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^{1}H chemical shifts in NMR: Part 22† – Prediction of the ^{1}H chemical shifts of alcohols, diols and inositols in solution, a conformational and solvation investigation

Raymond J. Abraham,[1]* Jonathan J. Byrne,[1] Lee Griffiths[2] and Rodothea Koniotou[1]

[1] Chemistry Department, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK
[2] Astra/Zeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

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The ^{1}H NMR spectra of a number of alcohols, diols and inositols are reported and assigned in $CDCl_3$, D_2O and DMSO-d_6 (henceforth DMSO) solutions. These data were used to investigate the effects of the OH group on the ^{1}H chemical shifts in these molecules and also the effect of changing the solvent. Inspection of the ^{1}H chemical shifts of those alcohols which were soluble in both $CDCl_3$ and D_2O shows that there is no difference in the chemical shifts in the two solvents, provided that the molecules exist in the same conformation in the two solvents. In contrast, DMSO gives rise to significant and specific solvation shifts. The ^{1}H chemical shifts of these compounds in the three solvents were analysed using the CHARGE model. This model incorporates the electric field, magnetic anisotropy and steric effects of the functional group for long-range protons together with functions for the calculation of the two- and three-bond effects. The long-range effect of the OH group was quantitatively explained without the inclusion of either the C—O bond anisotropy or the C—OH electric field. Differential β and γ effects for the 1,2-diol group needed to be included to obtain accurate chemical shift predictions. For DMSO solution the differential solvent shifts were calculated in CHARGE on the basis of a similar model, incorporating two-bond, three-bond and long-range effects. The analyses of the ^{1}H spectra of the inositols and their derivatives in D_2O and DMSO solution also gave the ring ^{1}H,^{1}H coupling constants and for DMSO solution the CH—OH couplings and OH chemical shifts. The ^{1}H,^{1}H coupling constants were calculated in the CHARGE program by an extension of the $\cos^2\phi$ equation to include the orientation effects of electronegative atoms and the CH—OH couplings by a simple $\cos^2\phi$ equation. Comparison of the observed and calculated couplings confirmed the proposed conformations of *myo*-inositol, *chiro*-inositol, quebrachitol and *allo*-inositol. The OH chemical shifts were also calculated in the CHARGE program. Comparison of the observed and calculated OH chemical shifts and CH.OH couplings suggested the existence of intramolecular hydrogen bonding in a *myo*-inositol derivative. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{1}H chemical shifts; alcohols; conformational analysis; NMR prediction; solvation

INTRODUCTION

Alcohols are of considerable practical and theoretical importance in chemistry, biology and commerce. Yet although the effect of the electronegative oxygen atom on ^{1}H chemical shifts has been known for about five decades[2] a definitive analysis of OH substituent chemical shifts (SCS) in proton spectra has not been performed to date, despite a number of investigations.[3,4] Zürcher[3a] was limited to observing only the methyl groups in steroids in his pioneering studies but concluded that the C—O bond anisotropy was not important for the OH group SCS. Schneider *et al*.[3b] regarded the electric field term as the dominant term, but Hall[3c] suggested that the chemical shift difference between the anomeric protons of the C(2)—O axial and C(2)—O equatorial sugars could be accounted for by C–O anisotropy alone. Yang *et al*.[4] concluded that electric field, anisotropy and a constant term were necessary to reflect the observed ether SCS in oxa steroids but did not consider any steric contributions. Abraham *et al*.[5] in a systematic study of acyclic and cyclic ethers showed that the ^{1}H chemical shifts in these systems could be predicted accurately using their CHARGE model. This included both oxygen steric and electrostatic terms but no C—O anisotropy.

The biologically important polyhydroxy compounds (sugars, etc.) are insoluble in $CDCl_3$, hence for a general prediction of the ^{1}H spectra of hydroxy compounds it is necessary to extend the analysis to include other solvents.

*Correspondence to: Raymond J. Abraham, Chemistry Department, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK. E-mail: abrahamr@liv.ac.uk
†For Part 21, see Ref. 1.

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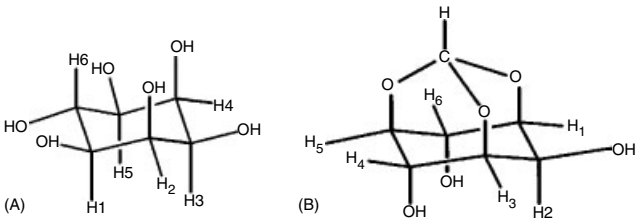
Here we consider the three most commonly used solvents for these compounds, $CDCl_3$, D_2O and DMSO. A major problem in such analyses is the conformational isomerism about the oxygen atom. For example, the SCS of the hydroxyl group may well be dependent on the position of the hydroxyl proton. The value of the CH–OH coupling in alcohols in solution shows that the OH proton is usually not in a single orientation but may have a preferred conformation.[6] However, it is very difficult to estimate accurately the populations of the different OH conformers, especially in D_2O solution. These considerations plus the very considerable problems of modelling solvation in these systems by quantum mechanics[7] mean that the very useful GIAO calculations[8] are impractical at this stage for these systems. We will use the semi-empirical CHARGE system as a basis for the calculations. This has been used successfully for a wide range of functional groups in $CDCl_3$ solution[1,9] and we shall show that specific solvation shifts may be incorporated into the model without requiring a detailed model of solvation. The criteria for the molecules selected for this investigation were (a) solubility in at least two solvents and (b) the requirement for the cyclic compounds to exist in one conformation in solution. Also, we include a selected group of polyhydroxy compounds, the inositols. These important compounds have the advantage (over, e.g., the sugar molecules) of a well-defined cyclohexane ring, making the determination of their conformation a relatively easy matter.

