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^{1}H chemical shifts in NMR: Part 23,† the effect of dimethyl sulphoxide *versus* chloroform solvent on ^{1}H chemical shifts

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The ^{1}H chemical shifts of 124 compounds containing a variety of functional groups have been recorded in $CDCl_3$ and DMSO-d_6 (henceforth DMSO) solvents. The ^{1}H solvent shift $\Delta\delta = \delta(\text{DMSO}) - \delta(CDCl_3)$ varies from −0.3 to +4.6 ppm. This solvent shift can be accurately predicted (rms error 0.05 ppm) using the charge model of α, β, γ and long-range contributions. The labile protons of alcohols, acids, amines and amides give both, the largest solvent shifts and the largest errors. The contributions for the various groups are tabulated and it is shown that for H.C.C.X γ-effects (X = OH, NH, =O, NH.CO) there is a dihedral angle dependence of the γ-effect. The group contributions are discussed in terms of the possible solvent–solute interactions. For protic hydrogens, hydrogen bonding is the dominant interaction, but for the remaining protons solvent anisotropy and electric field effects appear to be the major factors. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H chemical shifts; DMSO solvent; NMR prediction; solvation

INTRODUCTION

The solvent dependence of ^{1}H chemical shifts has been investigated since the beginning of high-resolution ^{1}H NMR. In a seminal paper, Buckingham *et al*.[2] defined four interactions responsible for solvent effects. These were hydrogen bonding, the anisotropy of the solvent molecules, polar and van der Waals effects (Eqn (1)). (We use here the accepted δ convention rather than Buckingham's shielding nomenclature (σ).)

This analysis has formed the basis for all subsequent investigations.

$$\Delta\delta = \delta_{HB} + \delta_A + \delta_E + \delta_W \quad (1)$$

The relative importance of these four contributions can vary considerably. When hydrogen bonding occurs with protic solutes, this is a major interaction with solvent effects of up to 5 ppm for the protic hydrogen.[2] Large anisotropy contributions of *ca* 1 ppm have also been observed for non-polar anisotropic solvents such as benzene and CS_2.[2,3] The effect of the solvent on the solute chemical shifts, due to the electric field of the polar solute molecule, has been calculated using variations of the Onsager reaction field model[2–5] despite its many limitations. van der Waals effects have been shown to be significant in gas-to-solvent shifts even for non-polar molecules in non-polar solvents.[6] This early work has been well summarised.[7,8]

Although the effect of solvent on chemical equilibria has been investigated in depth recently by both molecular modelling and quantum theory,[9–11] there has been no quantitative treatment of differential solvent effects on the ^{1}H chemical shifts of organic solutes. The problems involved in the quantitative calculation of the four contributions of Eqn (1) for a polar, anisotropic, protic solvent are prohibitive. Barone *et al*.[11] have recently employed the polarizable continuum model (PCM) solvation routine[12] to calculate ^{1}H and ^{13}C chemical shifts in solution via the quantum mechanical GIAO approach in the Gaussian suite.[13] However, this model is the quantum mechanical formulation of the Onsager reaction field model and does not include any solvent hydrogen bonding, van der Waals or anisotropy contributions.

The absence of any tested predictive package for ^{1}H chemical shifts in polar, anisotropic solvents severely limits the usefulness of such solvents for characterisation purposes. In previous parts of this series, the CHARGE programme has been developed to provide a model capable of accurately predicting the ^{1}H chemical shifts of a variety of organic compounds in $CDCl_3$ solution.[1,13,14] DMSO is the solvent of choice for pharmaceutical compounds due to its excellent solubility properties for many protic and charged molecules, which are insoluble in $CDCl_3$. It is also non-toxic, water miscible, biodegradeable and has a strong deuterium lock.

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We now wish to include ^{1}H chemical shifts in DMSO as solvent in this predictive package. ^{1}H chemical shifts in DMSO can differ by up to 5 ppm from the corresponding shifts in $CDCl_3$ and therefore, the calculations for $CDCl_3$ cannot be used with confidence to predict chemical shifts in DMSO.

Few detailed studies of the effects of DMSO on ^{1}H chemical shifts have been carried out. Gottlieb *et al*.[15] gave the ^{1}H (and ^{13}C) chemical shifts of 36 common impurities in seven common solvents and, more recently, Jones *et al*.[16] recorded similar data for 60 common solvents in $CDCl_3$, DMSO, D_2O and CD_3OD. GlaxoWellcome[17a] and Pfizer[17b] have produced pamphlets with the ^{1}H shifts of *ca* 50 common compounds in the same four solvents. Hobley *et al*.[18] have given the ^{1}H (and ^{13}C) shifts of 11 monosaccharides in both the α and β forms in D_2O and DMSO solution and an algorithm for predicting the shifts. Abraham *et al*.[13] observed, for a selection of aromatic aldehydes and ketones, small solvent effects of either sign for DMSO vs $CDCl_3$ solvent and Perez[19] recorded the ^{1}H shifts of a number of aliphatic and aromatic amides in both solvents.

We present here a comprehensive data collection of ^{1}H chemical shifts of organic compounds in DMSO vs $CDCl_3$ solvent and show how the CHARGE programme can be simply extended to provide a satisfactory prediction of the shifts in DMSO. This analysis is particularly relevant for the protic hydrogen in alcohols, amides, etc. The large concentration dependence of these chemical shifts in $CDCl_3$ due to inter-molecular hydrogen bonding means that these shifts have not been used for diagnostic purposes. In contrast, the corresponding shifts in DMSO solvent show no concentration dependence and can be used for diagnostic purposes in a precisely similar manner to other ^{1}H shifts.

COMPUTATIONAL

The CHARGE programme has been developed using data acquired in $CDCl_3$ solvent. To obtain the corresponding shifts in DMSO, we correct the shifts calculated in $CDCl_3$ by adding a contribution for DMSO solvent, i.e. $\Delta\delta = \delta(\text{DMSO}) - \delta(CDCl_3)$. The aim of this work is to measure and then simulate the values of $\Delta\delta$ for a variety of compounds and functional groups.

For any solute molecule, CHARGE calculates $\delta(CDCl_3)$ in the usual way. The value of $\Delta\delta$ is then calculated in the 'DMSO' subroutine. These calculations follow a similar procedure to the main programme. For the fragment I-J-K-L, there is an α-effect on atom I from atom J, a β-effect from atom K and a γ-effect from atom L. All effects over more than three bonds are termed *long-range effects*. Each functional group can have, in principle, α-, β-, γ- and long-range effects.

The only exceptions are the hydroxyl and amide protons. The large concentration dependence of these ^{1}H chemical shifts in $CDCl_3$ solution has not allowed any analysis of the effects of functional groups on these shifts. In contrast, these ^{1}H chemical shifts in DMSO have no concentration dependence. Thus, the effects of functional groups on the OH and amide NH chemical shifts in DMSO solution may be treated in CHARGE in the same manner as any other proton. This analysis will be shown to accurately predict these chemical shifts in DMSO solvent. Also, with modern spectrometers, the OH protons of alcohols and phenols can be routinely detected at such low concentrations (*ca* 1 mg ml^{-1}) that the OH chemical shift approximates to the limiting ∞ dilution value.[20] All the alcohol and phenol OH shifts recorded in the tables are these limiting values, and these chemical shifts can also be treated in the normal manner by the CHARGE programme. Owing to exchange broadening of the acid and amide protic hydrogens, these protons are difficult to detect at these low concentrations and this precludes a similar analysis for these protons.

For polyfunctional molecules, $\Delta\delta$ will be affected by all the functional groups. It was found that, in practice, short-range effects dominate, with any long-range effects being reduced by the presence of the short-range functional group. Compounds with low-molecular dipole moments either lack polar functional groups or are highly symmetrical. Experimental $\Delta\delta$ values of the first type of non-polar compound are low, whereas those having polar groups and high symmetry may have large $\Delta\delta$ values. The CHARGE programme calculates the partial atomic charges and hence the dipole moment of the molecule considered. For molecules with dipole moments <0.5 D the α-, β- and γ-effects take effect, but long-range effects are omitted. It will be shown that these simple corrections give very good agreement with the experimental data for all non-polar molecules.

EXPERIMENTAL

All the compounds and solvents were obtained commercially (Sigma-Aldrich Co. Ltd). The $CDCl_3$ and DMSO solvents were stored over molecular sieves of 3 Å pore size and used without further purification. Solutions of $\sim$10 mg ml^{-1} concentration were used except for the alcohols and phenols in $CDCl_3$ solvent in which the OH chemical shift was obtained for *ca* 1 mg ml^{-1} concentration. TMS was used as the internal reference to eliminate all bulk susceptibility corrections. The ^{1}H spectra were obtained on a Bruker Avance 400-MHz NMR spectrometer operating at 400.13 MHz using 5-mm tubes. Typical running conditions were 128 transients, spectral width 3300 Hz and 32 K data points, giving an acquisition time of 5 s. The FIDs were zero-filled to 64 K. COSY, HMQC, HMBC and DEPT experiments were also performed. The molecular geometries used for the dihedral angle studies were obtained from PC model version 9[21] using

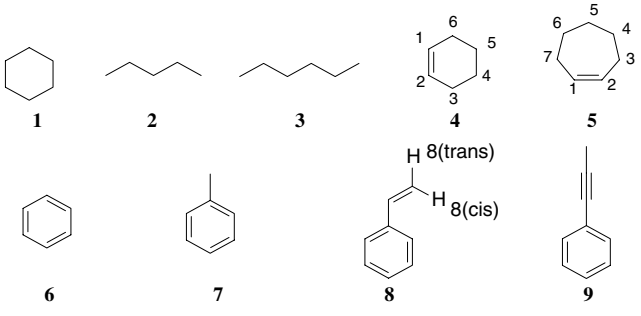

Figure 1. Non-polar compounds.

