1

Introduction to ^{1}H NMR Chemical Shifts

1.1 Historical Background

^{1}H NMR spectroscopy began in 1945 when two groups of physicists, Bloch, Hansen and Packard[1] at Stanford and Purcell, Torrey and Pound[2] at Harvard, first detected the radiofrequency signal from atomic nuclei when placed in a magnetic field. They shared the 1952 Nobel Prize in Physics for this work. This was ^{1}H NMR as they used the hydrogen nuclei in water and paraffin wax to obtain their signals. As the technology developed other nuclei were found to exhibit NMR signals, but the resonance frequency of these signals depended on the chemical environment of the nuclei. This was first observed by Knight[3] in metals and metal salts and later by Dickinson[4] for the ^{19}F nuclei in fluorocompounds. Also Proctor and Yu[5] observed two signals in the ^{14}N spectrum of ammonium nitrate. They attributed this unexpected result to some 'nasty chemical effect'. Thus the phenomenon of nuclear chemical shifts was discovered. Further advances in magnet resolution allowed the historic experiment of Arnold, Dharmatti and Packard,[6] when they resolved the three types of hydrogen atoms in ethanol (Figure 1.1), the first example of ^{1}H chemical shifts and this illustrated the immense potential of ^{1}H NMR in structural organic chemistry.

Since this original discovery ^{1}H NMR spectroscopy is now widely used in all scientific disciplines from physics to medicine and is now even part of the high school syllabus. It is also the most common and powerful analytical tool of the research scientist. The detection of the hydrogen atom ^{1}H resonances in a molecule was possible since this isotope has a spin of $1/2$, is magnetically active, has a high natural abundance and is present in most organic compounds. The other nucleus of general interest for the organic chemist, the carbon ^{12}C isotope, has zero spin and therefore no magnetic moment. The ^{13}C nucleus has spin $1/2$ but has a natural abundance of only ca. 1 %. For this reason it took another two decades for the first ^{13}C NMR spectrum with acceptable quality to be produced.

Modelling ^{1}H NMR Spectra of Organic Compounds: Theory, Applications and NMR Prediction Software
Raymond Abraham and Mehdi Mobli

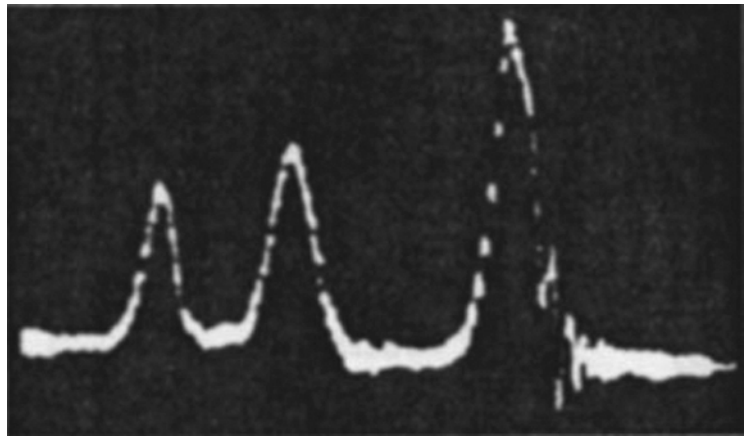


Figure 1.1 *The first NMR spectrum of ethanol (from Arnold, Dharmatti and Packard,[6] reproduced by permission of the American Institute of Physics).*

In the subsequent years immense advances in instrumentation, such as cryomagnets and extensive computational facilities, led to the development of Fourier-Transform (FT) NMR spectrometers as well as multidimensional techniques. At this point NMR methods had become so advanced that they were being used for study of biomolecules, complex chemical matrices and even for imaging of living organisms. The significance of these developments in NMR have been recognized with several Nobel Prizes being awarded to researchers in this field. In 1991 Richard Ernst received the prize for his work on multidimensional techniques, in 2002 Kurt Wüthrich for his work on determining the structure of biomolecules using NMR and most recently in 2003 Paul Lauterbur and Peter Mansfield for their work on imaging (MRI) of living organisms.

In this book we consider one important aspect of ^{1}H NMR, the solution spectra of organic compounds. Recent progress in this area has been directed towards obtaining NMR data more rapidly and enhancing the sensitivity of the equipment. Improved automated methods combined with automatic sample changers have enabled both one dimensional and multidimensional experiments to be performed with minimal interaction with the instruments. This has led to the development of high throughput systems including liquid chromatography (LC)–NMR systems coupled with solid phase extraction (SPE) methods.[7,8] Sensitivity has been improved significantly through the use of cryoprobes and also by using probes and NMR tubes with smaller dimensions (currently probes for NMR tubes with a 1 mm diameter are available).[7]

Utilizing these methods it is possible to run up to a 1000 samples per day. The major bottleneck of the process therefore lies not in the acquisition of data but rather the interpretation and assignment of the spectra produced. The development of tools for automatic assignment of spectral data is therefore highly desirable and this is particularly the case for ^{1}H NMR, the most common NMR spectra. Unfortunately ^{1}H chemical shifts have proved to be the most difficult to predict as well. Protons tend to be in the periphery of the molecule and can therefore easily be influenced by non-bonded interactions such as neighbouring groups (intramolecular) or neighbouring solute and solvent molecules (intermolecular). The

narrow range of proton resonances, typically 10–15 ppm, reinforces the need for accurate predictions of their chemical shifts and this is the main objective of this work.

When we consider the importance of this technique in structural chemistry it is remarkable that there is still no routine method of predicting ^{1}H chemical shifts of organic compounds. Recent advances in *ab initio* calculations are giving promising results (see later) but are not applicable for quick calculations on moderately sized molecules. Also they do not give any breakdown of the different interactions in the ^{1}H chemical shift calculations, thus they do not directly assist our understanding of the interactions responsible. We present here a simple mechanistic theory of ^{1}H chemical shifts and also detail the methods we have used in this semi-empirical scheme to overcome this challenge. We also include a chapter on HH couplings and the analysis of NMR spectra in order to present a complete picture of ^{1}H NMR spectra. In the accompanying CD computer programs are presented which allow the user (a) to draw a molecule on the screen and minimize the conformational energy, (b) to calculate from this file the ^{1}H couplings and chemical shifts and (c) to predict and display the resulting ^{1}H NMR spectrum. The applications and uses of these programs are discussed in Chapter 9.

