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Standardization of chemical shifts of TMS and solvent signals in NMR solvents

Roy E. Hoffman*

Department of Organic Chemistry, The Hebrew University of Jerusalem, Safra Campus, Givat Ram, Jerusalem 91904, Israel

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The standard for chemical shift is dilute tetramethylsilane (TMS) in $CDCl_3$, but many measurements are made relative to TMS in other solvents, the proton resonance of the solvent peak or relative to the lock frequency. Here, the chemical shifts of TMS and the proton and deuterium chemical shifts of the solvent signals of several solvents are measured over a wide temperature range. This allows for the use of TMS or the solvent and lock signal as a secondary reference for other NMR signals, as compared with dilute TMS in $CDCl_3$ at a chosen temperature; 25 °C is chosen here. An accuracy of 0.02 ppm is achievable for dilute solutions, provided that the interaction with the solvent is not very strong. The proton chemical shift of residual water is also reported where appropriate. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H; ^{2}D; TMS; solvent; chemical shift; variable temperature

INTRODUCTION

Tetramethylsilane (TMS) is widely used as a reference for measuring proton chemical shifts and, in dilute solution, has been recommended by the International Union of Pure and Applied Chemistry (IUPAC) as a universal reference for all nuclides.[1] When data obtained in different solvents and at different sample temperatures are compared, the implicit assumption is often made that the chemical shift of TMS does not vary with temperature or solvent, but that assumption is wrong.

The common practice today is to measure the chemical shift relative to the solvent peak in the proton spectrum, to the signal of TMS (TSP or DSS in D_2O) or to rely on the spectrometer to set the frequency relative to the deuterium signal of the solvent.[1] In order to convert between measurements using these practices and the IUPAC standard of TMS in $CDCl_3$, it is necessary to measure the chemical shifts of the reference compounds, the proton solvent signals and the deuterium solvent signals.

The NMR resonant frequency of a sample is dependent on many factors, often ignored, in addition to the chemical shift. Bulk susceptibility combined with shape factor – termed the bulk magnetic susceptibility (BMS) shift[2] – affects the frequency by typically 3 ppm, although in most cases the effect varies only by about 1 ppm between samples.[3] Recent work has revealed the temperature dependence of the ^{1}H TMS chemical shift, and found practical means to determine the effect of susceptibility and shape factor on its observed shift.[4] Using these recent developments, it is now possible to tabulate accurate measurements of proton and deuterium chemical shifts of TMS and residual solvent and water signals in several common NMR solvents over a wide temperature range. This can be used, at least to a first approximation, to correctly determine the chemical shift without repeating tedious experiments. Of course, the accuracy will be compromised by concentration and ionic strength effects, but for dilute solutions these tables will usually be sufficient.

*Correspondence to: Roy E. Hoffman, Department of Organic Chemistry, The Hebrew University of Jerusalem, Safra Campus, Givat Ram, Jerusalem 91904, Israel. E-mail: roy@huji.ac.il
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EXPERIMENTAL

Instrumentation

NMR measurements were recorded on a Bruker DRX 400 spectrometer (^{1}H TMS resonance 400.130 MHz). ^{1}H NMR was measured using a 5 mm BBI probe and ^{3}He measurements were made using a similar BBI probe taken from a 300 MHz spectrometer, tuned to the helium frequency of the 400 MHz spectrometer (304.816 MHz) with the BB channel used for the lock.[5] ^{2}D NMR was measured using both probes. The assumed deuterium shifts for the solutions were as provided by the spectrometer manufacturer, relative to a basic frequency of 61.42239123 MHz at zero ppm. Relative to the IUPAC standard (400.13 MHz $\times 0.153\,506\,09 = 61.422\,391\,79$ MHz), the Bruker reference frequency, δ_{Bruker}, is at $-0.009\,2$ ppm. All the ^{1}H and ^{3}He spectra were acquired with deuterium locked to the methyl of methanol-d_4 at 61.42259392 MHz (basic frequency +3.30 ppm) or DMSO-d_6 at 61.42254417 MHz (basic frequency +2.49 ppm). All samples were spun at 20 Hz to reduce instability arising from convection[6,7] and allowed to thermally equilibrate for at least 15 min before acquisition. ^{1}H spectra were usually acquired with one transient and ^{2}D spectra with about 32 transients. The helium probe could not be tuned to 400 MHz proton, so temperature calibration had

to be achieved with deuterium spectra of methanol-d_4 and ethylene glycol (natural abundance deuterium). ^{3}He spectra were acquired with a single transient on a 2-amagat sample.

Sample preparation

^{3}He gas 99.9% from ICON, methanol-d_4 99.8+ a.% D from Aldrich DMSO-d_6 99.9 a.% D that contained 0.4% water itself and 7% deuterated from Aldrich were used without further purification. Ethylene glycol was dried under vacuum at room temperature to a pressure of 0.05 mbar. A stock solution of 3.0% v/v DMSO-d_6 in ethylene glycol was sealed in several ampoules that were opened immediately before use. $CDCl_3$ and TMS were dried with P_2O_5 and vacuum-transferred. $CDCl_3$ was transferred at room temperature while TMS was transferred from a dry ice/acetone bath (−80 °C) to reduce the transfer rate. Even so, opening the TMS valve for one second was sufficient. The resulting 'chloroform' sample was found to contain 0.04% TMS in $CDCl_3$ 99.76 a.% D. The second 'chloroform' sample that was used for high-pressure measurements contained 0.08% TMS. The DMSO-d_6 sample contained 0.2% TMS, and the methanol-d_4 sample contained 0.3% TMS.

D_2O '99.9%' with TSP (0.05% wt TSP) was measured to be 99.88 a.% D. D_2O '99.96%' and DSS was measured to be 99.963 a.% D with approximately 0.04% wt DSS. D_2O '99.96%' with TMS was measured to be 99.969% D with approximately 0.003% wt TMS dissolved at room temperature. The amount of TMS dissolved varied with temperature.

Acetone-d_6 (Sigma) was 99.9 a.% D and contained 0.1% water (30% deuterated) and 0.3% TMS. Acetonitrile-d_3 (CIL) was 99.8 a.% D and contained 0.05% water and 0.1% TMS. THF-d_8 was 99.8 a.% D and contained 0.02% water and 0.2% TMS.

Temperature measurement

The temperature was measured from the deuterium, $^{D}\Delta\delta$, or proton, $^{H}\Delta\delta$, chemical shift separation of methanol or glycol[4] (Eqns (1)–(3)).

$$T_{CD_3OD} = -14.68(^{D}\Delta\delta)^2 - 65.06^{D}\Delta\delta + 159.48 + 3.8 \times 10^{-15}e^{-13.2^{D}\Delta\delta} \quad (1)$$

$$T_{(CH_2OH)_2} = -3.22(^{H}\Delta\delta)^2 - 97.58^{H}\Delta\delta + 191.87 \quad (2)$$

Equation (2) was calibrated against a combination of CD_3OD and previously published[8,9] glycol scales, as previously described.[4]

$$T_{(CH_2OH)_2} = -2.80(^{D}\Delta\delta)^2 - 98.26^{D}\Delta\delta + 189.71 \quad (3)$$

Sample tubes

Samples were measured in a 5 mm tube containing a closed 4 mm tube attached to a 3 mm tube (Fig. 1). In some samples, the tube was closed in the middle with solid glass. The lock and temperature calibration solvent or mixture was in the outer tube while the ^{3}He gas or TMS in solution was sealed in the inner tube. For high-pressure samples, the tubes were annealed and tested in an oil bath before being inserted into the spectrometer to reduce the risk of damaging the instrument.