The ^1H spectra of the simple alcohols have been well documented but the conformations of the 1,2-diols and derivatives in solution has been the subject of some controversy. In ethylene glycol, recent NMR investigations[10] found that the *gauche* form predominates with ca 10–20% of the *trans* form in solution and other investigations on related diols have obtained similar results.[11] The conformation of *cis*-cyclohexane-1,3-diol was determined in a variety of solvents by measuring the appropriate $^3J(H,H)$ couplings.[12] In polar solvents the diequatorial form predominates but in $CDCl_3$ the diequatorial and diaxial conformers are of about equal energy owing to an intramolecular hydrogen bond between the 1,3-diaxial hydroxy groups. Intramolecular hydrogen bonds have also been observed in both *cis*- and *trans*-cyclohexane-1,2-diol.[13] Cyclopentanol and *cis*- and *trans*-cyclopentane-1,2-diols have been shown to be interconverting between several conformations in $CDCl_3$ solution by a combined modelling and LIS investigation.[14]

Inositols and their derivatives have attracted a great deal of attention because of their diverse biological activities.[15,16] There are eight diastereomers; seven are achiral and one (*chiro*-inositol) chiral. The ^1H and ^{13}C spectra of a number of inositols and their *O*-methyl derivatives have been reported in D_2O solution and assigned.[17–19] The $^1H,^1H$ coupling constants for *myo*-, *chiro*- and *epi*-inositol and the methyl ether of *scyllo*-inositol were obtained from first-order analyses.[17] A ^1H study of *myo*-inositol in a lyotropic liquid crystal at 90 MHz[20] gave the direct couplings between the protons but could not deduce the molecular structure owing to the low degree of order in the mesophase. Also, a ^1H and ^{13}C study of inositol phosphates in aqueous solutions showed the influence of pH on the conformational preferences of these molecules.[21]

Intramolecular hydrogen bonds in sugars and inositols in DMSO solution have been investigated by several NMR techniques. These include the temperature dependence of the OH signal,[22] the effects of partial isotopic substitution (the SIMPLE NMR method)[23] and the use of the CH.O.H coupling in DMSO solution.[24] Interestingly, there have been no reports of the use of the OH chemical shift (see later). The only intramolecular hydrogen bonds found in DMSO solution were formed between OH groups in a 1,3-diaxial orientation. Examples of this were the C-2 and C-4 OH groups in *epi*-inositol[24] (**A**) and the C-4 and C-6 OH groups in 1,3,5-methylidene myo-inositol[22] (**B**).



THEORY

As the theory has been given previously,[1,9] only a brief summary of the latest version (CHARGE8A[25]) will be given here. The theory distinguishes between short-range substituent effects over one, two and three bonds, which are attributed to the electronic effects of the substituents, and long-range effects due to the electric fields, steric effects and anisotropy of the substituents.

Short-range effects

The CHARGE scheme calculates the effects of neighbouring atoms on the partial atomic charge of the atom under consideration based on classical concepts of inductive and resonance contributions. If we consider an atom I in a four-atom fragment I–J–K–L the partial atomic charge on I is due to three effects. There is a α-effect from atom J given by the difference in the electronegativity of atoms I and J and a β-effect from atom K proportional to both the electronegativity of atom K and the polarizability of atom I. There is also a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L for I = H and L = F, Cl, Br, I. However, for chain atoms (C, N, O, S, etc.) the γ effect (i.e. C.C.C.H) is parameterized separately and is given by $A + B\cos\theta$, where θ is the C.C.C.H dihedral angle and A and B are empirical parameters.

The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using the equation

$$\delta = 160.84q - 6.68 \quad (1)$$

Long-range effects

The effects of distant atoms on the ^1H chemical shifts are due to steric, electric field and anisotropic contributions. H···H steric interactions are shielding in alkanes and deshielding

in aromatics and X···H (X = C, O, Cl, Br, I) interactions deshielding, according to a simple r^{-6} dependence (Eqn. 2) where a_S is the steric coefficient for any given atom.

$$\delta_{steric} = a_S/r^6 \quad (2)$$

The effect of the electric field from a C—X bond (X = H, F, Cl, Br, I, O) is calculated from Eqn (3), where A_Z was empirically determined to be 3.67×10^{-12} esu (63 ppm au) and E_Z ($E_{deshielding} + E_{shielding}$, in Fig. 1) is the component of the electric field along the C—H bond according to Eqn (4).

$$\delta_{el} = A_Z E_Z \quad (3)$$

$$E_Z = -\frac{q^- \cos\theta_1}{r_1^3} + \frac{q^+ \cos\theta_2}{r_2^3} \quad (4)$$

The electric field for a univalent atom (e.g. Cl) is calculated as due to the charge on the chlorine atom and an equal and opposite charge on the attached carbon atom (Fig. 1). The vector sum gives the total electric field at the proton concerned and the component of the electric field along the C—H bond considered is calculated from Eqn (4).

The contribution of the magnetic anisotropy of a bond is obtained from the appropriate McConnell equation.[26] This differs for bonds with cylindrical symmetry (e.g. C≡C) with one anisotropy contribution and non-symmetric groups such as C=C in which the parallel and perpendicular anisotropy of the bond must be considered. In the CHARGE model only double and triple bonds have so far been shown to have significant anisotropies.

For aromatic compounds, it is necessary to include the shifts due to the aromatic ring current and the π electron densities in the aromatic ring.[27–29] The equivalent dipole approximation is used to calculate the ring current shifts and the π electron densities are calculated from Hückel theory.[29,30] The Coulomb and resonance integrals for a carbon 2pz atomic orbital and the factors modifying these integrals for orbitals other than sp^2 carbon are obtained so that the π densities calculated from the Huckel routine reproduce the π densities from *ab initio* calculations.