1.2 Basic Theory of NMR

The theory of NMR is common to all experiments and all nuclei, but we shall concentrate here on the ^{1}H nucleus. This has a nuclear spin (I) of $^1/_2$ in units of ($h/2\pi$) and nuclear moment (μ), proportional to I (Equation (1.1)) where γ is called the magnetogyric ratio.

$$\mu = \gamma I h/2\pi \tag{1.1}$$

It is unique for each nucleus: γ for deuterium (^{2}D) is ca. 1/6th that of ^{1}H.

In a magnetic field there are $2I + 1$ allowed orientations of the nuclear magnet, thus a ^{1}H nucleus has two allowed orientations, defined by the value of the magnetic quantum number m_I. For ^{1}H m_I has values of $\pm^1/_2$.

The energy of interaction of the nucleus and magnetic field is equal to the field times the nuclear moment. Using Equation (1.1) gives Equation (1.2) where **B** is the applied magnetic field.

$$\mathbf{E} = -\gamma h/2\pi . m_I \, \mathbf{B} \tag{1.2}$$

The selection rule for NMR transitions is that m_I can only change by one unit, i.e. $\Delta m_I = \pm 1$. Thus the resonance condition for all NMR experiments is given by Equation (1.3) and

$$h\nu = \Delta E = \gamma h \mathbf{B}/2\pi \tag{1.3}$$

eliminating h gives Equation (1.4), the resonance equation for all NMR experiments.

$$\nu = \gamma \mathbf{B}/2\pi \tag{1.4}$$

Note in particular the relationship in Equation (1.4) between field (**B**) and frequency (ν). In older continuous-wave (CW) experiments the frequency or the field was varied and the spectrum obtained. Present day FT experiments remove this dichotomy but we note that all NMR spectra are measured in frequency units (Hz) which increase from right to left.

1.3 The ^{1}H Chemical Shift

Definition. When a molecule containing the ^{1}H nuclei under observation is placed in a magnetic field, the electrons within the molecule shield the nuclei from the external applied field. The s electrons in the molecule are spherically symmetric and circulate in the applied magnetic field (Figure 1.2). A circulating electron is an electric current and this current produces a magnetic field at the nucleus which *opposes* the external field. In order to obtain the resonance condition (Equation (1.4)) it is necessary to increase the applied field over that for the isolated nucleus. If $\mathbf{B}_{ext}$ is the applied field and $\mathbf{B}_0$ the field at the nucleus then the nuclear shielding ($\Delta\mathbf{B}$) is given by Equation (1.5). This increase in the shielding is called the

$$\Delta\mathbf{B} = \mathbf{B}_{ext} - \mathbf{B}_0 \tag{1.5}$$

diamagnetic shift. Diamagnetism is universal as every molecule has s electrons. There is no spherical symmetry for p electrons. These electrons produce large magnetic fields which when averaged over the molecular motions give low-field shifts. This deshielding is called the *paramagnetic* shift.

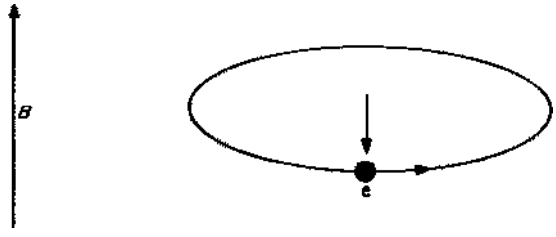


Figure 1.2 *Circulating s-electrons in a magnetic field.*

1.3.1 Nuclear Shielding and Reference Compounds

The **nuclear shielding** $\Delta\mathbf{B}$ is *proportional* to the applied field and the *chemical shift* is defined as the nuclear shielding divided by the applied field. Thus the chemical shift is a molecular quantity. It is a function only of the nucleus and its environment. It is always measured from a suitable reference compound. The standard procedure is to use tetramethylsilane (TMS) ($Si(CH_3)_4$) as an internal reference compound added to the solution investigated. Sometimes an external reference may be used (e.g. when the solution is very reactive). In this case the external reference could be contained in a capillary tube placed within the sample tube or a coaxial tube outside the sample tube. ^{1}H chemical shifts are usually measured on the δ scale (Equation (1.6)).

$$\delta_H = (\nu_H - \nu_R)/\nu_0 \times 10^6 \text{ ppm} \tag{1.6}$$

Where ν_H is the resonance frequency (Hz) of the proton considered, ν_R the corresponding frequency of the TMS internal reference and ν_0 is the spectrometer frequency. We note that the TMS is at 0 and the scale is from right to left which is the direction of increasing frequency.

In a ^{1}H NMR spectrum at 100 MHz, two peaks with a separation of 100 Hz are 1 ppm apart. The same two peaks when observed in a 500 MHz spectrometer would be 500 Hz apart. It is for this reason that, when the basic data of a spectrum are given, the spectrometer frequency *must* be recorded. In contrast, the chemical shift δ in ppm is, of course, a molecular parameter dependent only on the sample conditions (solvent, concentration, temperature) and not on the spectrometer frequency. An alternative scale used in early experiments is the τ scale in which TMS is at 10.0 and the scale is from 0 to 10 from left to right. Thus $\delta = 10 - \tau$.

As TMS is insoluble in water it is not used for this solvent. The recommended reference is TSP, sodium 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid ($Me_3SiCD_2CD_2SO_3Na$) in which the reference protons of the methyl groups are defined as 0.0δ. Other useful secondary reference compounds for aqueous solution are given in Table 1.1.

Table 1.1 *Reference compounds for aqueous solution*

TSP	tBuOH	CH_3CN[a]	Acetone[a]	DMSO[b]	$Me_4N^+Br^-$	Dioxane
0.0	1.23	2.06	2.22	2.71	3.18	3.75

[a] Exchanges in alkaline solution.
[b] Unsuitable for acid solution.