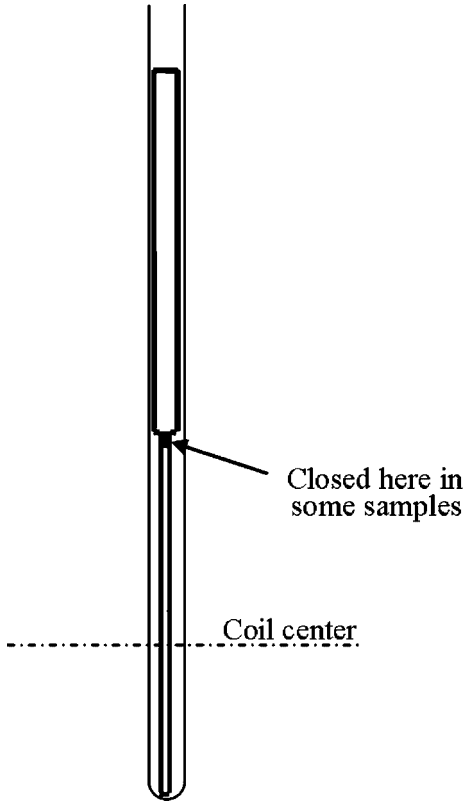

Figure 1. Sample tube arrangement.

RESULTS AND DISCUSSION

Evaluation of the BMS shift

The frequency of helium, proton and deuterium signals were calibrated against the deuterium signal of both methanol-d_4 and DMSO-d_6.[4] Comparing the two frequencies, the chemical shift of helium gas could be determined. Firstly, the observed frequency of TMS had to be corrected for the BMS effects using the published assumption that the molar susceptibility is practically constant throughout the temperature range.[4] To do this calculation, one needs to know the molar volume of the solvent. This was done using a modified Rackett equation, Eqn (4),[10] where a, b, c and d are the empirical parameters (that cannot be readily assigned units) for the modified Rackett equation, T is temperature in °C and V_M is the molar volume in cm^3 mol^{-1}. The Rackett equation is less accurate for very polar solvents, so for D_2O, the Kell equation[11] for water was fitted to the properties of D_2O[12] (Eqn (5)). The Rackett equation is accurate to within 1% for methanol despite its high polarity.[13]

$$V_M/\text{cm}^3\ \text{mol}^{-1} = \frac{b^{1+[1-(T+273.15)/c]^d}}{a} \quad (4)$$

$$V_M(D_2O)/\text{cm}^3\ \text{mol}^{-1} = \frac{20.0276 + 0.33806T}{1.1048 + 0.18878T - 8.2083 \times 10^{-6}T^2 - 7.4291 \times 10^{-8}T^3 + 3.0322 \times 10^{-10}T^4 - 7.9207 \times 10^{-13}T^5} \quad (5)$$

For $CHCl_3$, the parameters a, b, c and d are 0.0010841, 0.25810, 536.40 and 0.27410, respectively.[13] On the assumption that the parameters b, c and d are not significantly affected by deuteration, the parameter a was adjusted according to the ratio of molar volumes at 25 °C[14] (Eqn (6) where a_H and a_D are the Rackett parameters for the protiated and deuterated compounds, respectively; V_{MH} and V_{MD} are the molar volumes of the protiated and deuterated compounds, respectively; FW_H and FW_D are the formula weights in g mol^{-1} of the protiated and deuterated compounds, respectively and ρ_H and ρ_D are the densities in g cm^{-3} of the protiated and deuterated compounds, respectively) (Table 1).

$$a_D = \frac{a_H V_{MD}}{V_{MH}} = \frac{a_H FW_D \rho_H}{FW_H \rho_D} \tag{6}$$

$$\text{For } CDCl_3,\ a_D = \frac{0.0010841 \times 120.38 \times 1.492}{119.38 \times 1.500} = 0.0010874$$

For example, the molar volume of $CDCl_3$ at −17.5 °C is

$$\frac{0.25810^{1+[1-(-17.5+273.15)/536.40]^{0.27410}}}{0.0010874} = 76.35\ cm^3 mol^{-1}$$

The chemical shift is the sum of the observed shift (δ_o) and the BMS shift (δ_χ) (Eqn (7))[2] where BMS is a function of the weighted average shape factor ($\bar{\alpha}$) and volume susceptibility (κ).

$$\delta = \delta_o + \delta_\chi = \delta_o - \left(\frac{1}{3} - \bar{\alpha}\right)\kappa \tag{7}$$

The effective mean shape factor, $\bar{\alpha}$, is dimensionless (Eqn (7)) but is usually quoted in ppm for diamagnetic systems. Note that in Eqn (7) the volume susceptibility and shape factor are in SI units in line with IUPAC recommendations. Most published tables of susceptibility are in CGS units and must be converted to SI units by multiplying by 4π. The susceptibility is calculated according to Eqn (8) (where $\mathbf{x}_0$ is the observed point, $\mathbf{x}'$ is the surface vector, $\hat{\mathbf{z}}$ is unit vector perpendicular to the surface, β is the angle subtended by $\hat{\mathbf{z}}$ to the magnetic field and ds is a surface element) and averaged over the region detected as in Eqn (9) (where I is the response of the volume element, dv). Equations (7) and (8) are as explained in the literature[3,14–17] but Eqn (8) has been divided by 4π to convert it to SI units. The effective mean shape factor is between 0.0005 and 0.0013 for the configuration used in this work, but its calculation is complicated and is beyond the scope of this paper, as has been described previously.[3]

$$\alpha(\mathbf{x}_0) = \frac{1}{4\pi}\int \cos\beta \frac{[(\mathbf{x}_0 - \mathbf{x}')\cdot\hat{\mathbf{z}}]}{|\mathbf{x}_0 - \mathbf{x}'|^3} \mathrm{d}s \tag{8}$$

$$\bar{\alpha} = \frac{\int \alpha I \mathrm{d}v}{\int I \mathrm{d}v} \tag{9}$$

In order to determine the volume susceptibility over a wide temperature range, one first measures the volume susceptibility at one temperature and then calculates the molar susceptibility (Table 2). The volume susceptibility was measured at 27.3 °C relative to the volume susceptibility of D_2O ($\kappa_0 = -8.837$ ppm).[12] The volume susceptibility of the solvent is determined from the observed shift differences ($\Delta\delta$) at the vertical and magic angles using Eqn (10), where $\bar{\alpha}_0$

Table 1. Rackett parameters for the molar volume of solvents

Solvent	a	b	c	d
$CDCl_3$	0.0010874	258.10	536.40	0.27410
CD_3OD	0.0023332	270.73	512.50	0.24713
CD_3CN	0.0013085	226.42	545.50	0.28128
DMSO-d_6	0.0011050	251.89	729.00	0.33110
Acetone-d_6	0.0012316	257.60	508.20	0.29903
THF-d_8	0.0012583	280.84	540.15	0.29120

Table 2. Measurement of susceptibility using magic angle measurements[a]

Solvent	$^D\delta$ (Magic angle)[b]	$^D\delta_o$ (Vertical)	Shape factor	κ/ppm	Molar[c] vol./cm^3 mol^{-1}	χ_M/ppm cm^3 mol^{-1}
$CDCl_3$	7.287	4.253	0.00088	−9.127	80.49	−734.6
D_2O	4.765	1.829	0.00105	−8.837	18.14[d]	−160.3[e]
Acetone-d_6	1.934	0.059	0.00078	−5.639	74.08	−417.7
CD_3CN	1.961	−0.226	0.00078	−6.578	52.85	−347.6
THF-d_8	1.656	−0.968	0.00075	−7.892	81.91	−646.4
	3.515	0.890				
CD_3OD	3.243	1.053	0.00082	−6.587	40.58	−267.3
	4.757	2.560				
DMSO-d_6	2.631	0.065	0.00069	−7.715	71.72	−553.3

[a] At 27.3 °C as determined from the methanol deuterium chemical shift difference.[4]

[b] The values in this column are from Ref. 20

[c] Molar volume (with the exception of D_2O) is derived by combining the expansion rates of the protiated solvent[13] with the density of the deuterated solvent[21] at 25 °C.