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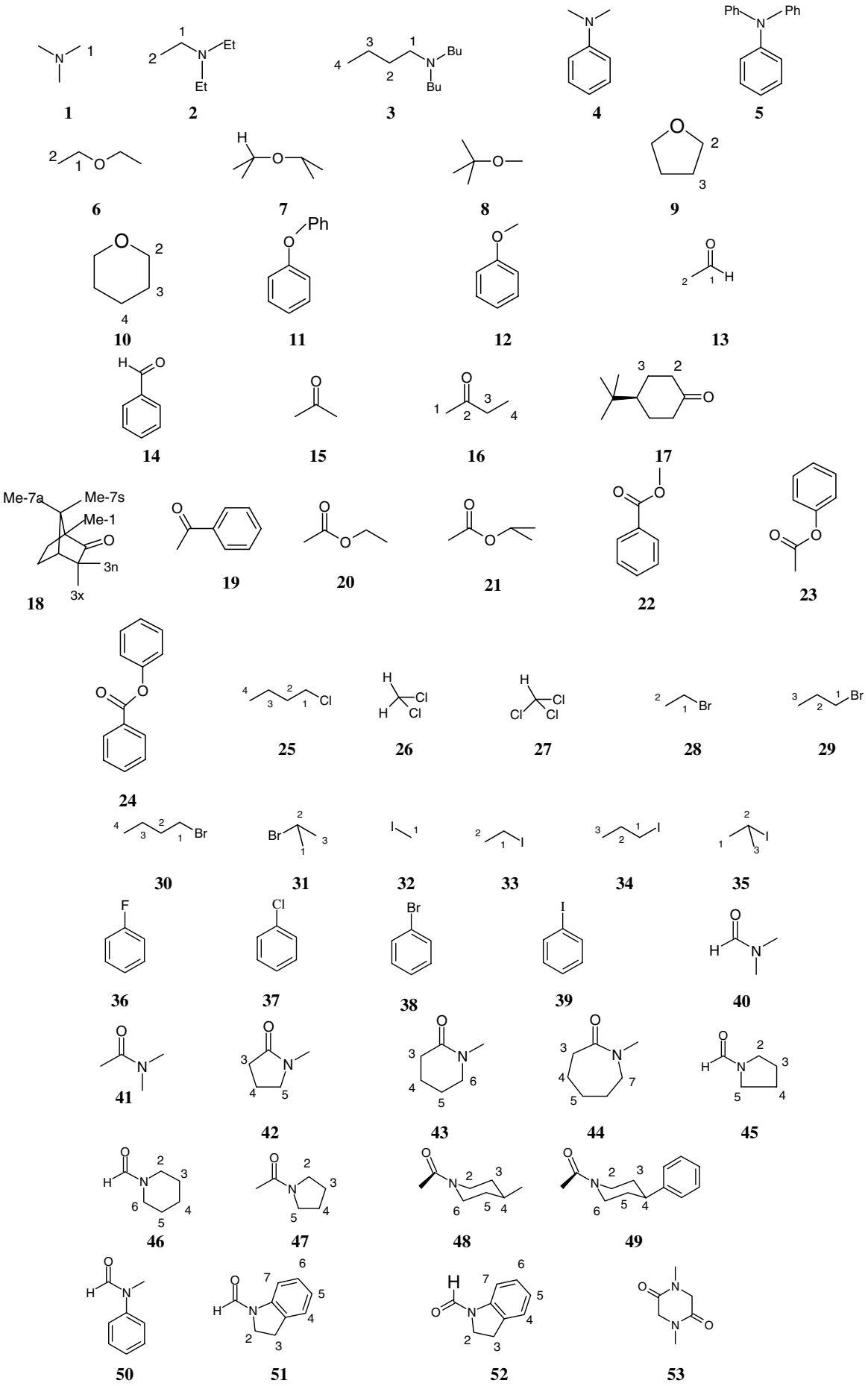

Figure 2. Aprotic polar compounds.

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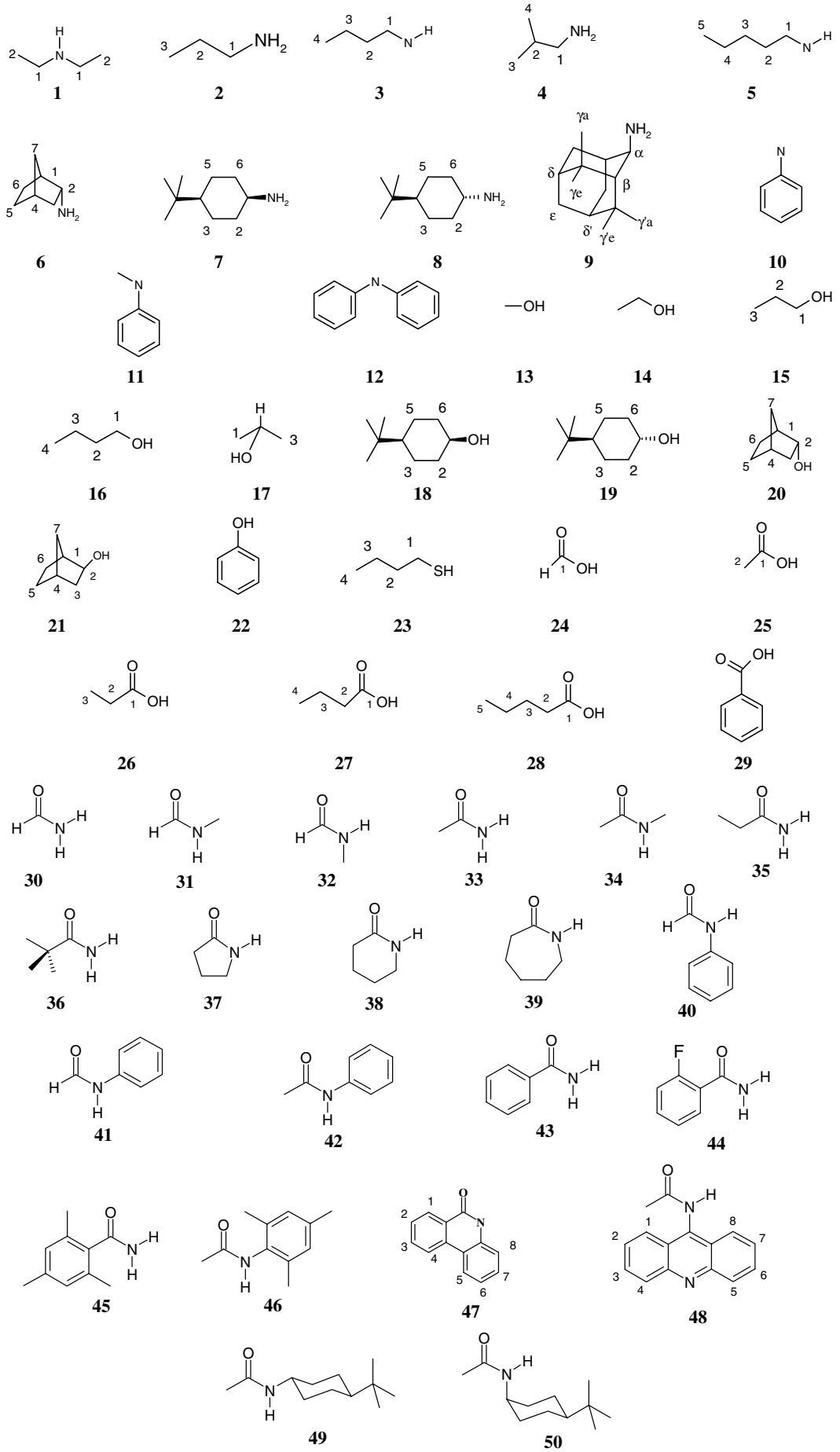

Figure 3. Protic compounds.

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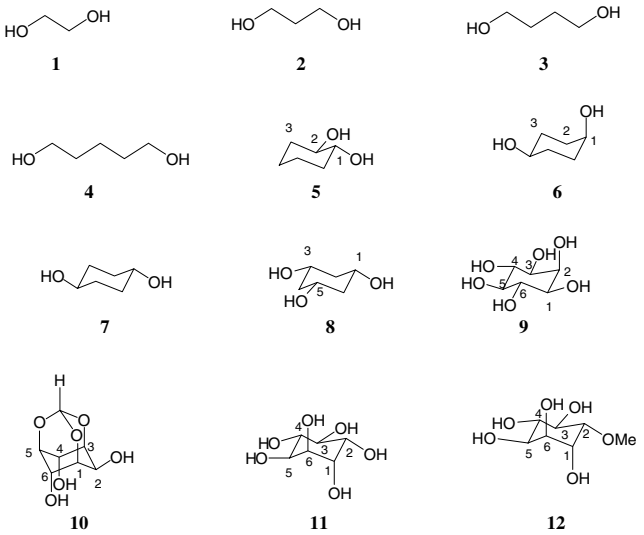

Figure 4. Diols and polyhydroxy compounds.

the MMFF94 force field and the Gaussian '03W programme[22] at the 6-31g**B3LYP[23] level.

The spectra were mainly first order and the assignments were straightforward. The data for the amides is from Ref. 19 and for the diols and inositols from Ref. 1.

RESULTS

It is convenient to separate the compounds into four groups: non-polar, polar aprotic, protic and polyhydroxy compounds. The non-polar group includes alkanes, alkenes, alkynes and aromatics. The polar aprotic group includes aliphatic/aromatic tertiary amines, ethers, ketones, esters and halides. The protic group includes aliphatic and aromatic primary and secondary amines, alcohols, thiols, aldehydes, carboxylic acids and amides and the last group diols, triols and inositols. The compounds measured are shown in Figs 1–4 and the results for these compounds are given in Tables 1–4.

DISCUSSION

Non-polar compounds

The $\Delta\delta$ values of the non-polar compounds (Table 1) are small; in many cases, not much greater than the experimental

Table 1. ^{1}H chemical shifts of non-polar solutes in $CDCl_3$ and DMSO

		δ(DMSO)		$\delta(CDCl_3)$		$\Delta\delta$(DMSO − $CDCl_3$)	
Compound	Proton	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
Cyclohexane (**1**)[a]	CH_2	1.40	1.40	1.43	1.40	−0.03	0.00
n-Pentane (**2**)	Me	0.86	0.84	0.88	0.84	−0.02	0.00
	2,4	1.27	1.14	1.27	1.14	0.00	0.00
	3	1.27	0.94	1.27	0.94	0.00	0.00
n-Hexane (**3**)	Me	0.86	0.84	0.88	0.84	−0.02	0.00
	2,5	1.25	1.15	1.26	1.15	−0.01	0.00
	3,4	1.25	0.96	1.26	0.96	−0.01	0.00
Cyclohexene (**4**)	=CH	5.65	5.75	5.69	5.75	−0.04	0.00
	3,6	1.95	2.05	1.99	2.05	−0.04	0.00
	4,5	1.55	1.55	1.60	1.55	−0.05	0.00
Cycloheptene (**5**)	=CH	5.77	5.62	5.79	5.62	−0.02	0.00
	3,7	2.08	2.06	2.12	2.06	−0.04	0.00
	4,6	1.45	1.43	1.50	1.43	−0.05	0.00
	5	1.69	1.44	1.75	1.44	−0.06	0.00
Benzene (**6**)	CH	7.37	7.34	7.34	7.34	0.03	0.00
Toluene (**7**)	Me	2.30	2.33	2.36	2.33	−0.06	0.00
	o	7.18	7.13	7.17	7.13	0.01	0.00
	m	7.25	7.28	7.25	7.28	0.00	0.00
	p	7.18	7.17	7.17	7.17	0.01	0.00
Styrene (**8**)	o	7.47	7.77	7.42	7.77	0.05	0.00
	m	7.35	7.38	7.32	7.38	0.03	0.00
	p	7.28	7.34	7.25	7.34	0.03	0.00
	=CH	6.74	6.73	6.72	6.73	0.02	0.00
	8(*cis*)	5.26	5.26	5.24	5.26	0.02	0.00
	8(*trans*)	5.84	5.93	5.75	5.93	0.09	0.00
Phenylacetylene (**9**)	CH	4.20	4.28	3.07	3.15	1.13	1.13
	o	7.49	7.56	7.50	7.56	−0.01	0.00
	m	7.40	7.35	7.33	7.35	0.07	0.00
	p	7.40	7.36	7.33	7.36	0.07	0.00

[a] Ref. 15.