The hydrogen nucleus is unique as it is the only nucleus, except helium without π-electrons and therefore there is no paramagnetic shielding term from its own valency electrons. The common range of ^{1}H chemical shifts in organic compounds is ca. 0–10δ which contrasts with shift ranges ≥ 200 ppm for all other nuclei. Modern NMR spectrometers routinely output these shifts to 0.001 ppm. This does not necessarily mean that the absolute accuracy of the chemical shift is to this figure as other interactions may affect these values. Solvent effects in ^{1}H NMR are often appreciable.[9] For example, the chemical shift of acetone in CCl_4, $CDCl_3$, DMSO, methanol and D_2O is 2.09, 2.17, 2.12, 2.15 and 2.22δ, respectively,[10,11] (in the anisotropic benzene solvent it is 1.55δ). To minimize these effects ^{1}H NMR spectra are commonly measured in dilute $CDCl_3$ solution. Even for such 'standardized' conditions variations in sample temperature and/or concentration may affect the chemical shifts and consideration of these factors suggests that routinely measured ^{1}H chemical shifts should be reliable to ca. ± 0.01 ppm.

1.4 ^{1}H Substituent Chemical Shift (SCS)

The influence of any substituent (X) on the chemical shift of any proton is termed the substituent chemical shift (SCS) and defined by Equation (1.7).

$$SCS = \delta(RX) - \delta(RH) \tag{1.7}$$

It is convenient to divide the SCSs into a one-bond or α effect (i.e. H—X), a two-bond or β effect (i.e. H—C—X) , a three-bond or γ effect (i.e. H—C—C—X) and long-range effects (> three bonds). The one-bond or α effect is clearly of considerable theoretical value but is of relatively little practical importance as the great majority of ^{1}H chemical shifts are of

hydrogens attached to carbon atoms. Protons attached to almost all other atoms (OH, NH, SH, F, Cl, Br, I, etc.) often show chemical shift changes with solvent and/or concentration of several ppm due to H-bonding interactions.[12] In consequence these chemical shifts have seldom been used for structural identification. We shall show later (Chapters 6 and 8) that given precise experimental conditions many of these protons can give reliable chemical shifts.

1.4.1 Two-bond (H.C.X) Effects

The two-bond or β SCS in methyl derivatives (MeX) was shown.[13,14] to be linearly related to the electronegativity of X and this is shown in Table 1.2.

Table 1.2 *^{1}H chemical shifts (δ) of CH_3X compounds vs. the electronegativity[a] of X*

X	δ_H	E_X	X	δ_H	E_X
$SiMe_3$	0.0	1.90	SMe	2.08	2.60
H	0.23	2.20	I	2.16	2.65
Me	0.86	—	NH_2	2.46	3.05
Et	0.90	—	Br	2.68	2.95
CCl_3	2.75	2.60	Cl	3.05	3.15
CN	1.98	—	OH	3.38	3.50
CO.Me	2.17	—	F	4.26	3.90

[a] Pauling electronegativity (see Huggins[15]).

The data in Table 1.2 shows the direct influence of the diamagnetic term. As the substituent becomes more electronegative, the electron density round the ^{1}H nucleus decreases deshielding the nucleus (i.e. increasing δ). The table also shows that for multivalent atoms (e.g. carbon) the chemical shift of the methyl protons is also a function of the γ substituent, e.g. X = Me vs. CCl_3, CN and CO.Me. Originally group electronegativity scales were proposed to take account of this γ effect. In the CHARGE scheme presented the β and γ effects of substituents are considered separately and additive (see later).

A simple and useful extension of the above data is Equation (1.8), originally due to Shoolery.

$$\delta_H = 0.23 + \Sigma \text{ contribution} \tag{1.8}$$

This allows the prediction of any CH_2XY chemical shift by simply adding the substituent shift to the chemical shift of methane (0.23δ). The substituent shifts for some common substituents are given in Table 1.3. The values are from a refined analysis of the SCSs.[16]

We have included the shift for H so that the rules can be extended to methyl compounds. The rules can also be used for methines (CHXYZ) but are much less accurate. For example, the shift for $CHCl_3$ is calculated as $0.23 + 3 \times 2.48 = 7.67\delta$ compared to the observed value of 7.27.

1.4.2 Three-bond (H.C.C.X) Effects

There are of course many three-bond or γ effects, but we shall consider here the most common one through two saturated carbon atoms. The γ effects of substituents are totally

Table 1.3 *Additive contributions to the chemical shifts of CH_2 groups*[a]

Group	Shift	Group	Shift	Group	Shift
H	0.17	$CO.NR_2$	1.39	F	3.15
CH_3	0.47	CO_2R	1.49	Cl	2.48
CH_2R	0.67	CO.Ph	2.08	Br	2.29
C=CR	1.33	OR	2.27	I	1.82
C≡CR	1.52	OH	2.46	NH_2	1.69
CN	1.73	O.Ph	2.89	NR_2	1.41
Ph	1.85	O.CO.R	2.98	NH.CO.R	2.23
CO.R	1.58	SR	1.63	SPh	1.92

[a] R = alkyl.

Table 1.4 *γ SCS (H.C.C.X) in ethyl derivatives*[a]

Substituent	CH_3	NH_2	OH	SH	F	Cl	Br	I
SCS	0.06	0.25	0.38	0.48	0.51	0.64	0.86	0.99

[a] From ethane (0.855 ppm).

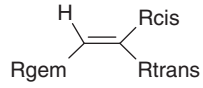
different from their β effects. Table 1.4 gives a selection of the γ effects of some common substituent groups in ethyl derivatives, i.e. the shift of the methyl protons in ethyl compounds from those in ethane. From Tables 1.2. and 1.4 we note that whereas the β effect of a methyl group is 0.64 ppm (ethane vs. methane) the γ effect of the methyl group is 0.04 ppm (propane vs. ethane). Also the γ effect is not a function of the electronegativity of the substituent. This is clearly demonstrated in Table 1.4 in which the methyl SCSs in the ethyl halides increase from fluorine to iodine, the opposite order of the electronegativity. This demonstrates that ^{1}H chemical shifts are not simply due to the transmission of inductive effects along the carbon–carbon σ bonds. There is a correlation between the methyl chemical shift and the polarizability (i.e. size) of the substituent for the halogen substituents in Table 1.4 and this suggests that the methyl chemical shift is more affected by steric or van der Waals interactions with the substituent rather than inductive effects. This will be considered in more detail subsequently.

1.4.3 ^{1}H SCSs in Olefins and Aromatics

The effects of substituents on ^{1}H chemical shifts in olefins and benzenes have also been determined and Tables 1.5 and 1.6 give the SCSs of some common substituent groups in ethylene and benzene. Table 1.5 is extracted from a more extensive list[17] and Table 1.6 from literature data.[18] Note the chemical shift for ethylene in Table 1.5 is the value in $CDCl_3$[19] and not the value for CCl_4 solution[19] (5.25δ).