The effect on the ^{1}H chemical shifts of the excess π electron density at a neighbouring carbon atom is given by considering the π densities on both the α and β carbon atoms with respect to the proton. The above contributions are added to Eqn (1) to give the calculated shift of Eqn (5).

$$\delta_{total} = \delta_{charge} + \delta_{steric} + \delta_{anis} + \delta_{el} + \delta_\pi + \delta_{rc} \quad (5)$$

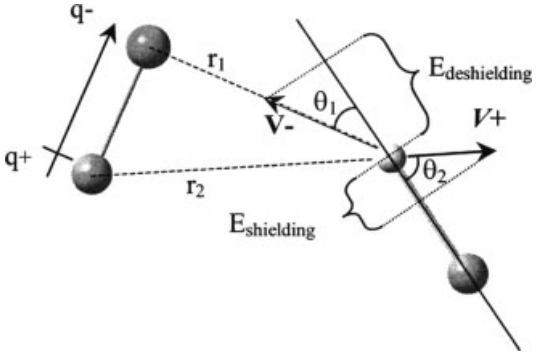


Figure 1. The geometry dependence of the electric field effect on ^{1}H chemical shifts, where $\mathbf{V}^-$ and $\mathbf{V}^+$ are the electric field vectors due to the negative (q^-) and positive (q^+) charges on the atoms in a C—X bond.

Application to alcohols

In order to apply the above theory to alcohols, both the short-range electronic effects of the OH group and the long-range contributions need to be obtained. The short-range effects include the γ (H.C.C.OH) parameters and also for the ethers the corresponding H.C.C.OMe and H.C.O.C parameters. We find that the 1,2-dioxy compounds need to be treated separately in this respect so that there is another set of parameters for the H.C(OR).C(OR) fragment.

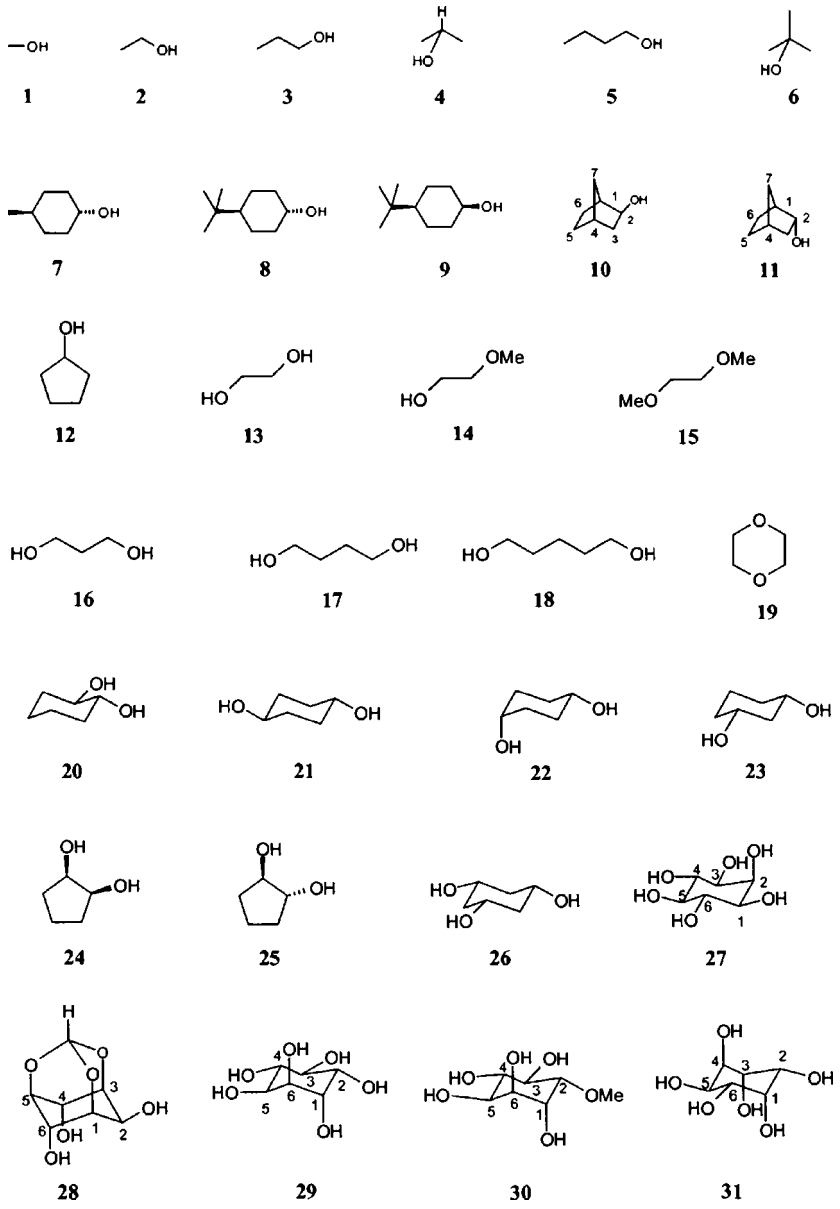
The long-range contributions include in principle steric, anisotropic and electric field effects. It has been shown in earlier investigations that the steric effect of the oxygen atom (i.e. the effective size of the atom) varies considerably in ethers,[5] phenols[31] and esters,[1] hence it is necessary to obtain the value of a_s [Eqn (2)] for the OH function. Again, it was found that the 1,2-diols required a separate, smaller value of a_s than the simple alcohols (see later). Also, in the calculations performed to date no anisotropic contributions were found for any single bond. Therefore, we shall assume that this is so for the C—O and O—H bonds of the alcohols.