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Table 2. ^{1}H chemical shifts of polar aprotic solutes in $CDCl_3$ and DMSO

		δ(DMSO)		$\delta(CDCl_3)$		$\Delta\delta$(DMSO − $CDCl_3$)	
Compound	Proton	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
Trimethylamine (**1**)	Me	2.09	2.19	2.22	2.28	−0.13	−0.09
Triethylamine (**2**)	Me	2.42	2.46	2.52	2.55	−0.10	−0.09
	CH_2	0.93	0.82	1.03	0.91	−0.09	−0.09
Tributylamine (**3**)	1	2.31	2.29	2.38	2.38	−0.07	−0.09
	2	1.34	1.20	1.41	1.28	−0.07	−0.08
	3	1.26	1.06	1.29	1.13	−0.03	−0.07
	Me	0.87	0.77	0.91	0.84	−0.04	−0.07
Dimethylaniline (**4**)	o	6.71	6.60	6.74	6.66	−0.03	−0.06
	m	7.17	7.10	7.24	7.10	−0.07	0.00
	p	6.63	6.66	6.72	6.66	−0.08	0.00
	Me	2.87	2.72	2.94	2.82	−0.06	−0.10
Triphenylamine (**5**)	o	6.99	7.07	7.08	7.13	−0.09	−0.06
	m	7.29	7.27	7.24	7.27	0.06	0.00
	p	7.03	7.05	7.00	7.05	0.03	0.00
Diethylether (**6**)	Me	1.09	1.08	1.21	1.17	−0.12	−0.09
	CH_2	3.38	3.45	3.48	3.55	−0.10	−0.10
Diisopropylether (**7**)	Me	1.04	1.08	1.13	1.17	−0.09	−0.09
	CH	3.60	3.63	3.65	3.74	−0.05	−0.11
*t*Bu-Me ether (**8**)	*t*Bu-Me	1.11	1.16	1.19	1.25	−0.08	−0.09
	Me	3.08	3.17	3.21	3.28	−0.13	−0.11
THF (**9**)	2,5	3.60	3.60	3.74	3.71	−0.14	−0.11
	3,4	1.76	1.44	1.85	1.53	−0.09	−0.09
THP (**10**)	2,6	3.53	3.55	3.65	3.65	−0.12	−0.10
	3,5	1.47	1.41	1.57	1.52	−0.10	−0.11
	4	1.58	1.48	1.64	1.55	−0.07	−0.07
Diphenylether (**11**)	o	7.01	7.17	7.01	7.17	0.00	0.00
	m	7.39	7.30	7.32	7.30	0.07	0.00
	p	7.14	7.18	7.09	7.18	0.05	0.00
Anisole (**12**)	o	6.93	6.80	6.90	6.80	0.02	0.00
	m	7.29	7.15	7.29	7.15	0.00	0.00
	p	6.93	6.87	6.94	6.87	−0.02	0.00
	Me	3.74	3.67	3.80	3.78	−0.06	−0.11
Acetaldehyde (**13**)	CHO	9.66	9.68	9.79	9.81	−0.14	−0.13
	Me	2.13	2.10	2.20	2.15	−0.08	−0.05
Benzaldehyde (**14**)	o	7.92	7.85	7.88	7.78	0.04	0.07
	m	7.62	7.55	7.53	7.48	0.09	0.07
	p	7.73	7.63	7.63	7.56	0.10	0.07
	CHO	10.03	9.82	10.03	9.82	0.00	0.00
Acetone (**15**)	Me	2.09	2.16	2.17	2.21	−0.08	−0.05
2-Butanone (**16**)	CO.Me	2.07	2.14	2.14	2.19	−0.07	−0.05
	CH_2	2.43	2.41	2.44	2.38	−0.01	0.03
	Me	0.91	0.78	1.06	0.85	−0.15	−0.07
4-*t*Butylcyclohexanone (**17**)	2a/6a	2.36	2.18	2.31	2.20	0.05	−0.02
	2e/6e	2.19	2.15	2.40	2.35	−0.21	−0.20
	3a/5a	1.35	1.32	1.44	1.39	−0.10	−0.07
	3e/5e	1.99	1.99	2.08	2.06	−0.10	−0.07
	4a	1.50	1.22	1.46	1.29	0.04	−0.07
	*t*Bu Me	0.89	0.85	0.92	0.92	−0.04	−0.07
Camphor (**18**)	3n	1.80	1.49	1.84	1.62	−0.04	−0.13
	3x	2.29	2.36	2.35	2.47	−0.06	−0.11
	4	2.05	2.04	2.09	2.11	−0.04	−0.07
	5n	1.30	1.05	1.34	1.12	−0.04	−0.07
	5x	1.87	2.05	1.95	2.12	−0.08	−0.07

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Table 2. (*Continued*)

Compound	Proton	δ(DMSO)		δ($CDCl_3$)		$\Delta\delta$(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
	6n	1.26	1.34	1.40	1.41	−0.14	−0.07
	6x	1.65	1.82	1.68	1.89	−0.03	−0.07
	Me-1	0.80	0.96	0.92	1.03	−0.12	−0.07
	Me-7s	0.76	0.67	0.84	0.74	−0.08	−0.07
	Me-7a	0.91	0.81	0.96	0.88	−0.05	−0.07
Acetophenone (**19**)	Me	2.58	2.56	2.60	2.61	−0.02	−0.05
	o	7.96	7.86	7.96	7.79	0.00	0.07
	m	7.53	7.56	7.46	7.49	0.07	0.07
	p	7.64	7.63	7.56	7.56	0.08	0.07
Ethyl acetate (**20**)	CH_2	4.03	4.06	4.12	4.17	−0.09	−0.11
	Me	1.99	2.01	2.04	2.07	−0.05	−0.06
	CO.Me	1.18	1.00	1.26	1.16	−0.08	−0.16
Isopropyl acetate (**21**)	CO.Me	1.96	2.02	2.01	2.07	−0.05	−0.05
	CH	4.86	4.74	4.99	4.85	−0.13	−0.11
	Me	1.17	1.03	1.23	1.12	−0.06	−0.09
Methyl benzoate (**22**)	o	7.97	7.98	8.04	7.91	−0.07	0.07
	m	7.53	7.59	7.43	7.52	0.10	0.07
	p	7.66	7.50	7.55	7.50	0.00	0.11
	Me	3.86	3.78	3.92	3.89	−0.05	−0.11
Phenyl acetate (**23**)	Me	2.26	2.17	2.29	2.22	−0.03	−0.05
	o	7.12	7.09	7.08	7.02	0.04	0.07
	m	7.41	7.30	7.37	7.23	0.04	0.07
	p	7.25	7.20	7.22	7.13	0.03	0.07
Phenyl benzoate (**24**)	o(ben)	8.14	8.01	8.21	7.94	−0.07	0.07
	m(ben)	7.62	7.57	7.52	7.50	0.10	0.07
	p(ben)	7.76	7.54	7.64	7.47	0.12	0.07
	o(ph)	7.29	7.21	7.22	7.14	0.07	0.07
	m(ph)	7.49	7.35	7.44	7.28	0.05	0.07
	p(ph)	7.33	7.26	7.28	7.19	0.05	0.07
Chlorobutane (**25**)	1	3.62	3.62	3.54	3.54	0.08	0.08
	2	1.69	1.49	1.76	1.56	−0.06	−0.07
	3	1.40	1.09	1.47	1.16	−0.06	−0.07
	Me	0.89	0.80	0.94	0.87	−0.05	−0.07
Dichloromethane (**26**)	CH_2	5.79	5.73	5.30	5.27	0.49	0.46
Chloroform (**27**)	CH	8.32	8.32	7.26	7.28	1.06	1.06
Bromoethane (**28**)	CH_2	3.53	3.64	3.43	3.52	0.10	0.12
	Me	1.60	1.58	1.67	1.65	−0.08	−0.07
1-Bromopropane (**29**)	1	3.51	3.46	3.39	3.35	0.12	0.11
	2	1.81	1.78	1.88	1.84	−0.07	−0.06
	Me	0.96	0.80	1.03	0.87	−0.07	−0.07
1-Bromobutane (**30**)	1	3.53	3.50	3.42	3.38	0.11	0.12
	2	1.78	1.59	1.84	1.66	−0.06	−0.07
	3	1.40	1.08	1.47	1.15	−0.07	−0.07
	Me	0.89	0.78	0.94	0.85	−0.05	−0.07
2-Bromopropane (**31**)	Me	1.66	1.64	1.71	1.70	−0.05	−0.06
	CH	4.43	4.42	4.29	4.30	0.14	0.12
Iodomethane (**32**)	Me	2.18	2.28	2.16	2.21	0.02	0.07
Iodoethane (**33**)	CH_2	3.26	3.34	3.19	3.27	0.06	0.07
	Me	1.76	1.80	1.85	1.87	−0.08	−0.07
Iodopropane (**34**)	1	3.27	3.16	3.18	3.09	0.08	0.07
	2	1.76	1.92	1.83	1.99	−0.07	−0.07
	Me	0.93	0.77	0.99	0.84	−0.06	−0.07
2-Iodopropane (**35**)	Me	1.84	1.85	1.89	1.92	−0.05	−0.07
	CH	4.43	4.55	4.32	4.48	0.12	0.07

(*continued overleaf*)

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Table 2. (*Continued*)