Although the σ inductive effect of substituents on ^{1}H chemical shifts is only appreciable over one or two bonds this is not true of π-electron shifts. In Table 1.5 large contributions are observed at the β (geminal) and γ (vicinal) protons and often the contributions are reversed for the geminal and vicinal atoms due to competing σ and π effects. For example, the F and OR substituents are π donors and σ acceptors and in consequence the SCSs of

Table 1.5 *^{1}H additive contributions to ethylene chemical shifts ($\Delta\delta$, ppm)*
$\delta(C{=}C.H) = 5.405 + \Delta\delta\ gem + \Delta\delta\ cis + \Delta\delta\ trans$



Substituent R	$\Delta\delta$ *gem*	$\Delta\delta$ *cis*	$\Delta\delta$ *trans*
H	0.0	0.0	0.0
Alkyl	0.45	−0.22	−0.28
Alkyl (cyclic)	0.69	−0.25	−0.28
CH_2OH	0.64	−0.01	−0.02
CH_2SH	0.71	−0.13	−0.22
CH_2X(X=F,Cl,Br)	0.70	0.11	−0.04
CH_2N	0.58	−0.10	−0.08
C=C	1.00	−0.09	−0.23
C=N	0.27	0.75	0.55
C≡C	0.47	0.38	0.12
C=O	1.10	1.12	0.87
COOH	0.97	1.41	0.71
COOR	0.80	1.18	0.55
CF_3	0.66	0.61	0.32
CHO	1.02	0.95	1.17
CO.N	1.37	0.98	0.46
CO.Cl	1.11	1.46	1.01
O.Al	1.22	−1.07	−1.21
O.CO.R	2.11	−0.35	−0.64
CH_2.CO;CH_2.CN	0.69	−0.08	−0.06
CH_2Ar	1.05	−0.29	−0.32
Cl	1.08	0.18	0.13
Br	1.07	0.45	0.55
I	1.14	0.81	0.88
N.Al	0.80	−1.26	−1.21
N.Ar	1.17	−0.53	−0.99
N.CO.	2.08	−0.57	−0.72
Ar	1.38	0.36	0.07
Ar(o-subs.)	1.65	0.19	0.09
S.R	1.11	−0.29	0.13
SO_2	1.55	1.16	0.93
F	1.54	−0.40	−1.02

F and OR at the geminal protons are large and positive whereas the corresponding SCSs at both the *cis* and *trans* vicinal protons are large and negative.

Conversely the carbonyl group is both a σ and π acceptor and this gives large positive SCSs at both the geminal and vicinal protons. The benzenes SCSs as may be anticipated lie between those of alkanes and olefins, though there is of course no β proton in substituted benzenes. For example, the γ (H.C.C.X) SCSs of the OH(OR) group is +0.38 ppm for ethanol (Table 1.4), −1.07 for the *cis* proton in ethylene (Table 1.5) and −0.56 for phenol (Table 1.6).

Table 1.6 *^{1}H substituent chemical shifts (Δδ) in benzenes*

Substituent	Δδ[a]		
	Ortho	Meta	Para
NO_2	0.95	0.26	0.38
$CO.OCH_3$	0.71	0.11	0.21
$CO.CH_3$	0.62	0.14	0.21
CHO	0.56	0.22	0.29
CN	0.36	0.18	0.28
$CH{=}CH_2$	0.13	0.04	−0.05
F	−0.29	−0.02	−0.23
Cl	0.03	−0.02	−0.09
Br	0.18	−0.08	−0.04
I	0.39	−0.21	0.00
OH	−0.56	−0.12	−0.45
OCH_3	−0.48	−0.09	−0.44
$O.CO.CH_3$	−0.25	0.03	−0.13
CH_3	−0.20	−0.12	−0.22
NH_2	−0.75	−0.25	−0.65
NMe_2	−0.66	−0.18	−0.67
CO.Ph	0.53	0.20	0.31
SO.Me	0.39	0.26	0.24
SO_2.Ph	0.69	0.26	0.27

[a] In ppm from benzene (δ_H, 7.341).

There have been many attempts to relate the substituent shifts in benzenes to the electron densities in the molecule, either total or π densities. It can be seen that strongly electron-withdrawing groups (NO_2, CO_2Me) deshield all the protons but the effect is largest at the *ortho* and *para* positions, as expected on simple resonance groups. The converse is true for the strongly electron-donating groups (NH_2, OH), while the halogens, as expected, show less pronounced effects. The general picture agrees with arguments based on electron densities. However, there are other long-range effects which contribute to ^{1}H chemical shifts and these will now be discussed.

1.5 Long-range Effects on ^{1}H Chemical Shifts

A pioneering investigation of the effects of substituent groups on distant protons in saturated compounds was given by Zurcher.[20] On this model the influence of a distant group on the chemical shift of a proton may be broken down into a number of separate contributions. These are:

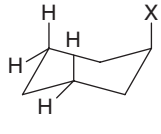
(1) Steric effects due to the proximity of the proton and the substituent ($\Delta\delta_S$).
(2) The electric field produced by the substituent polarizes the C—H bond of the proton considered which affects the proton chemical shift ($\Delta\delta_{EL}$).
(3) Magnetically anisotropic substituents will give rise to magnetic fields at the proton considered which do not average to zero over the molecular tumbling ($\Delta\delta_{AN}$).

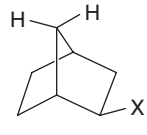
In addition for unsaturated compounds there are the effects due to the π densities and in aromatics there are the important ring current shifts. Finally there are the large shifts due to hydrogen bonding.