The electric field term requires some consideration. The O—H, O—C and C—H bond dipole moments are ca 1.53, 0.86 and 0.3 D.[32] These bond dipoles are opposed in the HC.OH system to give a resultant dipole moment along the C—O bond of ca 0.3 D. The major component of the C.OH dipole is perpendicular to the C—O bond. However, the OH proton is rapidly rotating between three different possible conformations. Hence the time average electric field produced along a given C—H bond by the rapidly rotating C.OH group will be very small. It was therefore decided to ignore any electric field effects due to the HC.OH group in the CHARGE chemical shift calculations.

EXPERIMENTAL

The compounds considered are shown in Scheme 1. The ^{1}H chemical shifts of methanol, ethanol, *n*-propanol, 2-propanol, *tert*-butanol, ethylene glycol and 2-methoxyethanol in all three solvents are from Ref. 33. The data for *endo*- and *exo*-norborneol in $CDCl_3$ solution are from Ref. 34 and those for *cis*- and *trans*-4-tert-butylcyclohexanols in $CDCl_3$ and *cis*-1,3-cyclohexanediol in all three solvents are from Ref. 12. The ^{1}H spectra of cyclopentanol and *cis*- and *trans*-1,2-cyclopentanediol in $CDCl_3$ and D_2O solution have been assigned[14] and the assignments for *cis*,*cis*-1,3,5-cyclohexanetriol, *myo*-inositol, *chiro*-inositol and quebrachitol in D_2O solution have been reported.[17,35] The ^{1}H spectra of cyclohexanetriol and the inositols were remeasured and assigned in D_2O at 400 MHz to obtain more accurate chemical shifts and ^{1}H,^{1}H coupling constants. The corresponding spectra in DMSO solution have not been reported previously.

The compounds examined here were obtained commercially (Aldrich). Where possible, solutions of ca 10 mg ml^{-1}



Scheme 1. Compounds investigated.

were made in the three solvents. In one case (*allo*-inositol), methanol-d_4 was used for a low-temperature experiment. The reference for the $CDCl_3$ and DMSO solutions was TMS and for the D_2O solutions DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate).

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Typical running conditions were 128 transients, spectral width 6000 Hz and 32K data points with an acquisition time of 2.7 s. ^{13}C NMR spectra were also recorded on the same machine operating at 100 MHz. Typical running conditions were spectral width 26 000 Hz, 64K data points with an acquisition time of 1.2 s. For the ^{1}H spectra the FID was zero filled to 128K to give a digital resolution of 0.1 Hz Also, Gaussian multiplication of the FID was carried out for some compounds. Typical values were LB = −0.5 Hz and GB = 30%. The 2D experiments were conducted using the Bruker Avance COSY and HMQC pulse sequences.[36]

The molecular geometries were obtained by molecular mechanics (PCMODEL v.8 with the MMFF94 force field).[37] Iterative analysis of the observed spectra to obtain the ^{1}H chemical shifts and couplings was performed with LAOCOON3[38] and the simulations of the calculated spectra used the Mestre-C v. 2.3 program.[39]

Spectral assignments

The assignments for *cis*- and *trans*-4-*tert*-butylcyclohexanol, cyclopentanol and *cis*- and *trans*-1,2-cyclopentanediol in DMSO follow immediately from their known assignments in $CDCl_3$.[12,14] The assignments of the spectra of *trans*-4-methylcyclohexanol, *trans*-cyclohexane-1,2-diol, *cis*- and *trans*-cyclohexane-1,4-diol and *cis*,*cis*-1,3,5-cyclohexanetriol in DMSO were obtained readily from the spectra and, where necessary, H/H COSY plots.

myo-Inositol (27)

The only equatorial proton (H-2) is readily identified and the remaining assignments followed from a COSY plot. In DMSO-d_6 solution all the signals are resolved and the OH

protons couple with the adjacent CH proton. The assignment follows that in D_2O solution and the individual OH signals were assigned by a COSY plot.

1,3,5-O-Methylidine-myo-inositol (28)

Symmetry considerations give five separate resonances in this spectrum and these are all resolved in D_2O. The bridge CH proton was assigned to the doublet signal at 5.61 ppm ($J = 1.6$ Hz). A long-range coupling to H-1,3 and H-5 would appear reasonable as they have the favoured W arrangement. However, such a coupling would give a quartet pattern. Another possibility is for a ^5J coupling with H-2 and similar couplings have been observed in fused cyclohexane rings.[40] This assigns H-2 and an H/HCOSY plot gave the remaining assignments. The spectral frequencies were iterated to give the ^{1}H,^{1}H coupling constants and shifts and the simulated and observed spectra are shown in Fig. 2. In DMSO-d_6 two separate OH resonances were observed and assigned by a ^{1}H/^{1}H COSY plot. The assignment of the remaining signals was the same as in D_2O.

(+)-chiro-Inositol (29)

The twofold axis of symmetry in *chiro*-inositol gives three pairs of equivalent protons and the assignment of the spectrum in D_2O is straightforward with H-1,6 at high frequency. The spectral frequencies of this AA′BB′CC′ system were iterated to give the ^{1}H,^{1}H couplings and shifts. The simulated and observed spectra for H-3,4 and H-2,5 are shown in Fig. 3. In DMSO solution three extra OH doublets were observed and readily assigned and the spectrum was analysed similarly.

*Quebrachitol (**30**): 2-O-methyl-*chiro*-inositol*

In D_2O, six separate proton resonances were observed including the methyl peak at 3.45 ppm. The remaining five resonances could not be assigned unambiguously. The assignment was resolved when the spectrum was acquired in DMSO-d_6. In DMSO one multiplet pattern (3.10 ppm) does not have an additional coupling and this is clearly H-2, the only ring proton with no geminal OH group. The remainder of the spectrum was then assigned by a ^{1}H/^{1}H COSY plot.