Compound	Proton	δ(DMSO)		$\delta(CDCl_3)$		$\Delta\delta$(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
Fluorobenzene (**36**)	o	7.19	7.03	7.05	7.03	0.14	0.00
	m	7.42	7.29	7.33	7.29	0.09	0.00
	p	7.21	7.07	7.13	7.07	0.09	0.00
Chlorobenzene (**37**)	o	7.44	7.27	7.33	7.27	0.11	0.00
	m	7.40	7.21	7.28	7.21	0.13	0.00
	p	7.34	7.20	7.22	7.20	0.12	0.00
Bromobenzene (**38**)	o	7.57	7.44	7.49	7.44	0.08	0.00
	m	7.34	7.17	7.22	7.17	0.12	0.00
	p	7.39	7.23	7.28	7.23	0.11	0.00
Iodobenzene (**39**)	o	7.74	7.67	7.70	7.67	0.04	0.00
	m	7.19	7.02	7.10	7.02	0.09	0.00
	p	7.40	7.24	7.32	7.24	0.08	0.00
N, *N*-Dimethylformamide (**40**)	Me(*cis*)	2.89	2.89	2.88	2.95	0.01	−0.06
	Me(*trans*)	2.73	2.74	2.94	2.94	−0.21	−0.20
	CHO	7.95	7.98	8.02	8.02	−0.07	−0.04
N, *N*-Dimethylacetamide (**41**)	Me(*cis*)	2.95	2.91	3.01	2.97	−0.06	−0.06
	Me(*trans*)	2.79	2.70	2.94	2.90	−0.15	−0.20
	MeCO	1.96	1.86	2.08	2.01	−0.12	−0.15
N-Methyl pyrrolidinone (**42**)	*N*−Me	2.69	2.75	2.85	2.95	−0.17	−0.20
	3	2.16	2.15	2.37	2.37	−0.21	−0.22
	4	1.91	2.00	2.03	2.10	−0.13	−0.10
	5	3.29	3.28	3.39	3.34	−0.10	−0.06
N-Methyl valerolactam (**43**)	*N*−Me	2.80	2.65	2.94	2.92	−0.15	−0.27
	3	2.18	2.12	2.37	2.34	−0.19	−0.22
	4	1.72	1.82	1.82	1.89	−0.09	−0.07
	5	1.70	1.72	1.81	1.89	−0.11	−0.17
	6	3.23	3.02	3.29	3.15	−0.06	−0.13
N-Methyl caprolactam (**44**)	*N*−Me	2.83	2.74	2.98	2.94	−0.15	−0.20
	3	2.40	2.30	2.52	2.48	−0.12	−0.18
	4	1.52	1.57	1.66	1.64	−0.15	−0.07
	5	1.65	1.55	1.70	1.62	−0.05	−0.07
	6	1.55	1.58	1.65	1.68	−0.09	−0.10
	7	3.34	3.14	3.36	3.20	−0.02	−0.06
Formyl pyrrolidine (**45**)	2	3.22	3.07	3.43	3.34	−0.21	−0.27
	3	1.79	1.57	1.90	1.74	−0.11	−0.17
	4	1.81	1.59	1.92	1.76	−0.11	−0.17
	5	3.44	3.27	3.43	3.40	0.02	−0.13
	CHO	8.17	7.98	8.26	8.02	−0.09	−0.04
Formyl piperidine (**46**)	2	3.29	3.24	3.30	3.30	−0.01	−0.06
	3	1.61	1.57	1.58	1.67	0.03	−0.10
	4	1.42	1.51	1.54	1.58	−0.12	−0.07
	5	1.47	1.47	1.69	1.57	−0.22	−0.10
	6	3.33	3.36	3.48	3.56	−0.15	−0.20
	CHO	7.95	7.98	8.01	8.02	−0.05	−0.04
N-Acetyl pyrrolidine (**47**)	2	3.38	3.21	3.46	3.41	−0.08	−0.20
	3	1.78	1.62	1.86	1.72	−0.08	−0.10
	4	1.87	1.67	1.96	1.77	−0.09	−0.10
	5	3.25	3.37	3.42	3.43	−0.17	−0.06
	CO.Me	1.93	1.85	2.05	2.00	−0.12	−0.15
4-Methyl-*N*-acetylpiperidine (**48**)	2a	2.97	2.48	2.54	2.68	0.43	−0.20
	2e	4.32	4.50	4.55	4.70	−0.23	−0.20
	3a	0.90	0.97	1.08	1.07	−0.17	−0.10
	3e	1.56	1.64	1.65	1.74	−0.09	−0.10
	4a	1.54	1.37	1.60	1.44	−0.06	−0.07

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Table 2. (*Continued*)

Compound	Proton	δ(DMSO) Obsd	δ(DMSO) Calcd	δ($CDCl_3$) Obsd	δ($CDCl_3$) Calcd	$\Delta\delta$(DMSO − $CDCl_3$) Obsd	$\Delta\delta$(DMSO − $CDCl_3$) Calcd
	5a	1.03	1.08	1.13	1.18	−0.10	−0.10
	5e	1.63	1.70	1.69	1.80	−0.06	−0.10
	6a	2.48	2.71	3.02	2.77	−0.54	−0.06
	6e	3.75	4.00	3.77	4.06	−0.02	−0.06
	Me(4e)	0.90	0.87	0.95	0.94	−0.06	−0.07
	CO.Me	1.96	1.80	2.08	1.96	−0.12	−0.16
4-Phenyl-*N*-acetylpiperidine (**49**)	2a	3.15	2.58	2.63	2.78	0.52	−0.20
	2e	4.56	4.58	4.79	4.78	−0.23	−0.20
	3a	1.60	1.69	1.61	1.79	−0.01	−0.10
	3e	1.79	1.98	1.88	2.08	−0.09	−0.10
	4a	2.61	2.73	2.73	2.80	−0.13	−0.07
	5a	1.46	1.81	1.65	1.91	−0.19	−0.10
	5e	1.72	2.02	1.91	2.12	−0.20	−0.10
	6a	2.78	2.82	3.16	2.88	−0.38	−0.06
	6e	3.95	4.09	3.92	4.15	0.02	−0.06
	CO.Me	2.06	1.85	2.14	2.00	−0.08	−0.15
	o	7.27	7.19	7.21	7.19	0.06	0.00
	m	7.33	7.32	7.32	7.32	0.01	0.00
	p	7.23	7.20	7.22	7.20	0.00	0.00
N-Methylformanilide (**50**)	*N*.Me	3.29	3.15	3.32	3.35	−0.03	−0.20
	o	7.34	7.22	7.18	7.06	0.16	0.16
	m	7.44	7.59	7.41	7.59	0.03	0.00
	p	7.26	7.46	7.29	7.46	−0.03	0.00
	CHO	8.53	8.73	8.48	8.68	0.04	0.05
endo-Formylindoline (**51**)	2	4.10	3.90	4.12	3.96	−0.02	−0.06
	3	3.11	2.99	3.20	3.09	−0.09	−0.10
	4	7.01	7.19	7.24	7.19	−0.23	0.00
	5	7.15	7.20	7.07	7.20	0.08	0.00
	6	7.25	7.31	7.21	7.31	0.04	0.00
	7	8.05	8.11	8.08	7.95	−0.03	0.16
	CHO	8.81	8.75	8.53	8.50	0.28	0.25
exo-Formylindoline (**52**)	2	3.89	3.71	4.07	3.91	−0.18	−0.20
	3	3.08	2.94	3.16	3.04	−0.08	−0.10
	4	7.25	7.25	7.26	7.25	−0.01	0.00
	5	7.15	7.26	7.06	7.26	0.09	0.00
	6	7.40	7.38	7.21	7.38	0.19	0.00
	7	7.00	7.27	7.18	7.11	−0.18	0.16
	CHO	9.01	8.74	8.95	8.69	0.06	0.05
Sarcosine (**53**)	CH_2	3.98	3.95	3.98	3.95	0.00	0.00
	Me	2.96	3.00	2.96	3.00	0.00	0.00

error with the notable exception of the acetylenic proton of phenylacetylene (**9**, Fig. 1). The α, β and γ contributions for all protons of these compounds are therefore set equal to zero, except for the acetylenic proton. These compounds all have dipole moments <0.5 D and the long-range effects are also set to zero.

Polar aprotic compounds

Larger $\Delta\delta$ values are found for the protons of polar aprotic compounds (Table 2), though the majority have values *ca* ±0.1 ppm. Large shifts occur with the geminal dihalo and trihalo compounds (e.g. CH_2Cl_2, $CHCl_3$ for which $\Delta\delta$ is +0.49 and +1.06 res), probably due to hydrogen bonding (see later). The $\Delta\delta$ values for the H.C.C═O protons are dependent on the H.C.C═O dihedral angle and the values for the four protons 2e, 2a and 3x, 3n in the conformationally rigid molecules **17** and **18** (Fig. 2) may be simulated by Eqn (2).

$$\Delta\delta = -0.047 - 0.091\ \cos\theta - 0.085\ \cos 2\theta \qquad (2)$$

The rotationally averaged value is −0.09 ppm (*cf* observed values of −0.08 and −0.07 for the Me.CO groups in acetone and 2-butanone).

Protic compounds

Very large positive $\Delta\delta$ values (1–4 ppm) are found for the labile hydrogens of these compounds (Tables 3 and 4). In addition, significant (~0.3 ppm) values are observed for

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Table 3. ^{1}H chemical shifts of protic solutes in $CDCl_3$ and DMSO