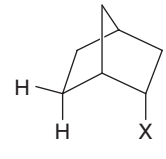
1.5.1 Steric (van der Waals) Effects

The earliest explanations of long-range substituent effects considered only the electric field and magnetic anisotropy of the substituents. However this explanation becomes questionable when the ^{1}H chemical shifts of saturated hydrocarbons are considered. These range over ca. 2 ppm. which is 20 % of the usual range of ^{1}H chemical shifts, yet these molecules possess neither magnetically anisotropic nor polar substituents. Clearly there are other factors determining the chemical shifts in hydrocarbons. It was then realized that the steric effect due to the proximity of the proton and the substituent was an important factor in ^{1}H chemical shifts. Some examples are shown in Table 1.7. Two contrasting effects can be seen. For each methylene group the proton nearer to the substituent experiences a deshielding effect roughly proportional to the size of the substituent. Also the other proton on the CH_2 group is generally shielded by the substituent. Fluorine is an exception (see below) but this applies even to the methyl group which is neither polar nor magnetically anisotropic. A possible explanation of this effect is as follows. The carbon electrons provide the dominant interaction with the substituent. The repulsion of the two electron clouds causes the electron cloud around the carbon to move away from the substituent. This would cause a deshielding of the closer hydrogen atom and a shielding of the more distant hydrogen on the methylene group as observed. This deshielding and associated shielding is called the 'push–pull' effect and will be considered in more detail in Chapters 4 and 6.

Table 1.7 *SCSs (ppm) of close substituents in cyclohexane and norbornane systems*[a]







X	H_{3ax}	H_{3eq}	H_{7syn}	H_{7ant}	H_{6en}	H_{6exo}
F	0.44	0.07	0.51	0.16	0.65	0.04
OH	0.46	−0.20	0.39	−0.06	0.72	−0.11
Cl	0.65	−0.18	0.59	0.06	0.84	−0.15
Br	0.68	−0.13	0.68	0.11	0.84	−0.07
Me	0.13	−0.15	0.15	−0.15	0.39	−0.20

[a] Data from Abraham.[21]

1.5.2 Electric Field Effects

An important interaction affecting the proton chemical shifts of molecules containing polar substituents is that due to the electric field of the substituent. In an early attempt to calculate the ^{1}H chemical shifts of fluoro- and chloro-substituted alkanes[22] it was noted that there

was a pronounced through space effect of the fluorine substituent on ^{1}H chemical shifts but in contrast to the other substituents investigated there was no push–pull effect for the fluorine substituent (cf. Table 1.7). This is illustrated in Figure 1.3 in which the deshielding due to the axial fluorine substituent in cyclohexane on the 3-axial proton may be compared with the very small effect of the equatorial substituent on the same proton.

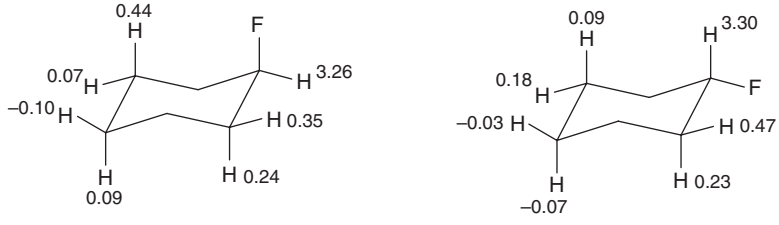


Figure 1.3 *Fluorine SCS (ppm) in axial and equatorial fluorocyclohexane.*

Also the deshielding due to the fluorine atom was better represented by an r^{-3} function than the r^{-6} function used for the other substituents. This suggested that the fluorine SCSs in the compounds examined were primarily due to the electric field produced by the fluorine atom and not due to steric effects. This seemed reasonable in that the fluorine atom was the only substituent atom of comparable size to the hydrogen atom (the hydrogen van der Waals radius is 1.2 Å and the fluorine 1.35 Å). Thus the replacement of a proton by a fluorine atom should not present any large steric perturbations. It will be shown later (Chapter 6) that the long-range (over >3 bonds) SCSs shown in Figure 1.3 can be quantitatively explained by calculating the electric field of the CF bond at the hydrogen atoms considered.

Anisotropic effects. The free circulation of electrons which gives rise to diamagnetic effects in spherically symmetric atoms can also occur around the axis of any linear molecule when the axis is parallel to the applied field. A good example is acetylene (RC≡CH). The electron circulation around the linear axis will give rise to a magnetic effect on neighbouring nuclei in exactly the same manner as any s electron (Figure 1.2). This gives shielding along the molecular axis (e.g. at the acetylenic proton) and deshielding perpendicular to this axis. On hybridization grounds we would expect the ^{1}H chemical shifts to be in the order of ethane, ethylene and acetylene. The actual shifts are acetylene (1.48δ) compared to ethane (0.88δ) and ethylene (5.31δ). The increased shielding of the acetylene protons is due to this diamagnetic circulation of the π electrons illustrated in Figure 1.4 which gives the sign of Δδ for the shielding contribution.

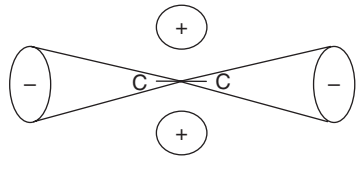


Figure 1.4 *The anisotropic shielding (Δδ) in an axially symmetric molecule such as acetylene.*

This effect occurs in all linear molecules. In the hydrogen halides HCl, HBr and HI, but not HF the same phenomenon gives rise to shielding at the protons and in the gas phase their proton chemical shifts are shielded with respect to TMS.[12] However, hydrogen bonding in solution deshields the protons. The large circulation of the electrons around the C—X bond in the halogens is treated in CHARGE in a similar manner to the acetylene case above (see Chapter 6, Section 6.3).

Most substituents are unsymmetric and therefore in principle magnetically anisotropic. However, in the CHARGE routine only unsaturated groups are regarded as anisotropic. In this case the circulation of the π electrons is less restricted about one molecular axis than the others. This produces a magnetic anisotropy and thus protons near the group will experience both shielding and deshielding effects depending on their position with respect to the anisotropic group.

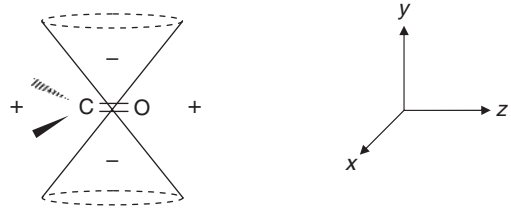
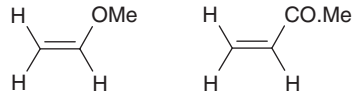


Figure 1.5 *Classical depiction of the shielding ($\Delta\delta$) of the carbonyl anisotropy.*

The most important anisotropic substituent is the carbonyl group. In this case the magnetic anisotropy shields nuclei lying in a cone whose axis is perpendicular to the C=O bond and deshields nuclei outside this cone (Figure 1.5). Thus, an aldehyde proton which lies outside this cone is deshielded due to this anisotropy and resonates at high frequencies (9.5–10.0δ). Figure 1.5 is an over simplification as the carbonyl group has no elements of symmetry and therefore has in principle three different magnetic susceptibilities along the three principal axes (Figure 1.5). This gives two anisotropic susceptibilities which are usually termed the parallel $\Delta\chi_{parl}(\chi_z - \chi_x)$ and perpendicular $\Delta\chi_{perp}(\chi_y - \chi_x)$ anisotropies (see Chapter 3, Section 3.5).