[d] Derived from the density of D_2O.[12]

[e] Ref. 12.

is the shape factor of the D_2O sample. (Note that at the magic angle the observed shift is equal to the chemical shift).[18–20]

$$\kappa = \frac{\Delta\delta_{\text{overtical}} - \Delta\delta_{\text{magic}} + \left(\frac{1}{3} - \bar{\alpha}_0\right)\kappa_0}{1/3 - \bar{\alpha}} \tag{10}$$

The volume susceptibility is calculated from the molar volume and molar susceptibility, χ_M (-732.1 ppm cm^3 mol^{-1} (Ref. 3) for $CDCl_3$, Eqn (11)).

$$\kappa = \frac{\chi_M}{V_M} = \frac{a\chi_M}{b^{1+[1-(T+273.15)/c]^d}} \tag{11}$$

For example, at -17.5°C,

$$\kappa = \frac{-7.321 \times 10^{-10}\ \text{m}^3\ \text{mol}^{-1}}{7.635 \times 10^{-5}\ \text{m}^3\ \text{mol}^{-1}} = -9.589\ \text{ppm}$$

Note that 'ppm' is used interchangeably with '$\times 10^{-6}$'.

The observed frequency (ν_o) and the frequency due to chemical shift (ν) are related as follows (Eqns (12) and (13)).

$$\nu = \nu_{\text{ref}}(1 + \delta) \tag{12}$$

$$\nu = \nu_o - \nu_{\text{ref}}\left(\frac{1}{3} - \bar{\alpha}\right)\kappa = \nu_o - \nu_{\text{ref}}\left(\frac{1}{3} - \bar{\alpha}\right)\kappa\frac{a\chi_M}{b^{1+[1-(T+273.15)/c]^d}} \tag{13}$$

If the chemical shift of a reference signal (e.g. TMS) is known, then the chemical shift measured relative to the reference as being zero (δ') can be used to calculate the correct chemical shift (Eqn (14), where δ_{TMS} is the chemical shift of TMS).

$$\delta = \delta' + \delta_{\text{TMS}} + \delta'\delta_{\text{TMS}} \approx \delta' + \delta_{\text{TMS}} \tag{14}$$

No difference was observed whether the tubes were open or closed in the center. No correction for bulk susceptibility is required for ^{3}He because its susceptibility is negligible. However, for the prime reference of dilute TMS in $CDCl_3$ a correction is necessary. For example, at -17.5 °C, the corrected frequency of dilute TMS in $CDCl_3$ is:

$$\frac{400\,129\,692.3\ \text{Hz}}{1 - \left(\frac{1}{3} - 0.00086\right)9.589\ \text{ppm}} - 0 = 400130968.0\ \text{Hz}$$

The resonant frequency of ^{3}He gas was remeasured with a new sample because of suspicions that the previously reported measurement[4] had been carried out on a sample contaminated with air. This would be expected to cause a paramagnetic shift due to oxygen. Over most of the temperature range, no significant difference was observed but at the lowest temperatures a slight deviation was observed of up to 0.022 ppm at -108 °C. The observed ^{3}He frequency relative to C$\underline{\text{D}}_3$OD = 61422593.92 Hz, as in Eqn (15), and relative to 3.0% (C$\underline{\text{D}}_3$)$_2$SO in $(CH_2OH)_2$ = 61422544.17 Hz, as in Eqn (16).

$$304815664.9 - 0.717T - 0.00145e^{-0.0768T} \pm 0.4\ \text{Hz}(-108^\circ\text{C} < T < 65^\circ\text{C}) \tag{15}$$

$$304815778.9 - 0.2777T - 0.00087T^2 \pm 0.4\ \text{Hz}(2^\circ\text{C} < T < 187^\circ\text{C}) \tag{16}$$

The chemical shift of ^{3}He gas relative to dilute TMS in $CDCl_3$ was determined using Eqn (17)[22] where $^{\text{He}}\Xi$ is the IUPAC standard ratio for ^{3}He of 76.179437%.[1]

$${}^{\text{He}}\delta_o = {}^{\text{He}}\delta = \frac{{}^{\text{He}}\nu - {}^{\text{He}}\Xi^{\text{H}}\nu_{\text{TMS}}}{{}^{\text{He}}\Xi^{\text{H}}\nu_{\text{TMS}}} \tag{17}$$

^{3}He was sealed in a 3 mm tube inside an NMR tube containing the lock solvent, as described previously,[4] CD_3OD or the solution of DMSO-d_6 described above. The chemical shift of ^{3}He was plotted against temperature relative to TMS being zero at all temperatures. A cubic fit gave a ^{3}He chemical shift of -6.033 ± 0.003 ppm at 25 °C. However, it is the helium chemical shift that is actually constant and not the TMS chemical shift[4] because the helium is unaffected by intra- and intermolecular interactions.[23] Therefore, we can replace ν_{TMS} with ν_{Href} as the absolute standard and invert Eqn (17) to yield Eqn (18).

$$\nu_{\text{Href}} = \frac{{}^{\text{He}}\nu}{{}^{\text{He}}\Xi(1 + {}^{\text{He}}\delta)} \tag{18}$$

The standard chemical shift of TMS or any other proton signal is calculated by comparing it with the standard frequency ν_{Href} (Eqn (19) with $\Xi = 100\%$). Likewise, signals of any other nucleus may be calculated from Eqn (19) using the Ξ value for that nucleus.

$$\delta = \frac{\nu - \Xi\nu_{\text{Href}}}{\Xi\nu_{\text{Href}}} \tag{19}$$

Returning to the example of dilute TMS in $CDCl_3$ at -17.5 °C,

$$\begin{aligned} {}^{\text{He}}\nu &= 304815664.9 + 0.717 \times 17.5 - 0.00145\text{e}^{0.0768\times 17.5} \\ &= 304815677.4\ \text{Hz} \\ \nu_{\text{Href}} &= \frac{304815677.4\ \text{Hz}}{76.179\,437\% \times (1 - 6.033\ \text{ppm})} \\ &= 400130961.0\ \text{Hz} \\ \text{and } \delta &= \frac{400130968.0\ \text{Hz} - 400130961.0\ \text{Hz}}{400130961.0\ \text{Hz}} \\ &= 0.017 \pm 0.003\ \text{ppm} \end{aligned}$$

Note that '%' is used interchangeably with '$\times 10^{-2}$'.