Compound	Proton	δ(DMSO) Obsd	δ(DMSO) Calcd	δ($CDCl_3$) Obsd	δ($CDCl_3$) Calcd	Δδ(DMSO − $CDCl_3$) Obsd	Δδ(DMSO − $CDCl_3$) Calcd
Diethylamine (**1**)	NH	1.29	1.65	0.80	1.01	0.49	0.64
	CH_2	2.50	2.39	2.66	2.55	−0.15	−0.16
	Me	0.99	0.74	1.11	0.87	−0.12	−0.13
n-Propylamine (**2**)	NH_2	–	1.73	1.78[d]	1.11	–	0.62
	1	2.48	2.43	2.65	2.67	−0.18	−0.16
	2	1.33	1.24	1.46	1.36	−0.12	−0.11
	Me	0.84	0.83	0.91	0.91	−0.08	−0.07
n-Butylamine (**3**)	NH_2	2.66	2.66	1.11[d]	1.12	1.55	0.64
	1	2.52	2.50	2.69	2.68	−0.18	−0.16
	2	1.32	1.19	1.43	1.20	−0.11	−0.11
	3	1.28	1.17	1.35	1.24	−0.07	−0.07
	Me	0.86	0.83	0.92	0.89	−0.06	−0.07
Isobutylamine (**4**)	NH_2	2.93[a]	1.82	1.71[a]	1.18	1.22	0.64
	1	2.34	2.40	2.50	2.56	−0.16	−0.16
	2	1.48	1.66	1.58	1.77	−0.11	−0.11
	Me	0.83	0.85	0.90	1.02	−0.07	−0.07
Amylamine (**5**)	NH_2	1.22	1.74	1.00	1.10	0.22	0.64
	1	2.50	2.50	2.68	2.68	−0.18	−0.16
	2	1.33	1.10	1.44	1.22	−0.12	−0.11
	3	1.26	0.99	1.32	1.05	−0.06	−0.07
	4	1.26	1.19	1.32	1.25	−0.06	−0.07
	Me	0.86	0.80	0.90	0.84	−0.04	−0.07
endo-2-Aminonorbornane (**6**)	NH_2	2.20[a]	1.79	–	1.15	–	0.64
	1	1.95	2.14	2.07	2.26	−0.13	−0.12
	2x	3.12	2.99	3.26	3.15	−0.14	−0.16
	3n	0.50	0.53	0.59	0.62	−0.09	−0.09
	3x	1.80	1.77	1.96	1.91	−0.16	−0.14
	4	2.05	2.12	2.14	2.19	−0.09	−0.07
	5n	1.14	1.19	1.22	1.26	−1.22	−0.07
	5x	1.44	1.44	1.55	1.51	−1.55	−0.07
	6n	1.78	1.57	1.73	1.64	−1.73	−0.07
	6x	1.24	1.37	1.37	1.44	−1.37	−0.07
	7a	1.19	1.15	1.30	1.22	−1.30	−0.07
	7s	1.30	1.14	1.39	1.21	−1.39	−0.07
4-*t*Bucyclohexylamine(*cis*) (**7**)	NH_2	1.24[b]	1.82	1.30[b]	1.18	–	0.64
	1e	3.03	3.05	3.15	3.21	−0.11	−0.16
	2a/6a	1.37	1.27	1.54	1.44	−0.17	−0.17
	2e/6e	1.56	1.51	1.65	1.61	−0.10	−0.10
	3a/5a	0.90	1.23	1.27	1.30	−0.37	−0.07
	3e/5e	1.37	1.62	1.53	1.69	−0.16	−0.07
	4a	0.94	1.00	0.96	1.07	−0.02	−0.07
	t-Bu Me	0.83	0.84	0.86	0.91	−0.03	−0.07
4-*t*Bucyclohexylamine(*trans*) (**8**)	NH_2	1.24[b]	1.72	1.30[b]	1.08	–	0.64
	1a	2.40	2.60	2.55	2.76	−0.15	−0.16
	2a/6a	0.94	1.11	1.03	1.22	−0.09	−0.11
	2e/6e	1.78	1.57	1.89	1.68	−0.11	−0.11
	3a/5a	0.94	0.98	1.03	1.05	−0.09	−0.07
	3e/5e	1.66	1.69	1.76	1.76	−0.09	−0.07
	4a	0.94	1.03	0.96	1.10	−0.02	−0.07
	t-Bu Me	0.82	0.84	0.84	0.91	−0.03	−0.07
2-Adamantanamine (**9**)	NH_2	1.46	1.94	–	1.30	–	0.64
	α	2.85	2.92	2.98	3.08	−0.13	−0.16
	β	1.60	1.78	1.72	1.89	−0.12	−0.11
	γa	2.05	1.94	1.98	2.01	0.07	−0.07
	γe	1.37	1.53	1.53	1.60	−0.16	−0.07
	δ	1.70	1.85	1.79	1.92	−0.09	−0.07

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Table 3. (*Continued*)

Compound	Proton	δ(DMSO)		δ($CDCl_3$)		$\Delta\delta$(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
	ε	1.65	1.61	1.72	1.68	−0.07	−0.07
	γ'a	1.66	1.59	1.73	1.66	−0.07	−0.07
	γ'e	1.76	1.63	1.85	1.70	−0.09	−0.07
	δ'	1.65	1.85	1.82	1.92	−0.17	−0.07
Aniline (**10**)	NH_2	4.94	4.87	3.61	3.54	1.34	1.33
	o	6.55	6.47	6.67	6.59	−0.12	−0.12
	m	6.98	7.03	7.14	7.11	−0.16	−0.08
	p	6.47	6.60	6.75	6.68	−0.13	−0.08
N-Methylaniline (**11**)	NH	5.52	5.29	3.66	3.64	1.86	1.65
	o	6.52	6.49	6.61	6.61	−0.09	−0.12
	m	7.07	7.03	7.18	7.11	−0.12	−0.08
	p	6.51	6.59	6.70	6.67	−0.20	−0.08
	Me	2.65	2.71	2.83	2.87	−0.18	−0.16
N-Phenylaniline (**12**)	NH	8.10	8.37	5.68	5.71	2.42	2.66
	o	7.06	6.91	7.07	7.03	−0.01	−0.12
	m	7.22	7.09	7.26	7.17	−0.04	−0.08
	p	6.81	6.69	6.92	6.77	−0.11	−0.08
Methanol (**13**)	OH	4.05	4.04	0.85	0.89	3.20	3.15
	Me	3.17	3.10	3.48	3.37	−0.31	−0.27
Ethanol (**14**)	OH	4.31	4.13	1.10	1.14	3.21	2.99
	CH_2	3.44	3.47	3.71	3.74	−0.27	−0.27
	Me	1.06	1.02	1.24	1.18	−0.18	−0.16
Propanol (**15**)	OH	4.31	4.13	1.22	1.14	3.09	2.99
	1	3.34	3.30	3.59	3.57	−0.25	−0.27
	2	1.42	1.29	1.59	1.46	−0.17	−0.17
	Me	0.84	0.78	0.94	0.85	−0.10	−0.07
n-Butanol (**16**)	OH	4.30	4.16	1.17	1.17	3.13	2.99
	1	3.38	3.32	3.64	3.59	−0.26	−0.27
	2	1.40	1.11	1.56	1.28	−0.16	−0.17
	3	1.30	1.08	1.39	1.15	−0.09	−0.07
	Me	0.87	0.77	0.94	0.84	−0.07	−0.07
2-Propanol (**17**)	OH	4.30	4.21	1.23	1.20	3.07	3.01
	Me	1.04	1.09	1.21	1.24	−0.17	−0.15
	CH	3.77	3.71	4.02	3.98	−0.25	−0.27
(*cis*) 4-*t*Bu cyclohexanol (**18**)	OH	4.11	4.29	1.40[c]	1.27	2.77	3.02
	1e	3.80	3.75	4.03	4.02	−0.23	−0.27
	2a/6a	1.34	1.38	1.49	1.52	−0.15	−0.14
	2e/6e	1.67	1.61	1.83	1.78	−0.16	−0.17
	3a/5a	1.34	1.28	1.35	1.35	−0.01	−0.07
	3e/5e	1.46	1.60	1.54	1.67	−0.08	−0.07
	4a	0.93	0.96	0.99	1.03	−0.06	−0.07
	*t*Bu Me	0.82	0.83	0.86	0.90	−0.04	−0.07
(*trans*) 4-*t*Bu cyclohexanol (**19**)	OH	4.39	4.26	1.40[c]	1.25	2.99	3.01
	1a	3.25	3.34	3.52	3.61	−0.27	−0.27
	2a/6a	1.07	1.18	1.22	1.35	−0.15	−0.17
	2e/6e	1.84	1.70	2.01	1.86	−0.17	−0.16
	3a/5a	0.96	0.99	1.05	1.06	−0.09	−0.07
	3e/5e	1.68	1.69	1.78	1.76	−0.11	−0.07
	4a	0.92	1.04	0.97	1.11	−0.05	−0.07
	*t*Bu Me	0.82	0.84	0.85	0.91	−0.03	−0.07
endo-2-Norborneol (**20**)	OH	4.43	4.19	–	1.18	–	3.01
	1	2.06	2.12	2.25	2.30	−0.19	−0.18
	2x	4.00	3.77	4.23	4.04	−0.23	−0.27
	3n	0.72	0.82	0.84	0.93	−0.13	−0.11
	3x	1.76	1.77	1.95	1.95	−0.19	−0.18

(*continued overleaf*)

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Table 3. (*Continued*)

Compound	Proton	δ(DMSO)		δ($CDCl_3$)		Δδ(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
	4	2.06	2.12	2.17	2.19	−0.11	−0.07
	5n	1.22	1.21	1.35	1.28	−0.13	−0.07
	5x	1.46	1.43	1.57	1.50	−0.12	−0.07
	6n	1.86	1.68	1.87	1.75	−0.01	−0.07
	6x	1.22	1.34	1.35	1.41	−0.13	−0.07
	7a	1.22	1.16	1.35	1.23	−0.13	−0.07
	7s	1.22	1.16	1.35	1.23	−0.13	−0.07
exo-2-Norborneol (**21**)	OH	4.38	4.26	–	1.26	–	3.00
	1	1.99	1.99	2.14	1.96	−0.14	0.03
	2n	3.52	3.51	3.76	3.78	−0.23	−0.27
	3n	1.49	1.46	1.66	1.64	−0.18	−0.18
	3x	1.16	1.13	1.29	1.24	−0.12	−0.11
	4	2.14	2.13	2.25	2.20	−0.12	−0.07
	5n	0.94	1.13	1.02	1.20	−0.08	−0.07
	5x	1.35	1.45	1.44	1.52	−0.09	−0.07
	6n	0.94	1.18	1.02	1.25	−0.08	−0.07
	6x	1.35	1.47	1.44	1.54	−0.09	−0.07
	7a	0.98	1.08	1.12	1.15	−0.14	−0.07
	7s	1.49	1.49	1.57	1.56	−0.09	−0.07
Phenol (**22**)	OH	9.29[e]	9.28	4.69[e]	4.71	4.60	4.57
	o	6.75	6.78	6.83	6.78	−0.08	0.00
	m	7.15	7.05	7.24	7.13	−0.09	−0.08
	p	6.76	6.78	6.93	6.86	−0.17	−0.08
n-Butylthiol (**23**)	SH	2.17	2.18	1.31	1.32	0.86	0.86
	1	2.47	2.32	2.53	2.37	−0.05	−0.05
	2	1.52	1.30	1.60	1.38	−0.08	−0.08
	3	1.36	1.09	1.41	1.16	−0.05	−0.07
	Me	0.87	0.77	0.91	0.84	−0.04	−0.07
Formic acid (**24**)	COOH	12.50	12.54	10.85	10.89	1.65	1.65
	CH	8.13	8.00	8.05	8.07	0.08	−0.08
Acetic acid (**25**)	COOH	11.91	11.92	11.51	11.07	0.40	0.85
	Me	1.91	1.98	2.10	2.08	−0.19	−0.10
Propionic acid (**26**)	COOH	11.90	11.95	10.35	11.10	1.55	0.85
	CH_2	2.21	2.28	2.39	2.30	−0.17	−0.02
	Me	1.00	1.13	1.16	1.20	−0.16	−0.07
Butyric acid (**27**)	COOH	11.91	11.96	11.10	11.10	0.81	0.86
	2	2.17	2.11	2.34	2.13	−0.16	−0.02
	3	1.51	1.76	1.67	1.83	−0.16	−0.07
	Me	0.88	0.90	0.98	0.97	−0.10	−0.07
Valeric acid (**28**)	COOH	–	11.96	–	11.10	–	0.86
	2	2.19	2.13	2.36	2.15	−0.16	−0.02
	3	1.48	1.58	1.63	1.65	−0.15	−0.07
	4	1.29	1.20	1.38	1.27	−0.09	−0.07
	Me	0.87	0.83	0.93	0.90	−0.06	−0.07
Benzoic acid (**29**)	COOH	–	13.72	–	12.07	–	1.65
	o	8.02	8.00	8.13	7.93	−0.10	0.07
	m	7.57	7.56	7.48	7.49	0.09	0.07
	p	7.69	7.53	7.62	7.46	0.07	0.07
Formamide (**30**)	NH(*cis*)	7.14	7.11	5.80	5.77	1.34	1.34
	NH(*trans*)	7.41	7.41	5.48	5.45	1.93	1.96
	CHO	7.98	8.00	8.23	8.25	−0.25	−0.25
N-Methylformamide(*trans*) (**31**)	NH(*trans*)	7.90	7.92	5.55	5.51	2.35	2.41
	NMe	2.59	2.47	2.86	2.74	−0.27	−0.27
	CHO	8.01	7.97	8.19	8.13	−0.18	−0.16
N-Methylformamide(*cis*) (**32**)	NH(*cis*)	7.90	7.62	5.86	5.83	2.04	1.79
	NMe	2.72	2.68	2.94	2.95	−0.22	−0.27
	CHO	7.81	7.97	8.06	8.13	−0.25	−0.16