1.5.3 π-Electron Effects

In olefins and aromatic compounds the effects of the π electrons on the chemical shifts of the surrounding protons must be considered. There are two major effects, the direct effect of the π electrons on the carbon atoms on the neighbouring protons and the ring current shifts due to the circulation of the π electrons in the magnetic field. Gunther[23] compared the proton chemical shifts of benzene with similar charged species (cyclopentadiene anion and tropylium cation) and derived the very useful rule that the CH proton is shielded by ca. 10 ppm for a unit increase in the π-electron density at the attached carbon atom. This rule is used in the CHARGE program for both olefinic and aromatic compounds (see Chapters 4 and 5).



An illustrative example of this effect is found in the vinyl compounds above. The calculated excess π-electron density at the β carbon atom is −85.3 me (milli-electrons) for methyl vinyl ether and +51.6 me for acrolein. On Gunther's rule this gives shifts at the attached (vicinal) protons of −0.85 and +0.52 ppm. When compared to the observed SCSs of −1.07 (*cis*) and −1.21 (*trans*) for the ether and 1.12 (*cis*) and 0.87 (*trans*) for the ketone (Table 1.5) it is clear that this is a major contribution to the SCSs. Obviously there are other contributing effects. In the ketone the anisotropy of the carbonyl group makes an appreciable contribution.

Aromatic ring currents. An important contribution to proton chemical shifts in aromatic compounds is due to the aromatic ring current. When a molecule of benzene is oriented perpendicular to the applied magnetic field **B** (Figure 1.6), the π electrons are free to precess in exactly the same way as the s electrons in Figure 1.2. There is now a molecular circulation of the π electrons and the resulting ring current is shown in Figure 1.6. (Remember that the current flows in the opposite direction to the electrons.) Again the induced current gives rise to a magnetic moment which opposes the applied field and the ring current produces the magnetic field shown. Along the sixfold symmetry axis of the benzene ring, the extra magnetic field produced by the ring current *opposes* the applied field, giving a shielding effect. Conversely, at the benzene ring proton the ring current field *adds* to the external field, giving a deshielding effect. The ring current is only induced when the applied magnetic field is perpendicular to the benzene ring. In practice, the benzene molecules are rapidly rotating in solution and the NMR shift is the average over all the orientations. This gives an observed shift equal to one-third of the value in the orientation of Figure 1.6.

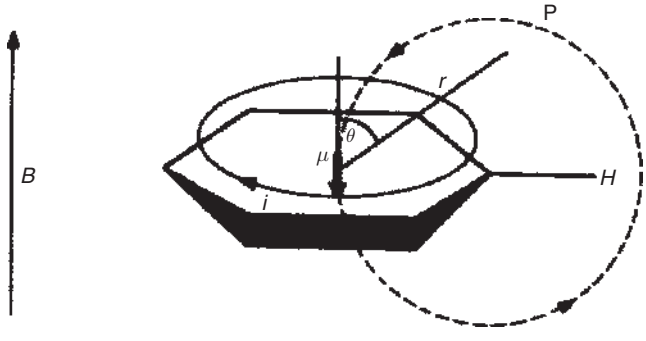


Figure 1.6 *The aromatic ring current of benzene.*

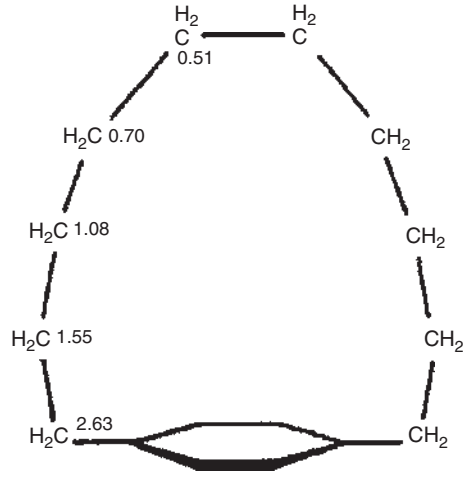
Many calculations of this ring current shift have been attempted. The simplest method is the equivalent dipole model of Pople.[24] In this the ring current shift is given by the field

of the equivalent dipole (μ) which is given, for any point P by Equation (1.9) where r and θ are as shown

$$\Delta\delta \text{ (ppm)} = \mu(1 - 3\cos^2\theta)/r^3 \tag{1.9}$$

in Figure 1.6. Thus, for $\theta = 0°$, i.e. above the benzene ring plane, $\Delta\delta$ is negative, i.e. there is a shielding effect and vice versa for $\theta = 90°$. Also note that when θ is 54.7°, i.e. ($\cos^2\theta = 1/3$) there is zero shift. This is the 'magic angle' in solid state NMR.

Many attempts have been made to estimate the ring current shift in benzene. The simplest is to compare the observed ^{1}H shifts in benzene (7.34δ) with the 2,3-olefinic protons of cyclohexa-l,3-diene (5.80δ) to give a ring current shift of 1.54 ppm. This ignores other effects such as the different hybridization of the benzene and olefenic protons, any other effects of the aromatic π-electrons, etc. The value of μ was obtained as 26.2 ppm Å^3 from a detailed analysis of the ^{1}H chemical shifts of a series of aromatic hydrocarbons.[25] For benzene ring protons, $r = 2.5$ Å, $\theta = 90°$; this gives a ring current shift of 26.2/2.5^3, i.e. 1.67 ppm, in good agreement with the observed data. More refined calculations of the magnetic field due to the two current loops have been performed[26–28] but the results are very similar to those using the simple equivalent dipole.



[10]-paracyclophane δ_H values

Many examples of this ring current effect are known. An interesting manifestation of the ring current occurs in [l0]-paracyclophane (above), in which the chemical shifts of the various methylene groups are due to their positions with respect to the aromatic ring, those directly above the ring being most shielded.