The chemical shift of dilute TMS in $CDCl_3$ and other solvents (Fig. 2) with respect to temperature was fitted to Eqn (20), where the temperature, T, is in °C. The parameters for the equation are tabulated in Table 3, as are the chemical shifts of the solvent and residual water signals.

$$\delta = a + bT + cT^2 + dT^3 + \text{e}T^4 \tag{20}$$

With deuterium, there is a further complication because the spectrum is acquired without lock. As a result, the measured frequency, ν_{unlocked}, is shifted slightly from what it would be if locked, which is given by Eqn (21), where ν_o is the frequency that would be observed if the spectrum were locked, ν_{lock} is the lock frequency (61422593.92 Hz and 61422544.17 Hz for C$\underline{\text{D}}_3$OD and DMSO-d_6, respectively) and

Table 3. Parameters for chemical shifts

Solvent	Nucleus	Peak	δ(25 °C)/ppm	Bruker value/ppm	a	b	c	d	e	$S(\delta)$/ppm[a]	T_{min}/° C	T_{max}/° C
D_2O	^1H	DSS	−0.074		−0.071	-9.9×10^{-5}	-5.9×10^{-7}	0	0	0.0020	−6.5	172.9
D_2O	^1H	TMS	−0.094		−0.097	2.32×10^{-4}	-3.34×10^{-6}	8.2×10^{-9}	0	0.0010	−6.3	176.2
D_2O	^1H	TSP	−0.083		−0.083	1.05×10^{-4}	-4.81×10^{-6}	1.69×10^{-8}	0	0.0020	−7.7	152.0
D_2O	^1H	HOD	4.717		4.995	-1.1684×10^{-2}	2.433×10^{-5}	-5.82×10^{-8}	0	0.0054	−7.7	176.2
D_2O	^2D	D_2O	7.188	4.70	5.073	-1.1949×10^{-2}	2.442×10^{-5}	-5.61×10^{-8}	0	0.0052	−7.7	176.2
$CDCl_3$	^1H	TMS	0.000		0.011	-3.89×10^{-4}	-2.77×10^{-6}	1.16×10^{-8}	0	0.0026	−70.3	166.4
$CDCl_3$	^1H	$CHCl_3$	7.261		7.284	-8.63×10^{-4}	-1.97×10^{-6}	9.7×10^{-9}	0	0.0025	−70.3	166.4
$CDCl_3$	^2D	$CDCl_3$	7.290	7.24	7.311	-8.27×10^{-4}	-2.06×10^{-6}	1.15×10^{-8}	0	0.0027	−70.3	166.4
CD_3OD	^1H	TMS	−0.106		−0.094	-4.02×10^{-4}	-3.17×10^{-6}	1×10^{-10}	1.30×10^{-10}	0.0060	−110.6	126.4
CD_3OD	^1H	CHD_2OD	3.206		3.211	-9.2×10^{-5}	-3.56×10^{-6}	-6.7×10^{-9}	1.27×10^{-10}	0.0042	−110.6	75.7
CD_3OD	^1H	CD_3OH	4.761		4.983	-8.595×10^{-3}	-1.115×10^{-5}	-2.60×10^{-8}	-1.80×10^{-10}	0.0043	−110.6	75.7
CD_3OD	^2D	CD_3OD	3.244	3.30	3.250	-1.39×10^{-4}	-3.82×10^{-6}	-5.9×10^{-9}	1.89×10^{-10}	0.0046	−110.6	126.4
CD_3OD	^2D	CD_3OD	4.772		4.999	-8.676×10^{-3}	-1.326×10^{-5}	-5.92×10^{-8}	1.53×10^{-10}	0.0140	−110.6	126.4
CD_3CN	^1H	TMS	−0.010		0.004	-5.39×10^{-4}	-1.76×10^{-6}	1.32×10^{-8}	0	0.0032	−50.1	160.3
CD_3CN	^1H	CHD_2CN	1.930		1.956	-1.037×10^{-3}	-1.59×10^{-6}	1.10×10^{-8}	0	0.0031	−50.1	160.3
CD_3CN	^1H	H_2O	2.132		2.241	-4.397×10^{-3}	2.15×10^{-6}	0	0	0.0025	−50.1	160.3
CD_3CN	^2D	CD_3CN	1.964	1.93	1.990	-1.022×10^{-3}	-1.40×10^{-6}	1.08×10^{-8}	0	0.0032	−50.1	160.3
DMSO-d_6	^1H	TMS	0.074		0.086	-4.59×10^{-4}	0	0	0	0.0022	16.8	179.5
DMSO-d_6	^1H	DMSO-d_5	2.578		2.599	-8.83×10^{-4}	8.1×10^{-7}	0	0	0.0019	16.8	179.5
DMSO-d_6	^1H	H_2O	3.403		3.528	-5.002×10^{-3}	0	0	0	0.0076	16.8	179.5
DMSO-d_6	^1H	HOD	3.383		3.514	-5.224×10^{-3}	0	0	0	0.0014	16.8	51.2
DMSO-d_6	^2D	DMSO-d_6	2.633	2.49	2.656	-9.30×10^{-4}	1.09×10^{-6}	0	0	0.0020	16.8	179.5
Acetone-d_6	^1H	TMS	−0.161		−0.153	-2.71×10^{-4}	-2.31×10^{-6}	1.52×10^{-8}	0	0.0041	−101.6	154.4
Acetone-d_6	^1H	Acetone-d_5	1.892		1.911	-7.64×10^{-4}	-1.36×10^{-6}	1.16×10^{-8}	0	0.0049	−101.6	154.4
Acetone-d_6	^1H	H_2O	2.675		2.874	-8.134×10^{-3}	5.78×10^{-6}	0	0	0.0044	−101.6	66.1
Acetone-d_6	^1H	HOD	2.641		2.842	-8.188×10^{-3}	6.08×10^{-6}	0	0	0.0045	−101.6	66.1
Acetone-d_6	^2D	Acetone-d_6	1.936	2.04	1.953	-6.83×10^{-4}	0	0	0	0.0050	−101.6	154.4
THF-d_8	^1H	TMS	−0.101		−0.094	-2.22×10^{-4}	-3.10×10^{-6}	1.79×10^{-8}	0	0.0039	−109.2	165.9
THF-d_8	^1H	THF-d_7 H2	3.473		3.479	-2.39×10^{-4}	-1.93×10^{-6}	3.77×10^{-8}	0	0.0040	−109.2	61.6
THF-d_8	^1H	THF-d_7 H3	1.620		1.630	-3.29×10^{-4}	-2.93×10^{-6}	2.12×10^{-8}	0	0.0046	−109.2	146.9
THF-d_8	^1H	H_2O	2.356		2.496	-5.474×10^{-3}	-5.27×10^{-6}	3.61×10^{-8}	0	0.0043	−109.2	124.3
THF-d_8	^2D	THF-d_8 D2	3.515		3.520	-1.77×10^{-4}	-9.5×10^{-7}	6.0×10^{-9}	0	0.0041	−109.2	145.2
THF-d_8	^2D	THF-d_8 D3	1.676	1.73	1.665	-2.73×10^{-4}	-9.1×10^{-7}	6.0×10^{-9}	0	0.0036	−109.2	145.2

[a] Precision is defined as the error deviation from the fitted polynomial. In most cases, an error deviation of 0.01 ppm can be assumed to represent the accuracy of the chemical shift. However, it is advised not to rely on the chemical shifts to an accuracy better than 0.02 ppm.

MRC

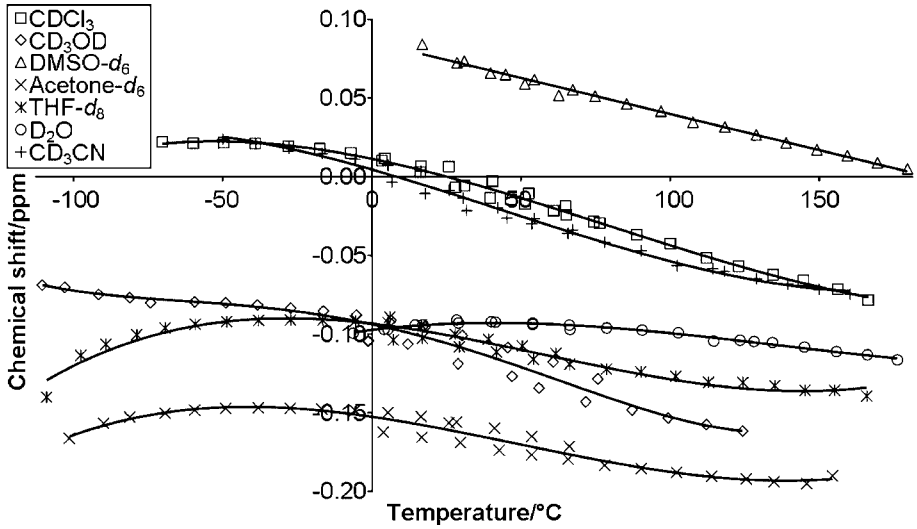

Figure 2. The chemical shift of dilute TMS as a function of temperature in several deuterated solvents relative to dilute TMS in $CDCl_3$ at 25 °C.