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Table 3. (*Continued*)

Compound	Proton	δ(DMSO)		δ($CDCl_3$)		$\Delta\delta$(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
Acetamide (**33**)	NH(*cis*)	6.70	6.66	5.42	5.81	1.29	0.85
	NH(*trans*)	7.30	7.11	5.42	5.22	1.88	1.89
	CO.Me	1.76	1.88	2.03	2.03	−0.27	−0.15
N-Me acetamide (**34**)	NH(*trans*)	7.70	7.58	5.53	5.25	2.17	2.33
	NMe	2.50	2.51	2.80	2.78	−0.30	−0.27
	CO.Me	1.78	1.87	1.98	2.02	−0.20	−0.15
Propionamide (**35**)	NH(*cis*)	6.62	6.71	6.14	5.87	0.48	0.84
	NH(*trans*)	7.16	7.14	5.38	5.25	1.78	1.89
	2	2.04	2.22	2.26	2.29	−0.22	−0.07
	3	0.97	1.00	1.17	1.07	−0.20	−0.07
Trimethylacetamide (**36**)	NH(*cis*)	6.64	6.75	5.56	5.91	1.08	0.84
	NH(*trans*)	6.97	7.15	5.22	5.25	1.74	1.90
	CO.Me	1.07	1.06	1.23	1.13	−0.16	−0.07
2-Pyrrolidinone (**37**)	NH	7.46	7.36	6.06	5.96	1.39	1.40
	3	2.07	2.15	2.30	2.38	−0.24	−0.23
	4	1.96	1.92	2.14	2.11	−0.18	−0.19
	5	3.20	3.28	3.40	3.42	−0.20	−0.14
Valerolactam (**38**)	NH	7.34	7.39	6.33	5.99	1.00	1.40
	3	2.11	2.13	2.36	2.36	−0.25	−0.23
	4	1.66	1.84	1.81	1.91	−0.15	−0.07
	5	1.65	1.64	1.79	1.90	−0.13	−0.26
	6	3.11	3.10	3.31	3.31	−0.21	−0.21
Caprolactam (**39**)	NH	7.34	7.33	6.35	5.98	0.99	1.35
	3	2.28	2.30	2.46	2.49	−0.17	−0.19
	4	1.52	1.60	1.69	1.66	−0.17	−0.06
	5	1.66	1.56	1.75	1.63	−0.10	−0.07
	6	1.49	1.49	1.65	1.68	−0.15	−0.19
	7	3.04	3.13	3.21	3.29	−0.16	−0.16
Formyl anilide(*cis*) (**40**)	NH	10.14	9.58	8.34	7.32	1.80	2.26
	o	7.15	6.98	7.09	6.92	0.06	0.06
	m	7.32	7.44	7.37	7.52	−0.05	−0.08
	p	7.07	7.28	7.21	7.36	−0.14	−0.08
	CHO	8.79	8.77	8.69	8.67	0.10	0.10
Formyl anilide(*trans*) (**41**)	NH	10.19	10.28	7.14	7.47	3.05	2.81
	o	7.59	7.32	7.55	7.26	0.05	0.06
	m	7.32	7.36	7.33	7.44	−0.01	−0.08
	p	7.09	7.16	7.15	7.24	−0.06	−0.08
	CHO	8.28	8.51	8.40	8.63	−0.13	−0.12
z-Acetanilide (**42**)	NH	9.88	10.15	–	7.39	–	2.76
	o	7.56	7.66	7.32	7.60	0.24	0.06
	m	7.28	7.35	7.49	7.43	−0.21	−0.08
	p	7.02	7.13	7.11	7.21	−0.09	−0.08
	CO.Me	2.03	1.96	2.18	2.12	−0.14	−0.16
Benzamide (**43**)	NH(*cis*)	7.34	7.30	6.08	5.86	1.26	1.44
	NH(*trans*)	7.93	7.59	6.08	5.90	1.85	1.69
	o	7.87	7.63	7.82	7.71	0.05	−0.08
	m	7.44	7.45	7.45	7.53	−0.01	−0.08
	p	7.51	7.49	7.53	7.57	−0.02	−0.08
2-Fluorobenzamide (**44**)	NH(*cis* to *O*)	7.59	7.42	6.09	5.99	1.50	1.43
	NH(*trans* to *O*)	7.66	8.01	6.72	6.31	0.94	1.70
	3	7.29	7.23	7.15	7.31	0.14	−0.08
	4	7.55	7.51	7.51	7.59	0.04	−0.08
	5	7.32	7.24	7.29	7.32	0.03	−0.08
	6	7.69	8.14	8.14	8.22	−0.45	−0.08

(*continued overleaf*)

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Table 3. (*Continued*)

Compound	Proton	δ(DMSO)		$\delta(CDCl_3)$		$\Delta\delta$(DMSO − $CDCl_3$)	
		Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
2,4,6-Trimethyl benzamide (**45**)	NH(*cis*)	7.34	7.66	6.22	6.23	1.12	1.43
	NH(*trans*)	7.59	7.57	5.74	5.88	1.85	1.69
	Me(*o*)	2.22	2.21	2.32	2.28	−0.10	−0.07
	m	6.81	6.81	6.84	6.89	−0.03	−0.08
	Me(*p*)	2.22	2.32	2.27	2.39	−0.05	−0.07
Trimethylacetanilide (**46**)	NH(*trans*)	9.20	8.85	6.66	6.10	2.54	2.75
	Me(*o*)	2.08	2.11	2.20	2.18	−0.12	−0.07
	m	6.85	6.78	6.90	6.86	−0.05	−0.08
	Me(*p*)	2.21	2.32	2.26	2.39	−0.05	−0.07
	CO.Me	2.01	1.97	2.20	2.21	−0.19	−0.24
Phenanthridone (**47**)	NH	11.65	11.55	9.17	9.25	2.48	2.30
	1	8.33	8.66	8.55	8.74	−0.22	−0.08
	2	7.65	7.56	7.62	7.64	0.02	−0.08
	3	7.86	7.74	7.82	7.82	0.04	−0.08
	4	8.51	8.47	8.31	8.55	0.20	−0.08
	5	8.39	8.46	8.24	8.54	0.15	−0.08
	6	7.27	7.46	7.32	7.54	−0.05	−0.08
	7	7.49	7.59	7.52	7.67	−0.03	−0.08
	8	7.38	7.38	7.22	7.24	0.16	0.14
Acridine amide (**48**)	NH	–	9.02	–	7.32	–	1.70
	1	8.08	7.82	7.86	7.82	0.22	0.00
	2	7.74	7.67	7.63	7.67	0.11	0.00
	3	7.93	7.83	7.81	7.83	0.12	0.00
	4	8.28	8.47	8.31	8.47	−0.03	0.00
	5	8.28	8.47	8.31	8.47	−0.03	0.00
	6	7.93	7.83	7.81	7.83	0.12	0.00
	7	7.74	7.67	7.63	7.67	0.11	0.00
	8	8.08	7.82	7.86	7.82	0.22	0.00
	CO.Me	2.25	1.95	2.29	2.17	−0.04	−0.22
trans-4-*t*Bu-*N*-acetyl-1-amino cyclohexane (**49**)	NH	7.66	7.20	5.56	5.90	2.11	1.30
	1a	3.85	3.75	4.11	4.07	−0.26	−0.32
	2a/6a	1.47	1.37	1.51	1.56	−0.03	−0.19
	2e/6e	1.70	1.64	1.85	1.83	−0.15	−0.19
	3a/5a	0.94	1.12	1.03	1.19	−0.09	−0.07
	3e/5e	1.51	1.74	1.66	1.81	−0.15	−0.07
	4a	1.22	1.05	1.04	1.12	0.18	−0.07
	*t*Bu Me	0.84	0.87	0.87	0.94	−0.03	−0.07
	CO.Me	1.83	1.84	1.99	1.99	−0.16	−0.15
cis-4-*t*Bu-*N*-acetyl-1-amino cyclohexane (**50**)	NH	7.61	7.61	5.42	5.27	2.19	2.34
	1e	3.40	3.39	3.67	3.70	−0.28	−0.31
	2a/6a	0.98	1.09	1.07	1.28	−0.09	−0.19
	2e/6e	1.81	1.68	2.01	1.87	−0.21	−0.19
	3a/5a	1.06	1.14	1.11	1.21	−0.05	−0.07
	3e/5e	1.71	1.73	1.78	1.80	−0.06	−0.07
	4a	0.93	1.04	1.01	1.11	−0.08	−0.07
	*t*Bu Me	0.83	0.86	0.84	0.93	−0.02	−0.07

–Peak not observed.

[a] Broad peak.

[b] Compounds 7 and 8 were run as a mixture of isomers and gave one NH_2 peak.

[c] Compounds 18 and 19 were run as a mixture of isomers and gave one OH peak.

[d] Ref. 24.

[e] Ref. 25.

