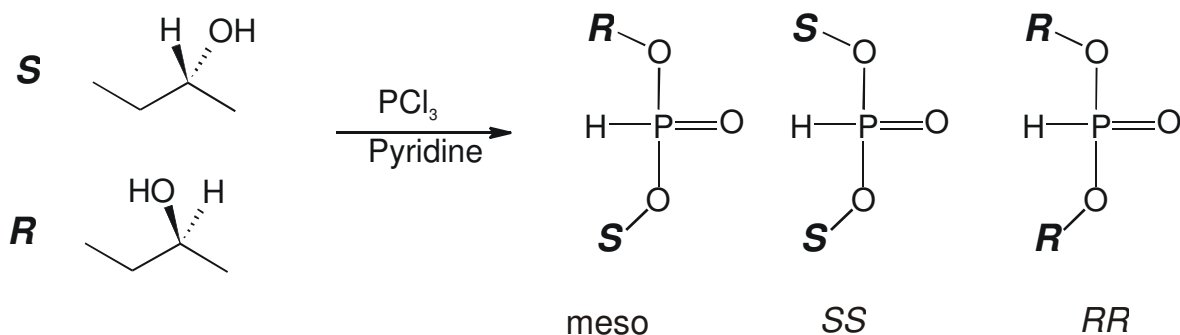
4.3 Measurement of enantiomeric excess:

As enantiomers can not be distinguished by NMR, measuring e.e. requires conversion of a mixture of enantiomers into a mixture of diastereomers. Use integration to determine ratio of diastereomers.

−   use chiral solvent or solvating agent (shift reagent, may be paramagnetic)

−   make derivative adding a chiral (optically pure) substituent

$$\begin{array}{ccc} & R\text{-reagent} & \\ \text{R-product + S-product} & \xrightarrow{\hspace{2cm}} & R\text{-}R\text{-derivative} + R\text{-}S\text{-derivative} \\ \text{enantiomers} & & \text{Diastereomers} \\ \text{Identical NMR spectra} & & \text{two sets of signals for mixture} \end{array}$$

−   Form dimers, *no chiral reagent needed*:

4.4   Isotope shifts

Note that substitution of a nucleus by another isotope constitutes a different molecule which can cause a slightly different shift for neighboring nucleus: $\delta^H(HCHCl_2) \neq \delta^H(HCDCl_2)$, $\delta^C(CDCl_3) \neq \delta(CHCl_3)$.

5   Consideration of Dynamics

So far static molecules were considered. Real molecules often undergo rapid conformational rearrangement and rotation about bonds.

In general, if the rate of interconversion between the conformers is much larger than the chemical shift difference measured in Hz between the conformers ($k_{AB} \gg \Delta v$), an weighted average shift is observed. If the interconversion is slow ($k \ll \Delta v$), separate signals are observed for each conformer.

Example: Cyclohexane has both equatorial and axial protons. But at room temperature only signal is observed in the proton NMR spectrum.   At very low temperature, separate signals are observed.
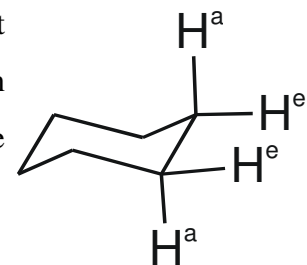
Methyl groups always rotate fast and give rise to one signal of relative intensity of three.

Double bonds usually exhibit no rotation, and groups give separate signals unless symmetry is present.
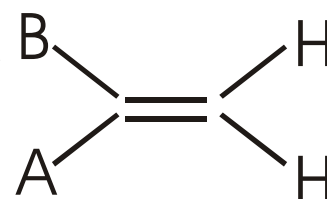
In the case the rate of interconversion is of the same order of magnitude as the chemical shift difference that $k_{AB} \approx \Delta v_{AB}$, an extremely broadened signal is observed, which often can be obscured in the baseline. That is often the case for acidic O-H and N-H protons, which can interchange with each other or water in the sample. Non protic hydrogen bond acceptors like DMSO tend to stabilize such protons and make them more likely to be observed. Also many compounds exhibit internal reorientations which are on the NMR timescale (for example N,N-dimethylformamide)