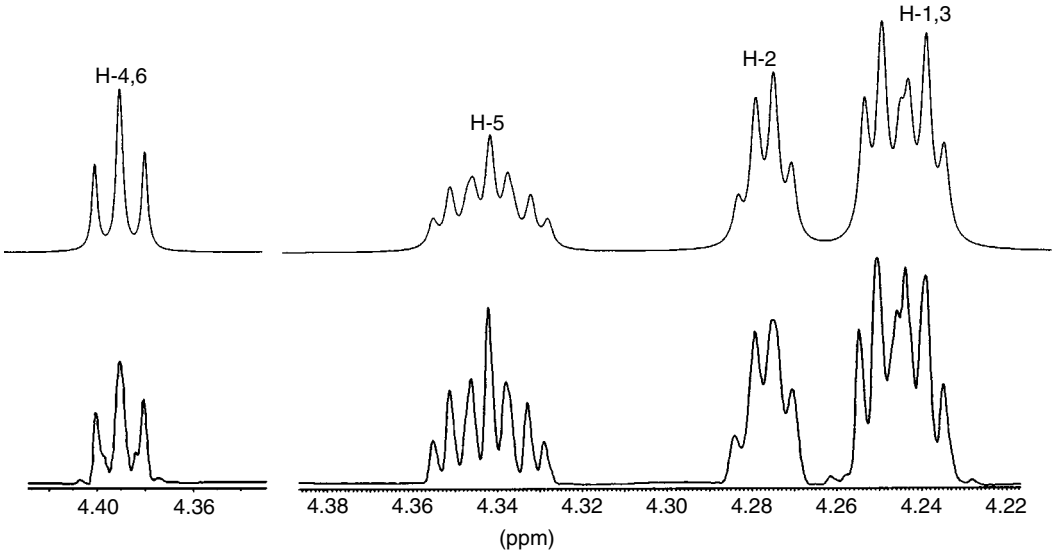


Figure 2. Simulated (above) and observed (below) proton spectra of 1,3,5-*O*-methylidine-*myo*-inositol (**28**) in D_2O.

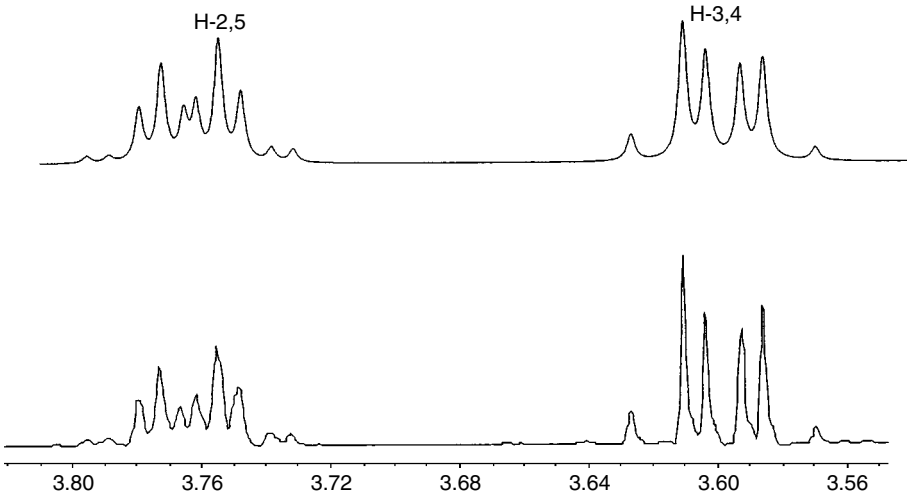


Figure 3. Calculated (above) and observed (below) proton spectra of H-3,4 and H-2,5 of (+)-*chiro*-inositol (**29**) in D_2O.

The $^1H,^1H$ coupling constants were obtained by iteration and the assignment in D_2O followed.

allo-Inositol (31)

The molecule interconverts between the two stereoisomeric chair forms (**31a** and **31b**),[17] which averages H-1 and H-2, H-3 and H-6, and H-4 and H-5. The ^1H spectrum in D_2O at room temperature is a broad unresolved pattern owing to the slow interconversion of the two forms. At 30 °C two separate broad peaks were observed at ca 3.9 and 4.2 ppm. To resolve the spectrum a VT experiment was performed in MeOD-d_4 with two drops of D_2O added to achieve complete solubility of the compound. At −40 °C the spectrum of the chair form was observed as six separate proton resonances. The assignment was aided by a $^1H/^1H$ COSY plot at the same temperature. The spectrum was analysed to give the vicinal $^1H,^1H$ coupling constants plus a long-range coupling of 1.8 Hz between H-1 and H-3. The observed and simulated spectra are shown in Fig. 4.

Iterative analyses of the observed spectra using LAOCOON3 were carried out for all the inositol spectra recorded here to give accurate values of the chemical shifts and $^1H,^1H$ coupling constants in the ring. The spectra were then simulated using Mestre-C v.2.3. to compare with the observed spectra. Full details and all the simulated and experimental spectra are given in Ref. 41. The observed ^1H chemical shifts and coupling constants of each compound are listed in Tables 1–4.