ν' is the frequency of the unreferenced lock peak in the unlocked spectrum (Eqn (21)).

$$\nu_o = \frac{\nu_{\text{unlocked}}\nu_{\text{lock}}}{\nu'} \tag{21}$$

For $CDCl_3$ at −17.5 °C, the calculation would proceed as follows, using Eqns (9), (4) and (7) in that order:

$$\nu_o = \frac{61422791.11\text{ Hz} \times 61422593.92\text{ Hz}}{61422596.61\text{ Hz}} = 61422788.42\text{ Hz}$$

$$\nu = \frac{61422788.42\text{ Hz}}{1 + \left(\frac{1}{3} - 0.00086\right) 9.589\text{ ppm}} = 61422984.25\text{ Hz}$$

$$\delta = \frac{61422984.25 - 15.350609\% \times 400130959.0}{15.350609\% \times 400130959.0} = 7.249\text{ ppm}$$

The DMSO-d_6 signal in glycol was often weak with respect to the solvent signal, so it was often more appropriate to lock on to the solvent signal. In this case, the unadjusted standard frequency, ν'_{Href}, needed to be changed to take into account the different lock (Eqn (22)). This also applied to the case of CD_3OD when measured against CD_3OD in the outer tube. The different shape factors led to a frequency difference of about 0.03 ppm. The frequency of the reference (DMSO-d_6 or CD_3OD, ${}^{D}\nu_{\text{ref}}$) is divided by one plus its tabulated chemical shift (2.49 or 3.30 ppm, $\delta_{\text{ref.table}}$). This is then multiplied by one plus the tabulated chemical shift of the lock signal ($\delta_{\text{lock-table}}$) plus the spectrometer reference chemical shift (in this case $\delta_{\text{Bruker}} = -0.0092$ ppm) and divided by the frequency of the lock in the unlocked deuterium spectrum (${}^{D}\nu_{\text{lock}}$).

$$\begin{aligned}\nu_{\text{Href}} &= \frac{\nu'_{\text{Href}}\,{}^{D}\nu_{\text{ref}}(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})}{{}^{D}\nu_{\text{lock}}(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}})} \\ &= \frac{\nu'_{\text{Href}}(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})}{(1 + {}^{D}\delta_{\text{lock}})(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}})}\end{aligned} \tag{22}$$

In the case of CD_3OD, the deuterium signals arising from the inner and outer tubes were too close together in frequency for the lock mechanism to separate them. The reference frequency was determined by measuring the deuterium spectrum of a double tube containing CD_3OD in both chambers at two temperatures. A linear fit to the frequency difference was made. This was applied as a correction to a single tube measurement at all the other temperatures. Therefore, in this case, ${}^{D}\nu_{\text{ref}}$ (Eqn (22)) is the interpolated corrected frequency and ${}^{D}\nu_{\text{lock}}$ is the measured deuterium frequency.

The deuterium spectrum can be analyzed with respect to the chemical shift rather than to the resonant frequency as in Eqn (22) by combining it with Eqn (12). The result is more complicated but can be approximated to a simple expression because the chemical shift difference between the lock and the reference is never more than a few ppm (Eqn (23)).

$$\begin{aligned}\delta_o &= \frac{\nu_o - \nu_{\text{ref}}}{\nu_{\text{ref}}} \\ &= \frac{\nu'_o - \dfrac{\nu_{\text{Href}}(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})}{(1 + {}^{D}\delta_{\text{lock}})(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}})}}{\dfrac{\nu_{\text{Href}}(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})}{(1 + {}^{D}\delta_{\text{lock}})(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}})}} \\ &= \frac{\begin{array}{l}\nu_{\text{Href}}(1 + \delta'_o)(1 + {}^{D}\delta_{\text{lock}})(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}}) \\ -\nu_{\text{Href}}(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})\end{array}}{\nu_{\text{Href}}(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})} \\ &= \frac{\begin{array}{l}(1 + \delta'_o)(1 + {}^{D}\delta_{\text{lock}})(1 + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}}) \\ -(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})\end{array}}{(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}})} \\ &= \frac{\begin{array}{l}\delta'_o + {}^{D}\delta_{\text{lock}} + {}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}} + \delta'_o{}^{D}\delta_{\text{lock}} + \\ \delta'_o({}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}}) + {}^{D}\delta_{\text{lock}}{}^{D}\delta_{\text{ref-table}} + \delta'_o{}^{D}\delta_{\text{lock}} \\ \times({}^{D}\delta_{\text{ref-table}} + \delta_{\text{Bruker}}) - {}^{D}\delta_{\text{ref}} - {}^{D}\delta_{\text{lock-table}} \\ -\delta_{\text{Bruker}} - {}^{D}\delta_{\text{ref}}({}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})\end{array}}{(1 + {}^{D}\delta_{\text{ref}})(1 + {}^{D}\delta_{\text{lock-table}} + \delta_{\text{Bruker}})} \\ &\approx \delta'_o + {}^{D}\delta_{\text{lock}} + {}^{D}\delta_{\text{ref-table}} - {}^{D}\delta_{\text{ref}} - {}^{D}\delta_{\text{lock-table}}\end{aligned} \tag{23}$$

Estimation of errors

The precision, $S(\delta)$, of the chemical shifts can be determined by measuring the scattering around the fitted line and

Table 4. Comparison of TMS chemical shifts measured in this work as compared with published results ($CDCl_3$ is set to zero as the standard)

	Acetone-d_6	$CDCl_3$	D_2O	DMSO-d_6	CD_3OD	THF-d_8
This work	−0.161	0.000	−0.093	0.074	−0.106	−0.120
Ref. 24	−0.16	0.000	−0.08	0.06	−0.11	−0.14[a]

[a] Misprinted as −0.02 in the reference.

is typically 0.004 ppm. The accuracy is more difficult to ascertain. There are inconsistencies between chemical shifts measured relative to CD_3OD and those measured relative to DMSO-d_6. This leads to an apparent splitting of the data in some of the diagrams and indicates that the inherent accuracy of the method is less than what the precision suggests. One could use arguments for attempting to use the assumed accuracy of the susceptibility. Comparisons of these results with published results[24] show that these estimations are inaccurate. There, the accuracy of the chemicals shifts was given as 0.04 ppm with most of the error being due to inaccuracy of susceptibility measurement based on gross line distortions at the vertical angle. Comparison with the values in this work (Table 4), based on more accurate susceptibility measurements by comparing vertical and magic angle measurements, shows that the error deviation as compared to that in Ref. 24 is 0.013 ppm. The susceptibility, dependent on the density of the liquid, is also the main error factor in this work. The accuracy of the modified Rackett equation used in this work for estimating the liquid density is on average 1%.[25] A 1% error in density and hence susceptibility would lead to a 0.03 ppm error at temperatures far from the standard 25 °C. However, for compounds that are not highly polar (such as acetone, chloroform, DMSO and tetrahydrofuran (THF)) the average error is 0.2[26] to 0.3%,[27] which would lead to a chemical shift error of 0.006 to 0.009 ppm at extreme temperatures. For D_2O, the Kell equation[11] was used instead of the Rackett equation[10] to improve accuracy. The standard error of the chemical shift near room temperature in this work is estimated to be 0.005 ppm increasing to 0.009 ppm at extreme temperatures with the exception of