Two further examples are shown in Figures 1.7 and 1.8. In Figure 1.7 the olefinic protons in cyclohexene occur at 5.67 ppm, the corresponding protons in 1,4-dihydronapthalene at 5.91 ppm and the aromatic β protons in naphthalene at 7.48 ppm. A ring current shift is observed across the cyclohexene ring in dihydronapthalene but of decreasing intensity. In Figure 1.8 the difference in the chemical shifts of the methyl groups in 1-methylcyclohexene (1.63 ppm) and toluene (2.34 ppm) are again solely due to the ring current.

A more spectacular example is the proton spectrum of *meso* tetra(para-tolyl)porphyrin (Figure 1.8 (bottom)). The large macrocycle of the porphyrin ring is aromatic (it has 18 π electrons) and gives rise to a large ring current. As a consequence, the protons on the periphery of the porphyrin ring are deshielded, the pyrrole protons occurring at 8.84 ppm and the NH protons in the middle of the ring experience a large shielding of several ppm and consequently appear at -2.75 ppm. Indeed, this one spectrum encompasses the entire common ^{1}H NMR region, showing the dramatic effect of the ring current.

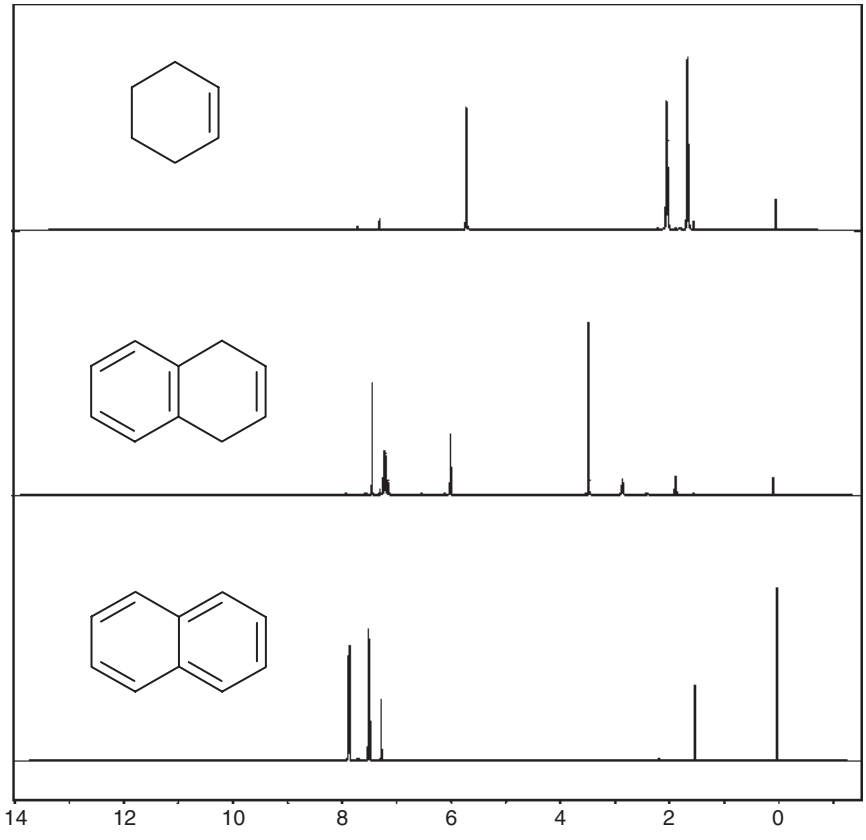


Figure 1.7 *The 400 MHz ^{1}H spectrum of cyclohexene (top), 1,4-dihydronapthalene (middle) and naphthalene (bottom) in $CDCl_3$ solution.*

Because of this large effect, the presence of a ring current is often used as a test for aromaticity. For example, in the annulenes (below), [16]-annulene has ^{1}H chemical shifts of 10.3δ (inner protons) and 5.28δ (outer protons), whereas [18]-annulene has shifts of -4.22δ (inner) and 10.75δ (outer). This shows very clearly that the $4n + 2$ annulene is aromatic, whereas the $4n$ annulene is not. Note both these results are for the low-temperature spectra. At room temperature, ring rotation processes take place, giving an averaged spectrum.

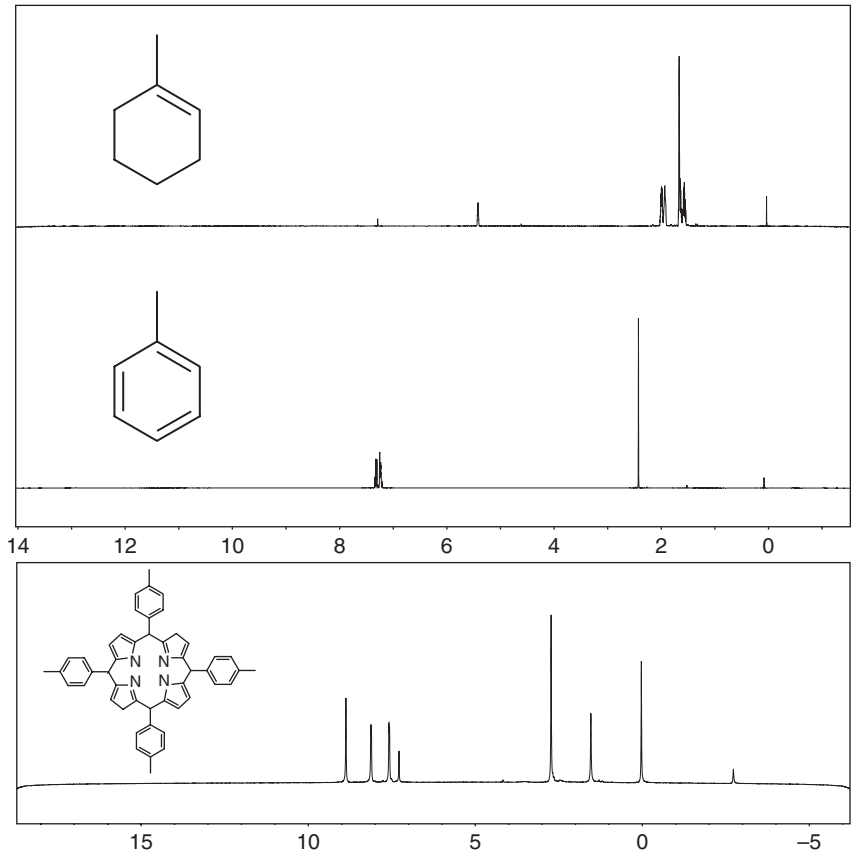
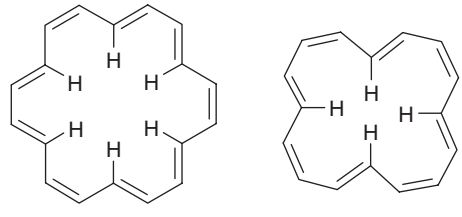