RESULTS AND DISCUSSION

The results in Tables 1–4 can now be evaluated. Inspection of the ^1H chemical shifts of the compounds in $CDCl_3$ and D_2O in Tables 1 and 2 shows remarkable consistency. For the 21 compounds which are soluble in both solvents and in which the conformational profile is unchanged in the two solvents, there are 79 distinct chemical shifts. The r.m.s. difference $\Delta\delta(D_2O - CDCl_3)$ of these 79 chemical shifts is 0.034 ppm, a value not much greater than the experimental errors. The largest difference, not surprisingly, is for the methyl group in methanol (0.12 ppm). We may conclude that for these compounds the ^1H chemical shifts in D_2O are essentially identical with those in $CDCl_3$. Inspection of other tabulated shifts[33] shows that this identity applies to other common functional groups, e.g. acetone 2.17 vs 2.22, acetonitrile 2.10 vs 2.06 and nitromethane 4.33 vs 4.40.

This identity only applies to compounds with the same conformational profile in the two solvents and this is illustrated by the results in the tables. For those compounds in which intramolecular hydrogen bonding is possible, the

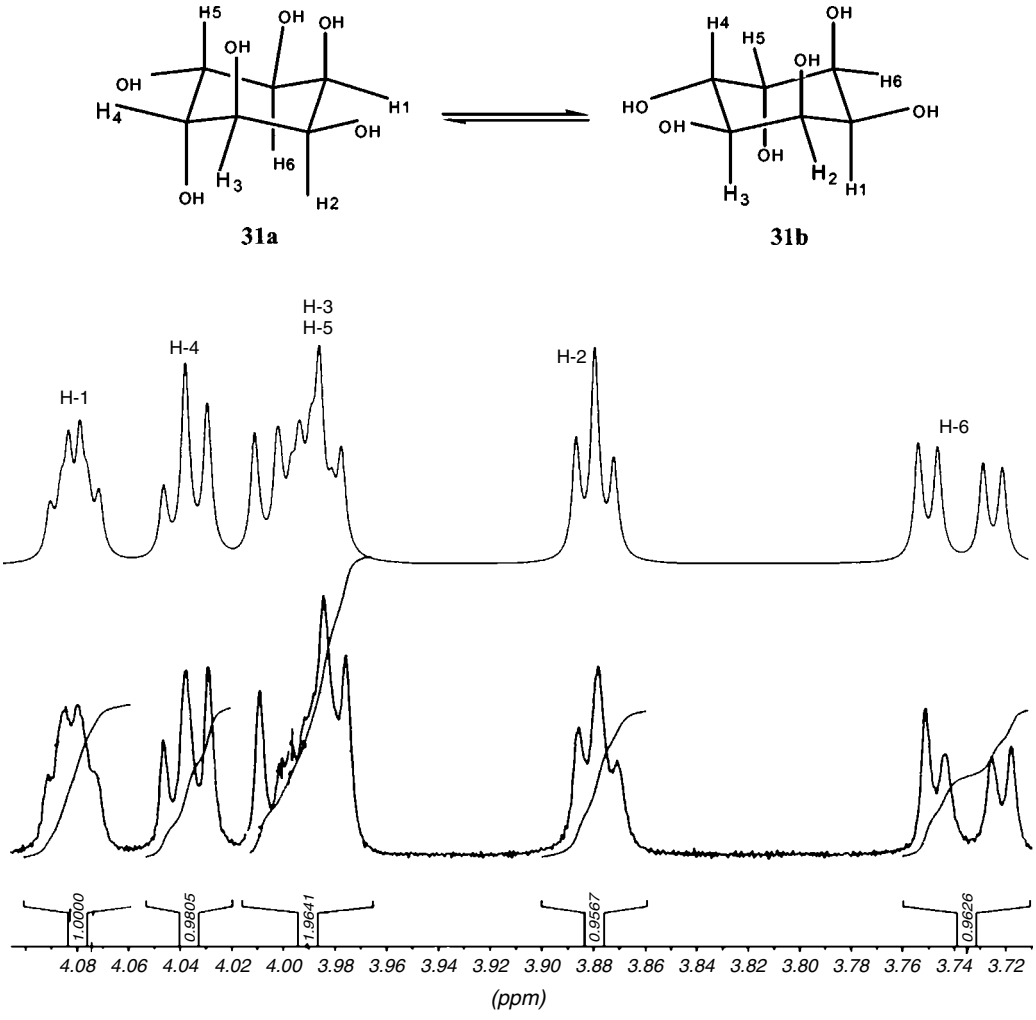


Figure 4. Simulated spectrum (above) and observed (below) proton spectrum of *allo*-inositol at −40 °C.

Table 1. Observed vs calculated ^{1}H chemical shifts (δ) of alcohols in $CDCl_3$, D_2O and DMSO solution[a]