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Table 4. ^{1}H chemical shifts of diols and polyhydroxy solutes in $CDCl_3$ (D_2O) and DMSO

		δ(DMSO)		δ($CDCl_3$)		Δδ(DMSO − $CDCl_3$)	
Compound	Proton	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
Ethylene glycol (**1**)	OH	4.47	4.17	1.78	1.82[a]	2.69	2.35
	CH_2	3.38	3.40	3.65	3.67	−0.27	−0.27
1,3-Propane diol (**2**)	OH	4.32	4.16	1.89	1.17	2.43	2.99
	1,3	3.45	3.32	3.69	3.59	−0.24	−0.27
	2	1.56	1.27	1.8	1.60	−0.24	−0.33
1,4-Butanediol (**3**)	OH	4.38	4.16	1.83	1.17	2.55	2.99
	1,4	3.39	3.33	3.63	3.60	−0.24	−0.27
	2,3	1.43	1.14	1.6	1.31	−0.17	−0.17
1,5-Pentanediol (**4**)	OH	4.34	4.16	1.24	1.17	3.10	2.99
	1,5	3.38	3.33	3.62	3.60	−0.24	−0.27
	2,4	1.41	1.08	1.58	1.31	−0.17	−0.23
	3	1.31	0.93	1.41	1.00	−0.10	−0.07
Cyclohexane-1,2-diol (*trans*) (**5**)	1a/2a	3.11	3.20	3.37	3.47	−0.26	−0.27
	3a/6a	1.13	1.14	1.25	1.33	−0.12	−0.19
	3e/6e	1.74	1.65	1.92	1.85	−0.18	−0.20
	4a/5a	1.13	1.16	1.25	1.22	−0.12	−0.06
	4e/5e	1.56	1.60	1.67	1.67	−0.11	−0.07
	OH	4.42	4.25	2.07	1.89	2.35	2.36
cis-Cyclohexane-1,4-diol (**6**)	1e/4a	3.51	3.52	3.81	3.79	−0.29	−0.27
	2a/6a/3e/5e	1.56	1.47	1.66	1.66	−0.11	−0.19
	2e/6e/3a/5a	1.40	1.48	1.66	1.67	−0.26	−0.19
	OH	4.25	4.27	1.55[b]	1.09	2.70	3.18
trans-Cyclohexane-1,4-diol (**7**)	1a/4a	3.36	3.33	3.66	3.60	−0.29	−0.27
	2a/6a/3a/5a	1.16	1.20	1.34	1.36	−0.18	−0.16
	2e/6e/3e/5e	1.74	1.68	1.93	1.85	−0.20	−0.17
	OH	4.38	4.26	1.55[b]	1.08	2.83	3.30

		δ(DMSO)		δ(D_2O)		Δδ(DMSO − D_2O)	
Compound	Proton	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
cis,cis,cis-1,3,5-Cyclohexane triol (eq) (**8**)	1/3/5	3.34	3.36	3.70	3.63	−0.37	−0.27
	2a/4a/6a	0.97	1.13	1.24	1.48	−0.27	−0.35
	2e/4e/6e	1.96	1.66	2.22	2.02	−0.26	−0.36
	OH	4.49	4.26	–	–	–	–
myo-Inositol (1ax−5eq) (**9**)	1e	3.72	3.67	4.07	3.94	−0.34	−0.27
	2a/6a	3.14	3.36	3.54	3.63	−0.40	−0.27
	3a/5a	3.37	3.40	3.64	3.68	−0.27	−0.28
	4a	2.93	3.22	3.27	3.49	−0.34	−0.27
	OH(1,3)	4.51	4.59	–	–	–	–
	OH(2)	4.55	4.83	–	–	–	–
	OH(4,6)	4.46	4.76	–	–	–	–
	OH(5)	4.31	4.77	–	–	–	–
1,3,5-*o*-Methylidine-*myo*-inositol (1eq−5ax) (**10**)	1e/3e	3.95	3.91	4.25	4.21	−0.29	−0.30
	2	4.01	3.94	4.28	4.21	−0.27	−0.27
	4e/6e	4.28	4.13	4.59	4.40	−0.32	−0.27
	5	4.07	3.92	4.34	4.21	−0.27	−0.29
	CH	5.46	5.32	5.61	5.47	0.00	−0.15
	OH(2)	5.32	5.51	–	–	–	–
	OH(4,6)	5.48	5.44	–	–	–	–
(+)-*chiro*-Inositol (4eq−2ax) (**11**)	1,6	3.65	3.67	4.03	3.94	−0.37	−0.27
	2,5	3.42	3.51	3.77	3.79	−0.34	−0.28
	3,4	3.27	3.37	3.60	3.64	−0.33	−0.27
	OH(1,6)	4.36	4.99	–	–	–	–
	OH(2,5)	4.03	4.51	–	–	–	–
	OH(3,4)	4.15	4.75	–	–	–	–

(*continued overleaf*)

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Table 4. (*Continued*)

Compound	Proton	δ(DMSO) Obsd	δ(DMSO) Calcd	δ(D_2O) Obsd	δ(D_2O) Calcd	Δδ(DMSO − D_2O) Obsd	Δδ(DMSO − D_2O) Calcd
Quebrachitol (4eq−2ax) (**12**)	1	3.87	3.88	4.27	4.15	−0.41	−0.27
	2	3.10	2.87	3.40	3.17	−0.30	−0.30
	3	3.38	3.61	3.62	3.88	−0.24	−0.27
	4	3.29	3.34	3.60	3.61	−0.31	−0.27
	5	3.43	3.54	3.75	3.81	−0.32	−0.27
	6	3.68	3.71	4.06	3.98	−0.38	−0.27
	OMe	3.41	3.32	3.47	3.43	−0.06	−0.11
	OH(1)	4.60	5.39	–	–	–	–
	OH(3)	4.39	5.13	–	–	–	–
	OH(4)	4.41	4.80	–	–	–	–
	OH(5)	4.26	4.78	–	–	–	–
	OH(6)	4.62	5.10	–	–	–	–

–Peak not observed.

[a] O.C.C.O gauche.

[b] Compounds 6 and 7 were run as a mixture to give one broad peak.

Table 5. Solvent contributions ($\Delta\delta$) vs Dihedral angle for the H.C.C.NH group

θ (degrees)	δ(DMSO)	δ($CDCl_3$)	Δδγ(exp)	Δδγ(calcd)	Exp-calcd	Source (compd/^{1}H)
7	0.50	0.59	−0.09	−0.09	0.00	3n, **5**, Fig. 4
54	1.56	1.65	−0.10	−0.11	0.01	2e, **6**, Fig. 4
56	0.94	1.03	−0.09	−0.11	0.02	2a, **7**, Fig. 4
57	1.60	1.72	−0.12	−0.11	−0.01	β-H, **8**, Fig. 4
62	1.78	1.89	−0.11	−0.11	0.00	2e, **7**, Fig. 4
74	1.95	2.07	−0.13	−0.12	−0.01	1H, **5**, Fig. 4
114	1.80	1.96	−0.16	−0.15	−0.01	3x, **5**, Fig. 4
170	1.37	1.54	−0.17	−0.17	0.00	2a, **6**, Fig. 4

some H.C.X protons. The NH protons of amides have an intriguing solvent dependence in that the *cis* and *trans* NH protons of formamide (**30**, Fig. 3) change assignments in going from $CDCl_3$ to DMSO solvent (Table 3). These assignments were obtained from the H.C.NH couplings and NOE data.[19] These effects were simulated by the expression $\Delta\delta$ (H.N.CO) $= -0.20 - 0.14 \cos\theta$, but, in this case, due to the approximate planarity of the amide group only dihedral angles of *ca* 0 and 180° are found.

For both the aliphatic H.C.C.NH protons of amines and the H.C.C.OH protons of alcohols, a dihedral angle dependence of $\Delta\delta$ was also found. The relevant data and corresponding graphs are given in Table 5 and Fig. 5 for the amines and Table 6 and Fig. 6 for the alcohols.

The rotationally averaged value of the above function is −0.13 ppm (*cf* observed values of −0.12, −0.12, −0.11 and −0.11 ppm for the methyl protons of diethylamine and the α-CH_2 protons of propylamine, butylamine and amylamine.

The rotationally averaged correction from Fig. 6 is −0.15 ppm (*cf* methyl of ethanol and 2-propanol obsd −0.18 and −0.17 res and $C_{(2)}H_2$ of *n*-propanol and *n*-butanol obsd −0.17 and −0.16 res).

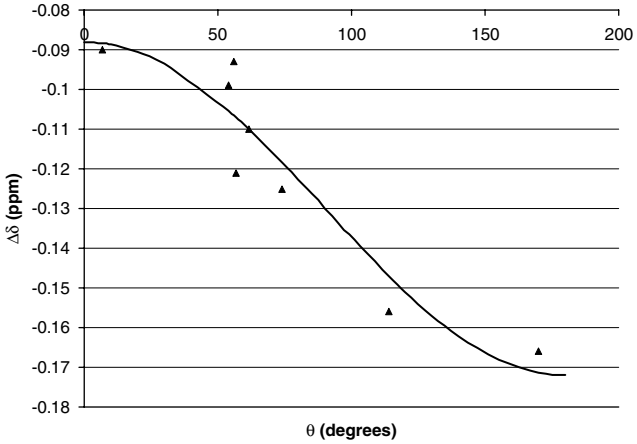

Figure 5. $\Delta\delta$ vs θ(H.C.C.NH) for protons in conformationally fixed amines. Observed points vs the function $\Delta\delta_\gamma = -0.13 + 0.042 \cos\theta$.

Diols and polyhydroxy compounds

These compounds include diols, triols and inositols. The polyhydroxy compounds are insoluble in $CDCl_3$, but soluble in D_2O. It has been shown recently[1,15] that the ^{1}H chemical shifts in D_2O for a wide variety of alcohols are identical to the corresponding shifts in $CDCl_3$. Thus, we have treated the solvent shifts $\Delta\delta = \delta$(DMSO) − δ(D_2O) in precisely the same manner as the solvent effects of DMSO vs $CDCl_3$ above.

These compounds may contain protons affected by β-, γ- and long-range effects from one or more hydroxyl and

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Table 6. Solvent contributions ($\Delta\delta$) vs dihedral angle for the H.C.C.OH group

θ (degrees)	$\Delta\delta$(exp)	$\Delta\delta$(calcd)	Source (compd/proton)
3	−0.12	−0.11	3x, **20**, Fig. 4
3	−0.13	−0.11	3n, **19,** Fig. 4
39	−0.14	−0.14	1H, **20,** Fig. 4
53	−0.16	−0.15	2e, **17**, Fig. 4
53	−0.15	−0.15	2a, **18**, Fig. 4
62	−0.17	−0.17	2e, **18**, Fig. 4
75	−0.19	−0.18	1H, **19**, Fig. 4
118	−0.19	−0.18	3x, **19**, Fig. 4
119	−0.18	−0.18	3n, **20,** Fig. 4
171	−0.15	−0.14	2a, **17,** Fig. 4

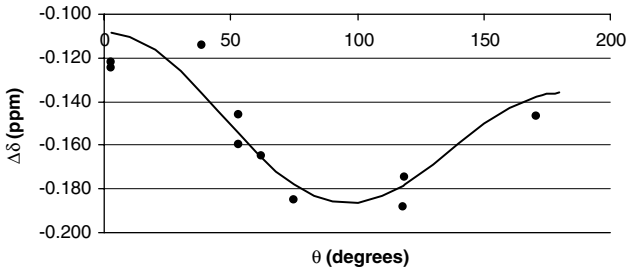

Figure 6. $\Delta\delta_\gamma$ vs θ(H–C–C–OH) for protons in conformationally fixed alcohols. Observed points vs $\Delta\delta_\gamma = -0.186 + 0.014\ \cos\ \theta + 0.064\ \cos^2\theta$.

ether groups simultaneously. The observed experimental $\Delta\delta$ values are much less than the cumulative additions of all these factors. For example, the observed $\Delta\delta$ value for the 3a/5a protons in *myo*-inositol (**9**, Fig. 4) is −0.27 ppm. If this correction was simply an additive function of all the effects present (i.e. 1 β-OH, 2 γ-OHs at *ca* 60° plus one long-range effect from the C_1OH), $\Delta\delta$ is calculated as −0.66 ppm. Thus, a priority system has been included in the programme. For these protons, only the β-OH correction is made, the remaining effects are ignored. This gives $\Delta\delta$ a value equal to −0.27 ppm, in good agreement with the observed value. For protons with no β-OH, but γ-OH interactions such as 2a/4a/6a of *cis,cis,cis*-1,3,5-cyclohexane triol (**8**, Fig. 4), both the γ-OH corrections are made, but long-range effects are ignored. This gives $\Delta\delta$ a value equal to −0.29 ppm (*cf* the observed value of −0.27 ppm). This approach has been applied to all the multifunctional compounds, with short-range effects taking priority over long-range effects. Where there is more than one of the same short-range effect, i.e. α, β or γ, all contributions are included. Also, for those compounds insoluble in $CDCl_3$, the only solvent in which the OH proton can be observed is DMSO. Thus, Table 4 for these compounds gives the observed vs calculated shifts for the OH proton in DMSO solvent. The data in Table 4 show that this approach gives good agreement generally.