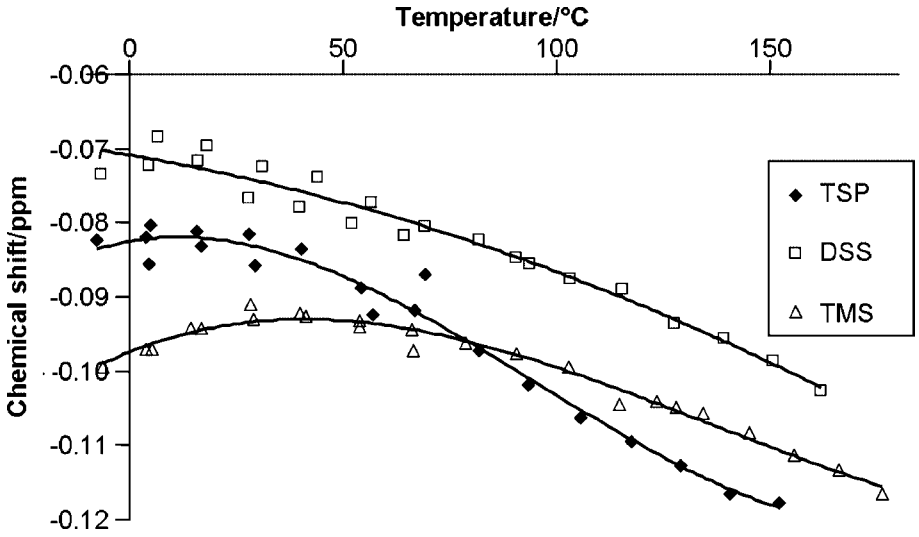

Figure 3. The chemical shifts of TMS, TSP and DSS in D_2O as a function of temperature.

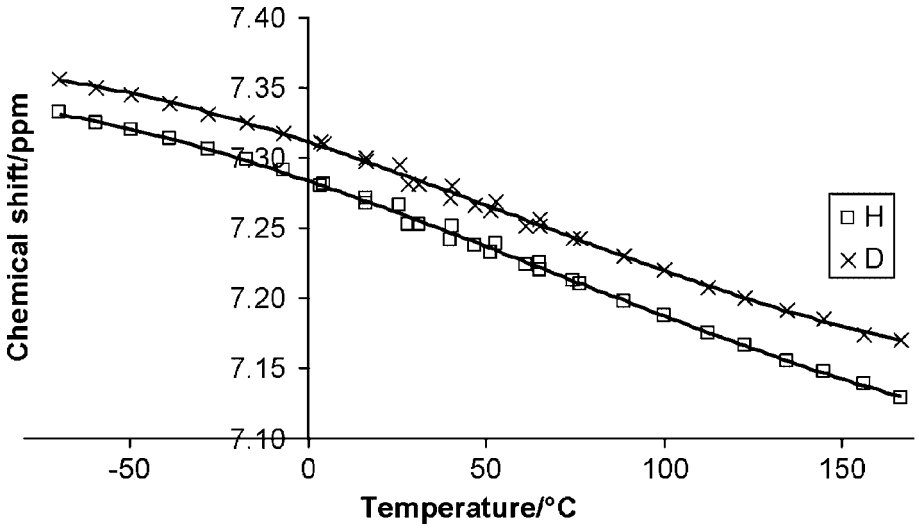

Figure 4. The ^1H and ^2D chemical shifts of the solvent signal of $CDCl_3$ as a function of temperature.

CD_3OD, where it may be as high as 0.03 ppm at extreme temperatures.

In most cases, therefore, the values given in this work can be relied upon to within 0.02 ppm for dilute samples where the interaction with the solvent is not very strong. Examples of very strong interactions with the solvent include acids in D_2O and paramagnetic compounds. If in doubt about the concentration effect, the sample should be measured at different concentrations and the observed shift extrapolated to zero concentration. The observed shift at zero concentration can then be used to calculate the chemical shift as described above. However, it should be noted that the concentration effect measured by this method is in the observed shift and not in the chemical shift.

Chemical shift referencing

The IUPAC 2001 definition[1] gives 0 ppm as the chemical shift of dilute TMS in $CDCl_3$. However, the chemical shift of TMS varies slightly with temperature, typically by −0.0004 ppm/°C. So, a temperature of 25 °C has been

Table 5. Comparison of the IUPAC 2001[1] and IUPAC-IUBMB-IUBAP 1998[28] chemical shift standards

IUPAC 2001			IUPAC-IUBMB-IUBAP 1998			
Nucleus	Secondary ref.	Ξ/%	Secondary ref.	Ξ as published	Ξ adjusted	δ_{ref}[a]
^{1}H	$TMS/CDCl_3$	100.000000	DSS/D_2O	100.000000	99.9999930	−0.07
^{2}D	$TMS\text{-}d_{12}/CDCl_3$	15.350609	DSS/D_2O	15.3506088	15.3506077	−0.08
^{13}C	$TMS/CDCl_3$	25.145020	DSS/D_2O	25.1449530	25.1449512	−2.74
^{15}N	CH_3NO_2	10.136767	NH_3	10.1329118	10.1329111	−380.40
^{31}P	H_3PO_4	40.480742	$(CH_3O)_3PO/D_2O$	40.4808636	40.4808607	2.93

[a] δ_{ref} is the chemical shift of the IUPAC-IUBMB-IUBAP 1998 standard on the IUPAC 2001 scale.

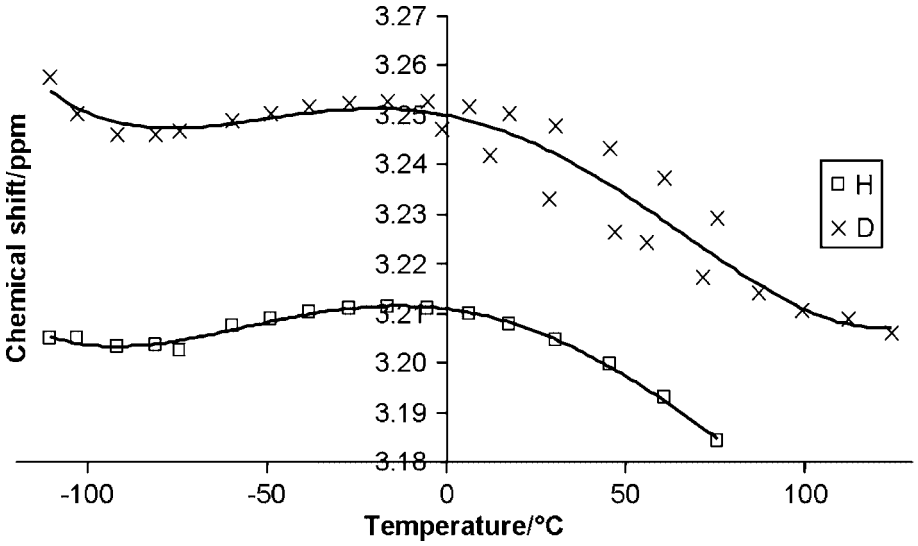

Figure 5. The ^{1}H and ^{2}D chemical shifts of methyl signals in CD_3OD as a function of temperature.