Molecule		Obs.			DMSO	
		$CDCl_3$	D_2O	Calc.	Obs.	Calc.
Methanol[b] (**1**)	Me	3.49	3.34	3.37	3.17	3.10
	OH	1.13	–	1.43	4.05	4.05
Ethanol[b] (**2**)	CH_2	3.71	3.65	3.74	3.44	3.47
	Me	1.24	1.17	1.18	1.06	1.02
	OH	1.51	–	1.37	4.31	4.20
n-Propanol[b] (**3**)	α-CH_2	3.59	3.61	3.57	3.34	3.30
	β-CH_2	1.59	1.57	1.48	1.42	1.35
	CH_3	0.94	0.89	0.85	0.84	0.78
	OH	1.51	–	1.33	4.31	4.17
2-Propanol[b] (**4**)	CH	4.04	4.02	3.98	3.78	3.71
	CH_3	1.22	1.17	1.25	1.04	1.09
	OH	1.36	–	1.20	4.30	4.29
n-Butanol (**5**)	α-CH_2	3.64	3.61	3.59[f], 3.62[g]	3.38	3.32[f], 3.46[g]
	β-CH_2	1.56	1.51	1.30, 1.47	1.40	1.16, 1.23
	γ-CH_2	1.39	1.35	1.16, 1.34	1.30	1.08, 1.23
	CH_3	0.94	0.91	0.84, 0.82	0.87	0.77, 0.77
	OH	1.50	–	1.40, 1.38	4.30	4.23, 4.21
tert-Butanol[b] (**6**)	*t*-Bu	1.28	1.24	1.30	1.18	1.15
	OH	1.37	–	1.13	4.19	4.38
trans-4-Methylcyclohexanol (**7**)	1ax	3.52	3.58	3.59	3.29	3.32
	2,6eq	1.94	1.90	1.84	1.76	1.73
	2,6ax	1.25	1.25	1.38	1.11	1.25
	3,5eq	1.70	1.70	1.63	1.60	1.56
	3,5ax	0.96	0.97	0.86	0.89	0.79
	4ax	1.33	1.33	1.36	1.25	1.29
	Me	0.88	0.86	0.87	0.83	0.80
	OH	2.30	–	1.26	4.44	4.29
trans-4-*tert*-Butylcyclohexanol[c] (**8**)	1ax	3.52	–	3.58	3.25	3.31
	2,6eq	2.01	–	1.84	1.84	1.72
	2,6ax	1.22	–	1.38	1.07	1.26
	3,5eq	1.78	–	1.64	1.68	1.67
	3,5ax	1.05	–	0.86	0.96	0.92
	4ax	0.97	–	1.01	0.92	0.93
	t-Bu	0.85	–	0.88	0.82	0.81
	OH	1.26	–	1.31	4.39	4.34
cis-4-*tert*-Butylcyclohexanol[c] (**9**)	1eq	4.03		4.02	3.80	3.75
	2,6eq	1.83	–	1.83	1.67	1.70
	2,6ax	1.49	–	1.53	1.34	1.49
	3,5eq	1.54	–	1.60	1.46	1.58
	3,5ax	1.35	–	1.34	1.34	1.27
	4ax	0.99	–	0.98	0.93	0.90
	t-Bu	0.86	–	0.89	0.82	0.82
	OH	1.25	–	1.29	4.11	4.33
2-*exo*-Norborneol[d] (**10**)	H-1	2.14	2.05	2.07	1.99	1.94
	2*en*	3.77	3.70	3.61	3.52	3.46
	3*ex*	1.29	1.38	1.25	1.16	1.16
	3*en*	1.67	1.67	1.66	1.49	1.53
	H-4	2.26	2.26	2.21	2.14	2.13
	5*ex*	1.43	1.41	1.55	1.35	1.46
	5*en*	1.02	1.00	1.18	0.94	1.22
	6*ex*	1.46	1.46	1.55	1.35	1.44
	6*en*	1.02	1.03	1.25	0.94	1.07
	7s	1.57	1.50	1.60	1.49	1.53

(*continued overleaf*)

Table 1. (*Continued*)

Molecule		Obs. $CDCl_3$	Obs. D_2O	Calc.	DMSO Obs.	DMSO Calc.
	7a	1.12	1.14	1.07	0.98	1.11
	OH	–	–	1.32	4.38	4.35
2-*endo*-Norborneol[d] (**11**)	H-1	2.25	2.24	2.36	2.06	2.19
	2*ex*	4.23	4.12	4.01	4.00	3.80
	3*ex*	1.96	1.92	1.99	1.76	1.87
	3*en*	0.84	0.83	0.90	0.72	0.79
	H-4	2.17	2.15	2.19	2.06	2.12
	5*ex*	1.57	1.56	1.53	1.46	1.43
	5*en*	1.34	1.38	1.27	1.22	1.21
	6*ex*	1.36	1.40	1.39	1.22	1.31
	6*en*	1.88	1.71	1.77	1.86	1.70
	7s	1.34	1.35	1.17	1.22	1.16
	7a	1.29	1.30	1.17	1.22	1.22
	OH	1.44	–	1.24	4.43	4.28
Cyclopentanol[e] (**12**)	H-1	4.32	4.30	3.94	4.09	3.67
	2,5*cis*	1.56	1.58	1.41	1.44	1.32
	2,5*tr*	1.76	1.79	1.79	1.61	1.69
	3,4*cis*	1.76	1.79	1.68	1.61	1.55
	3,4*tr*	1.56	1.58	1.50	1.44	1.45
	OH	1.28	–	1.25	4.33	4.28

[a] This work unless stated otherwise.
[b] Ref. 33.
[c] Ref. 12.
[d] Ref. 34.
[e] Ref. 14.
[f] All-*trans* conformer.
[g] C.C.C.O *gauche*.

Table 2. Observed vs calculated ^{1}H chemical shifts (δ) of diols and related ethers in $CDCl_3$, D_2O and DMSO solution[a]