Chemical shift contributions

The discrete contributions (a, β, γ and long-range) to $\Delta\delta$ discussed above are collected in Table 7 for the individual functional groups examined.

Table 7. Contributions to the DMSO solvent effect ($\Delta\delta$) ppm for individual functional groups

Group/ aliphatic	α(H.X)	β(H.C.X)	γ(H.C.C.X)	LR (H.C···X)
NH_2, NHR	0.64	−0.16	Fig. 5	−0.05
OH	2.88	−0.27	Fig. 6	−0.08
SH	0.86	−0.05	−0.08	−0.08
CO_2H	1.13	0.08	−0.17	−0.08
NH.CO	–	1.63	See text	−0.08
NR_2	–	−0.09	−0.09	−0.05
OR	–	−0.11	−0.09	−0.06
CHO	–	−0.14	−0.08	−0.06
CO.R	–	–	Eqn (1)	−0.06
CO_2R	–	−0.09	−0.05	−0.06
Hal[a]	–	0.10	−0.07	−0.06
Aromatic				
NH_2	1.34	–	−0.12	−0.20
NHR	1.65	–	−0.07	−0.16
H.N.Ph_2	2.66	–	−0.07	−0.07
OH	4.60	–	−0.08	−0.13
CO_2H	a	–	−0.11	0.08
≡CH	1.13	–	–	0.00
NR_2	–	–	−0.07	−0.07, 0.05 ($\underline{N}Ph_2$)
OR	–	–	−0.01	0.03
CHO	–	–	0.00	0.09
CO.R	–	–	0.00	0.07
CO_2R	–	–	0.06	0.11
F	–	–	0.14	0.09
Cl	–	–	0.11	0.12
Br	–	–	0.08	0.12
I	–	–	0.04	0.09

a, the acid proton was not observed in either solvent.
[a] $CHCl_2$ and $HCCl_3$ have additional contributions = 0.49 and 1.08 ppm res.

The prediction of the ^{1}H shifts in DMSO solution is dependent on both the accuracy of the original prediction of the shifts in $CDCl_3$ and on the DMSO correction. The accuracy of the CHARGE prediction has been dealt with previously.[1,13] The observed vs calculated correction $\Delta\delta$(DMSO − $CDCl_3$) is shown in Fig. 7 for all the observed shifts in this study. The linear correlation through the origin shown has the slope equal to 0.991 with an rms error of 0.05 ppm for the 1138 protons. In Fig. 7, the largest errors are for the labile protons of the acids, amides and diols, as expected. This is often due to the large concentration dependence of these protons owing to inter-molecular hydrogen bonding.[26] Large errors also occur in some diols where intra-molecular hydrogen bonding occurs in $CDCl_3$ solvent, which is not observed in DMSO. Thus, in propane-1,3-diol and butane-1,4-diol, the OH chemical shift in $CDCl_3$ solution is less shielded than in the simple alcohols due to the presence of an intra-molecular hydrogen bond. In DMSO solution, the OH shift is normal, as expected. In contrast, diols with no intra-molecular hydrogen bond such as *cis*-cyclohexane-1,4-diol (**6**, Fig. 4) give large $\Delta\delta$ values, which are well reproduced. Intra-molecular hydrogen bonding in these diols is considered in more depth elsewhere.[27]

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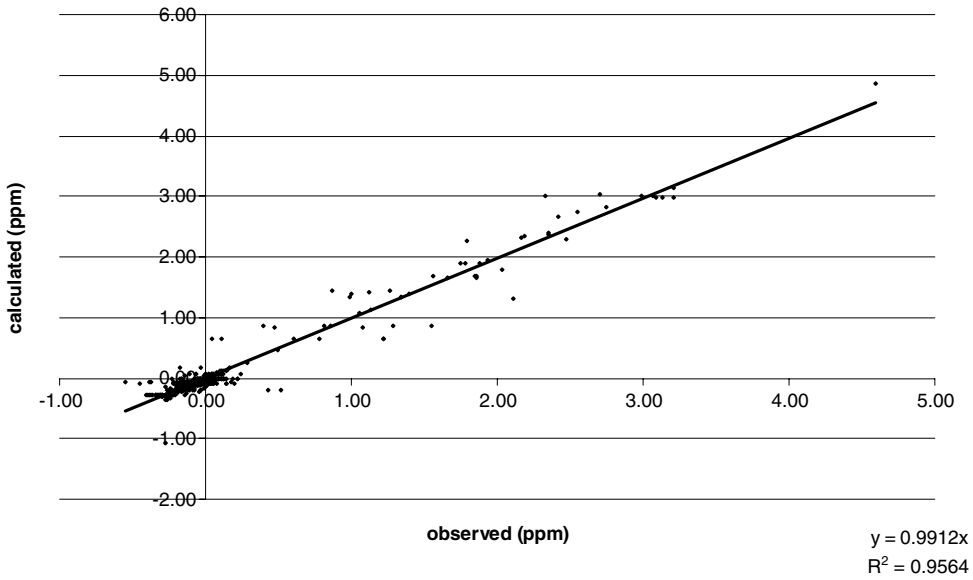

Figure 7. Calculated vs experimental solvent shifts $\Delta\delta(\text{DMSO} - \text{CDCl}_3)$.

The dilution shifts of other labile protons (e.g. amides, acids, etc.) are also large, but these protons often give broad signals that are difficult to observe. For these reasons, we have concentrated in predicting these shifts in DMSO solvent (in which there is no appreciable dilution shift) and the observed vs calculated shifts in DMSO are in good agreement. This is discussed in more detail elsewhere[1] for the alcohol shifts.

The ^{1}H shifts of the NH protons of the aliphatic amines show little consistency in either solvent and often the signals are too broad to observe. The NH_2^+ protons of dimethylamine hydrochloride occur at 9.2 ppm in $CDCl_3$ compared to the freebase at *ca* 1 ppm;[24] hence, traces of acid will produce large shifts of the NH protons and also broaden the signal due to exchange. This is the most probable reason for the lack of consistency of these shifts in either solvent. These protons are thus not useful for diagnostic purposes.

The aliphatic halo compounds are aprotic, but can give large $\Delta\delta$ values for geminal di and trihalo compounds. All the halo alkanes examined exhibit similar behaviour, with the β-proton(s) deshielded and the γ- and long-range protons shielded (Table 7). For monohalo substitution, the β-HCX contribution is small (*ca* 0.10 ppm, Table 7). This increases to 0.49 ppm in dichloromethane and 1.08 ppm in chloroform. The solvation site of these solute molecules appears to be the β-protons, suggesting that these protons are hydrogen bonding to the DMSO (see below).

The long-range effects for protons in polar compounds are all quite small. There is a constant value of *ca* −0.06 ppm for aliphatic protons. For aromatic protons, the values are *ca* ±0.1 ppm, but there is no obvious trend, and each aromatic substituent is considered separately.

The above model of the solvent effect of DMSO on the solute ^{1}H chemical shifts does not give any chemical explanation of these effects. It is thus pertinent to consider the possible causes of these shifts with reference to Eqn (1). For protic solutes, hydrogen bonding is the generally accepted mechanism for the solvent effects in DMSO solution. All the labile protons are deshielded from $CDCl_3$ to DMSO. In a separate investigation, it has been shown that the solvent effect of DMSO vs $CDCl_3$ on the protic hydrogen chemical shifts (at limiting dilution in $CDCl_3$) is closely correlated with the hydrogen bond acidity (A value) of the solute.[28] This correlation is valid not only for the simple alcohols and amides but also for the carbon hydrogen bond acceptors of $CHCl_3$ and CH_2Cl_2. Thus, the large positive shifts of these protons in DMSO, *cf* $CDCl_3$ can be attributed to the direct effect of the hydrogen bond. This large positive effect on the α-proton is accompanied, in most cases, by a negative effect on the β-(H.C.XH) proton (Table 7). This could be due to the effect of the hydrogen bond being transmitted to the β-proton or due to the direct effect of the attached DMSO molecule. The ^{1}H shifts of all the alcohols in Tables 3 and 4, which are soluble in D_2O and $CDCl_3$, are identical in the two solvents.[1] These alcohols will be strongly hydrogen bonded to the D_2O solvent, and this suggests that the primary cause of the β-, γ- and long-range proton shifts in DMSO is due to the direct effect of the attached DMSO molecule and not due to any transmission via the hydrogen bond.

The accepted effects of the solvent from Eqn (1) are the anisotropy, the electric field and the van der Waals shielding due to the solvent molecule. Of these three effects, the van der Waals shielding can be eliminated, as, again, if it is present, it should also occur in D_2O solvent. There is also no noticeable electric field effect in D_2O (due to the identity of the shifts in D_2O and $CDCl_3$). However, the dipole moment of DMSO (3.9 D) is much greater than that of D_2O (1.85 D). Thus, these considerations suggest that the major cause of the β-, γ- and long-range proton shifts in DMSO is the electric field and magnetic anisotropy of the DMSO solvent.

CONCLUSIONS

The above model of the solvent effect of DMSO on the solute ^{1}H chemical shifts provides a quantitative estimate of these shifts for a wide range of compounds. This includes the OH proton shifts of alcohols and phenols in dilute $CDCl_3$

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solution, but not the protic hydrogen of acids and amides in $CDCl_3$ solvent. An alternative method of approach is to directly calculate these shifts in DMSO solution and this is used here to give reasonably accurate shifts for the OH protons of alcohols and NH protons of amides in DMSO solution. Neither approach was tenable for the NH protons of amines since these shifts were scattered in both solvents, probably due to traces of acid in the medium.

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