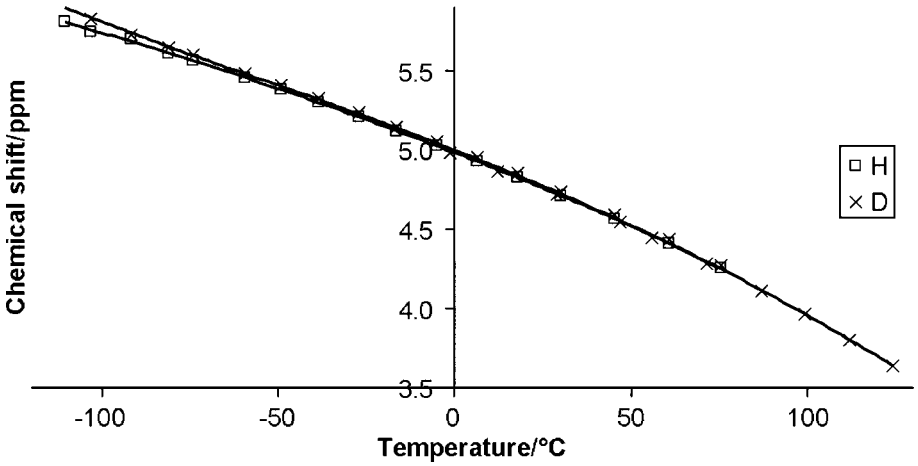

Figure 6. The ^{1}H and ^{2}D chemical shifts of hydroxyl signals in CD_3OD as a function of temperature.

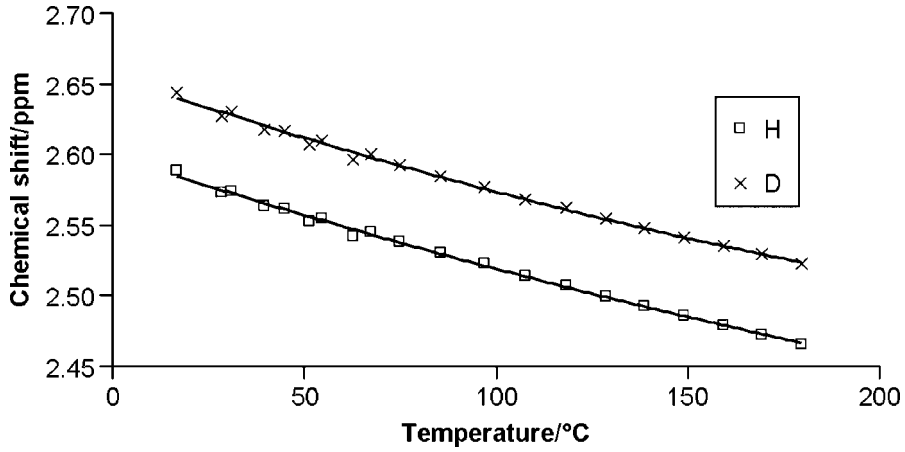

Figure 7. The ^{1}H and ^{2}D chemical shifts of DMSO-d_6 as a function of temperature.

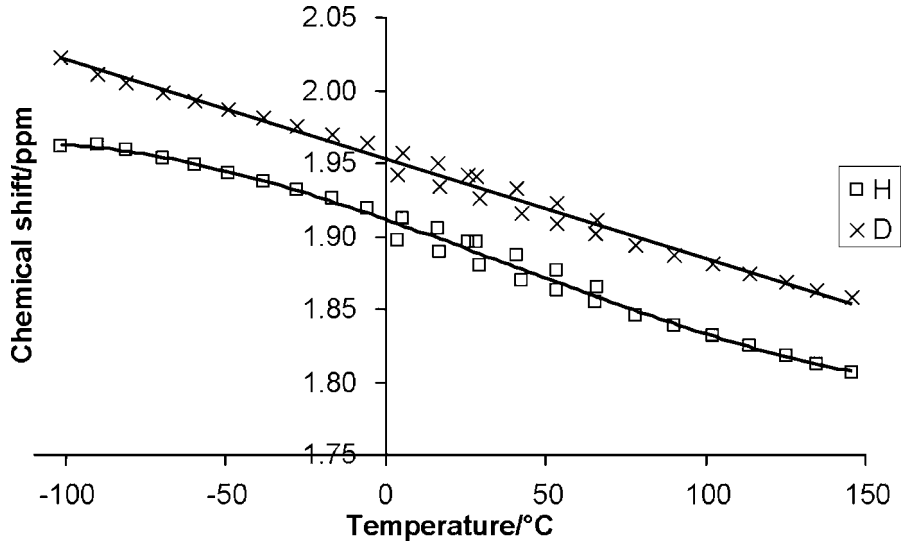

Figure 8. The ^{1}H and ^{2}D chemical shifts of acetone-d_6 as a function of temperature.

chosen here as the standard temperature, even though IUPAC has not defined a standard temperature for chemical shift referencing. The chemical shift of TMS differs by up to 0.24 ppm between the selected nonaromatic solvents. However, the chemical shift of TMS in aromatic solvents[24] (not measured in this work) is significantly lower due to $\sigma-\pi$ bonding between the TMS and the solvent: benzene-d_6 at -0.45 ppm, toluene-d_8 at -0.42 ppm and nitrobenzene-d_5 at -0.64 ppm, all at 25 °C.

TMS is not very soluble in D_2O, yielding a 0.003% solution at room temperature. While this is detectable by ^{1}H NMR, the similar but more soluble compounds TSP and DSS are more widely used, as their ^{1}H chemical shifts are within 0.03 ppm (Table 3, Fig. 3) of that of TMS. The IUPAC-IUBMB-IUBAP 1998 standard[28] adopts DSS in D_2O as the prime chemical shift standard. However, at 25 °C, this is -0.07 ppm as compared to the IUPAC 2001 standard.[1] A comparison of the two standards is shown in Table 5. The largest discrepancy is for ^{15}N where very different standards were chosen. As the IUPAC 2001 standard sets the Ξ ratios permanently irrespective of future, more accurate, measurements,[1] the previous IUPAC-IUBMB-IUBAP 1998Ξ ratios are adjusted (Table 5, column Ξ adjusted) to fit the IUPAC 2001 standard.

The spectrum can be referenced to the deuterium signal. The chemical shift at the proton reference frequency (e.g. 400.13 MHz for a 400 MHz Bruker spectrometer) should be set to $\delta_{\text{lock-table}} + \delta_{\text{Bruker}} - \delta_{\text{lock}}$. For example, for $CDCl_3$, δ_{lock} is 7.290 ppm and $\delta_{\text{lock-table}}$ is 7.24 ppm (Table 3, Fig. 4), so the reference frequency of 400.13 MHz is at -0.041 ppm. Referencing to the lock is dependent on the lock phase. A grossly dephased lock, apart from being difficult to lock, leads to a deviation of about 0.03 ppm from the correct chemical shift. For small phasing errors of up to 20°, the effect is approximately 0.0001 ppm/deg. In addition, the linewidth of the deuterium signal in ppm is much larger than the proton linewidth. Therefore, more accurate results are achieved by referencing to a signal in the proton spectrum.