Figure 1.8 *The 400 MHz ^{1}H spectrum of 1-methyl cyclohexene (top), toluene (middle) and meso tetra (para tolyl) porphyrin (bottom) in $CDCl_3$ solution.*

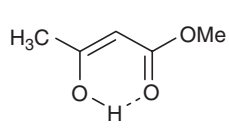
Finally, note that as the ring current is a magnetic effect, the ring current shift will be exactly the same (in ppm) for any nucleus. However, as all other nuclei have chemical shift ranges of greater than 200 ppm compared with ca. 10 ppm for protons, the ring current shifts are much less noticeable for all other nuclei.



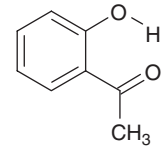
[18]- annulene [16]-annulene

1.5.4 Hydrogen Bonding Shifts

A hydrogen bond (X—H •••Y) is normally formed when both X and Y are electronegative atoms, usually O, N or halides. To a good approximation the interaction may be regarded as electrostatic in character, i.e. the charge distribution X—H •••Y determines the attractive energy of the bond, and, in consequence, when a hydrogen bond is formed, this charge distribution will be slightly enhanced. Thus, the hydrogen becomes more positive and atoms X and Y more negative. Therefore the proton will be deshielded, i.e. moved to increase δ on forming a hydrogen bond. This is precisely what is observed. In compounds capable of forming intermolecular hydrogen bonds (ROH, RNH_2), the proportion of H-bonded complexes and therefore the observed chemical shift will depend critically on concentration, solvent, etc. For example, the OH proton in neat ethanol is observed at 5.34δ but on dilution in $CDC1_3$ the OH signal moves to low frequencies until in dilute $CDC1_3$ solution it resonates at 1.1δ.



methyl acetoacetate



ortho-hydroxyacetophenone

Compounds in which intramolecular H-bonding occurs show, as expected, less dependence of the chemical shifts on dilution, but now the OH chemical shift will be deshielded compared to the analogous compound. For example, in phenol the OH signal moves from 7.45 to 4.60δ on increasing the dilution in $CDC1_3$, but the corresponding proton of o-hydroxyacetophenone occurs at 12.0δ but shows little change on dilution. A particular example of strong intramolecular hydrogen bonding occurs in enols, in which the OH signal is very deshielded. For example, in the enol form of methyl acetoacetate (shown above) the OH signal occurs at 12.1δ.

1.6 Tables of ^{1}H Chemical Shifts of Common Unsaturated and Saturated Cyclic Systems

Table 1.8 *^{1}H chemical shifts of some unsaturated cyclic systems*

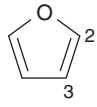
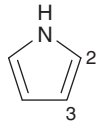
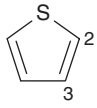
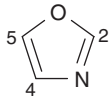
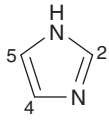
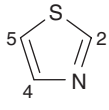
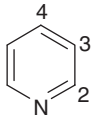
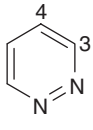
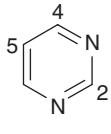
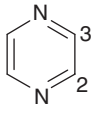
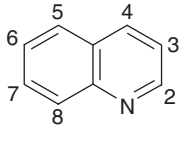
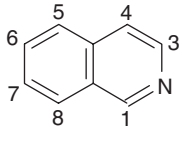
Molecule	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
	—	7.420	6.380						
	8.00	6.710	6.230						

Table 1.8 (*Continued*)

Molecule	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9
		7.310	7.090						
	—	7.90	—	7.15	7.68				
	—	7.74	—	7.13	7.13				
	—	8.88	—	7.98	7.41				
	—	8.609	7.266	7.657					
	—	—	9.220	7.560					
	—	9.250	—	8.770	7.270				
	—	8.600	8.600						
	—	8.915	7.377	8.139	7.803	7.533	7.709	8.114	
	9.251	—	8.522	7.635	7.808	7.680	7.594	7.955	

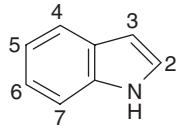
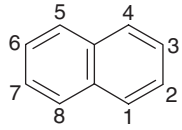
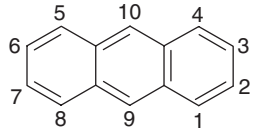
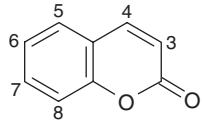
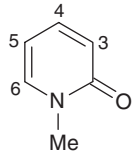
	—	7.207	6.558	7.647	7.115	7.185	7.396	
	7.844	7.477						
	8.009	7.467						8.431
	—	—	6.406	7.705	7.502	7.290	7.502	7.290
	3.540	—	6.530	7.350	6.170	7.330		

Table 1.9 *^{1}H chemical shifts of some saturated heterocyclic systems*

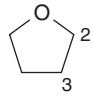
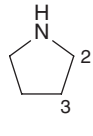
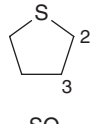
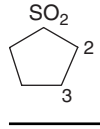
Molecule	H-1	H-2	H-3	H-4	H-5
	—	3.83	1.85		
	1.60	2.85	1.68		
	—	2.82	1.93		
	—	3.03	2.22		

Table 1.9 (*Continued*)

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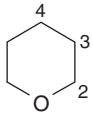
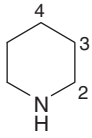
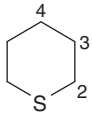
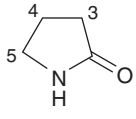
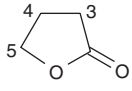
		3.67	1.63	1.67	
		1.50	2.80	1.53	1.48
		2.60	1.81	1.58	
	0.3				
		2.6			
	0.0	1.6			
		2.38			
	6.06	—	2.30	2.14	3.40
	—	—	2.490	2.260	4.320

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