Most of the solvent signal chemical shifts (Table 3, Figs 4–12) vary by less than 0.001 ppm/ °C, and so can be reliably used for calibration. However, the hydroxyl signal in CD_3OD and the D_2O solvent signal have temperature dependences that are an order of magnitude larger with that of D_2O being -0.011 ppm/ °C at room temperature. As a result, accurate temperature calibration is required if they are to be used as chemical shift references. The same is true of residual water signals in other solvents that are, in

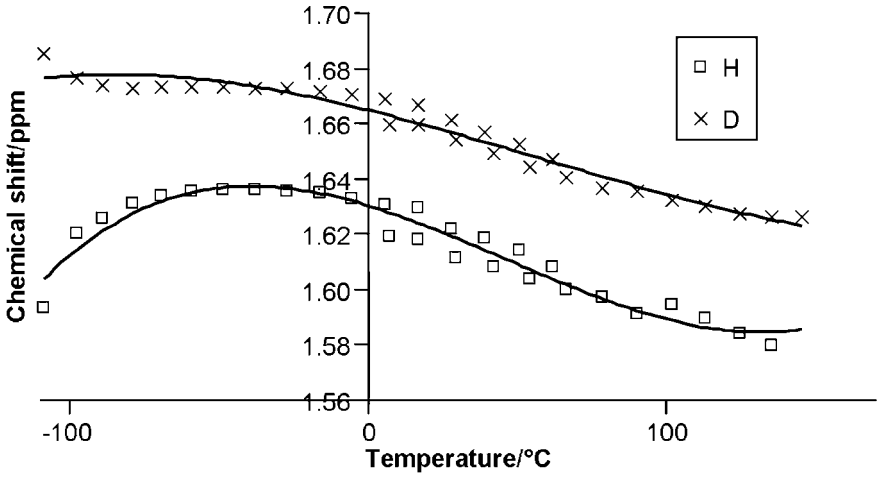

Figure 9. The ^{1}H and ^{2}D chemical shifts of THF-d_8 at position 3 as a function of temperature.

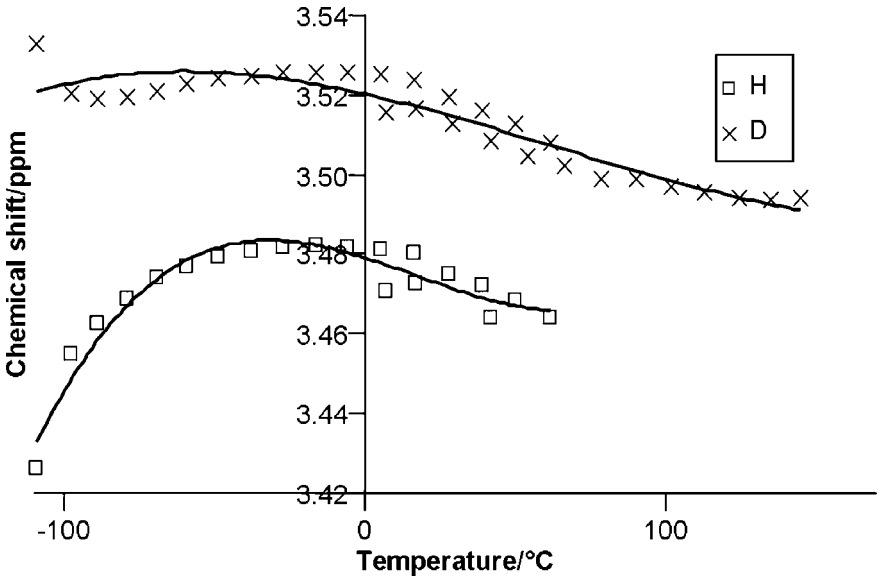

Figure 10. The ^{1}H and ^{2}D chemical shifts of THF-d_8 at position 2 as a function of temperature.

addition, very sensitive to acidic impurities. These residual water signals are therefore not recommended as chemical shift references, especially as the more reliable solvent signal is also available for this purpose. However, the tabulated water chemical shift can be helpful in identifying the water signal in the spectrum.

In the case of $CDCl_3$, the chemical shift of the residual water is very dependent on the photo-oxidation of the solvent (Scheme 1). The water signal chemical shift in vacuum-distilled $CDCl_3$ is approximately 0.8 ppm at 25 °C but very quickly returns to the more familiar 1.5 ppm on exposure to air. The water chemical shift in $CDCl_3$ is not reported here because consistent results could not be achieved.

CONCLUSIONS

Proton chemical shifts of TMS and proton and deuterium chemical shifts of solvent signals have been measured in several solvents over a wide temperature range. These graphs and equations make the measurement of the chemical shift effect of varying temperatures and solvents practical and easy for the first time. This can be achieved by comparing the proton signal of TMS with the proton signal of the residual solvent or with the deuterium (usually the lock) signal of the solvent. This method is applicable to an accuracy of 0.02 ppm for dilute solutions in which the interaction with the solvent is not very strong.

$$CDCl_3 + \tfrac{1}{2}O_2 + h\nu \rightarrow CCl_2O + DCl$$

Scheme 1

Acknowledgements

I thank the Margaret Thatcher Center of Interdepartmental Scientific Equipment for NMR facilities. This work was undertaken as part of an IUPAC Project[29] and was supported in part by IUPAC. The results presented here will be submitted to the project task group for inclusion in their report and eventual publication as an IUPAC recommendation after appropriate review and public comment. Until then, these results should not be considered as having been endorsed by IUPAC. I thank the other members of the IUPAC task group for useful discussions.

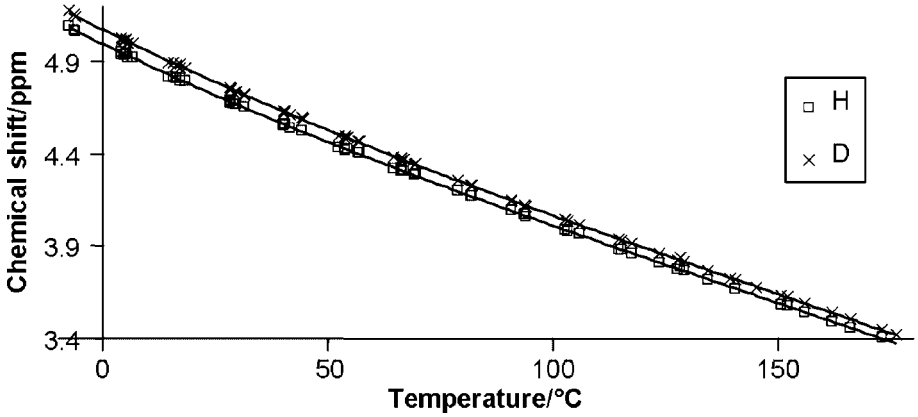

Figure 11. The ^{1}H and ^{2}D chemical shifts of D_2O as a function of temperature.

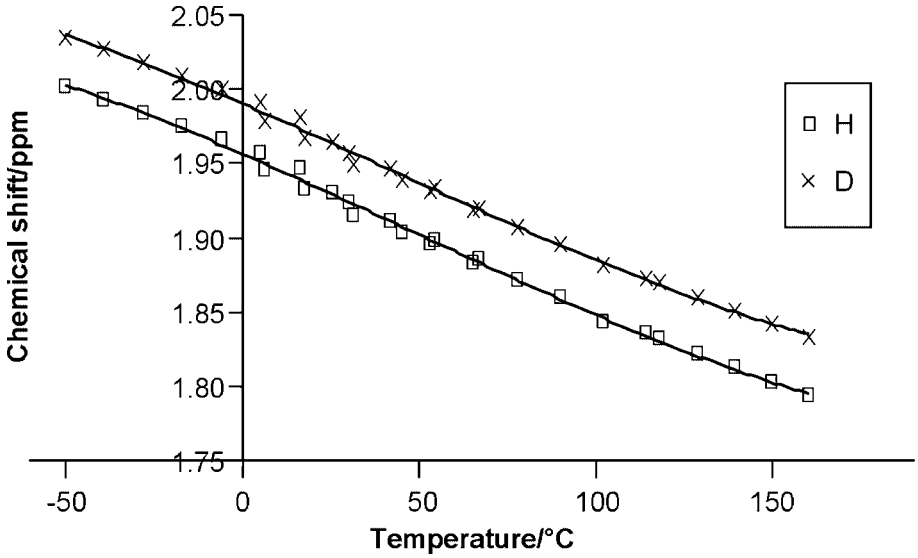

Figure 12. The ^{1}H and ^{2}D chemical shifts of CD_3CN as a function of temperature.

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