Molecule		Obs. $CDCl_3$	Obs. D_2O	Calc.	DMSO Obs.	DMSO Calc.
Ethylene glycol[b] (**13**)	CH_2	3.73	3.65	3.72	3.38	3.45
	OH	2.53	–	1.49	4.47	4.17
2-Methoxyethanol[b] (**14**)	α-CH_2	3.70	3.71	3.85	3.48	3.58
	β-CH_2	3.51	3.56	3.48	3.33	3.28
	Me	3.40	3.38	3.35	3.24	3.28
	OH	3.10	–	1.35	4.59	4.18
1,2-Dimethoxyethane[b] (**15**)	Me	3.40	3.37	3.34	3.24	3.27
	CH_2	3.55	3.60	3.62	3.43	3.42
1,3-Propanediol (**16**)	α-CH_2	3.85	3.69	3.60[f], 3.77[g]	3.45	3.32[f], 3.49[g]
	β-CH_2	1.82	1.80	1.65, 1.75	1.56	1.37, 1.52
	OH	2.63	–	1.40, 3.25	4.32	4.22, 5.40
1,4-Butanediol (**17**)	α-CH_2	3.68	3.63	3.60[f], 3.77[g]	3.39	3.33[f], 3.49[g]
	β-CH_2	1.68	1.60	1.34, 1.53	1.43	1.19, 1.32
	OH	2.81	–	1.40, 2.60	4.38	4.22, 6.20
1,5-Pentanediol (**18**)	α-CH_2	3.67	3.62	3.60[f], 3.62[g]	3.38	3.33[f], 3.34[g]
	β-CH_2	1.61	1.58	1.33, 1.44	1.41	1.12, 1.23
	γ-CH_2	1.47	1.41	1.01, 1.19	1.31	0.93, 1.11
	OH	1.78	–	1.40, 1.40	4.34	4.22, 4.23
Dioxane[b] (**19**)	CH_2	3.71	3.75	3.74	3.57	3.53
trans-1,2-Cyclohexanediol (**20**)	1,2ax	3.33	3.37	3.49	3.11	3.22
	3,6eq	1.95	1.92	1.86	1.74	1.66

Table 2. (*Continued*)

Molecule		Obs.			DMSO	
		$CDCl_3$	D_2O	Calc.	Obs.	Calc.
	3,6ax	1.24	1.25	1.38	1.13	1.16
	4,5eq	1.69	1.67	1.67	1.56	1.60
	4,5ax	1.24	1.25	1.26	1.13	1.19
	OH	4.30	–	1.40	4.42	4.31
trans-1,4-Cyclohexanediol (**21**)	1,4ax	3.68	3.66	3.61	3.36	3.33
	2,3eq	1.97	1.93	1.86	1.74	1.73
	2,3ax	1.36	1.34	1.39	1.16	1.24
	OH	–	–	1.26	4.38	4.29
cis-1,4-Cyclohexanediol (**22**)	1,4	3.83	3.81	3.80	3.51	3.52
	2,3*cis*	1.75	1.66	1.74	1.40	1.47
	2,3*tr*	1.66	1.66	1.67	1.56	1.49
	OH	–	–	1.41	4.25	4.45
cis-1,3-Cyclohexanediol[c] (**23**)	1,3	3.82	3.65	3.61	3.36	3.33
	2eq	1.97	2.22	2.03	2.01	1.76
	2ax	1.36	1.21	1.49	1.02	1.20
	4,6eq	2.01	1.89	1.84	1.71	1.64
	4,6ax	1.22	1.13	1.40	0.96	1.18
	5eq	1.78	1.78	1.70	1.60	1.62
	5ax	1.05	1.25	1.28	1.11	1.20
	OH	–	–	1.27	–	4.31
cis-1,2-Cyclopentanediol[d] (**24**)	1,2	4.00	4.00	3.65	3.75	3.38
	3,5*cis*	1.66	1.64	1.52	1.48	1.32
	3,5*tr*	1.86	1.84	1.90	1.65	1.66
	4*cis*	1.80	1.77	1.63	1.65	1.55
	4*tr*	1.52	1.53	1.54	1.36	1.46
	OH	–	–	1.38	4.23	4.28
trans-1,2-Cyclopentanediol[d] (**25**)	1,2	4.00	4.00	3.50	3.73	3.23
	3,5*cis*	1.53	1.55	1.34	1.35	1.14
	3,5*tr*	2.01	2.00	2.07	1.78	1.82
	4	1.71	1.72	1.57	1.57	1.50
	OH	–	–	1.35	4.45	4.26

[a] This work unless stated otherwise.
[b] Ref. 33.
[c] Ref. 12.
[d] Ref 14.
[f] C.C.C.O *trans*.
[g] C.C.C.O *gauche*.

chemical shifts in D_2O and $CDCl_3$ differ considerably. The clearest example is *cis*-1,3-cyclohexanediol, which has been shown to exist solely in the diequatorial conformation in D_2O but as a 1 : 1 mixture of the diequatorial and diaxial conformers in $CDCl_3$.[12] As expected the chemical shifts differ considerably in the two solvents. Another possible example is 1,3-propanediol, in which an intramolecular hydrogen bond is likely in the *gauche* conformer. We note that 1,4-butanediol and 1,5-pentanediol do not show any evidence of a different conformational profile in the two solvents and this is consistent with the higher energy of the seven- and eight-membered rings needed to form an intra-molecular hydrogen bond in these compounds.

This identity of the ^{1}H shifts in the two solvents for these compounds may be rationalized by noting that both these solvents are not very anisotropic and they have similar dipole moments. Neither of these factors is true for DMSO and as a result the ^{1}H shifts in this solvent differ considerably from those in $CDCl_3$ (cf. Tables 1–3). These will be considered later. There is one caveat to the above conclusion. Charged molecules would not be expected to give the same ^{1}H shifts in $CDCl_3$ and D_2O. Both the species present (distinct ions, ion pairs, etc.) and the effect of the integral charge would be expected to differ considerably in the two solvents.

Substituent chemical shifts (SCS) of the OH group

The experimental chemical shifts in $CDCl_3$ and D_2O in Tables 1–3 allow a detailed investigation of the effect of the OH and OMe groups on ^{1}H chemical shifts and also provide a critical test of the application of the CHARGE model to these compounds. An interesting example of the large effect of methylation on a ^{1}H spectrum is given in

Table 3. Observed vs calculated ^{1}H chemical shifts (δ) of cyclohexane-1,3,5-triol and inositols in D_2O and DMSO solution[a]

Molecule		D_2O		DMSO	
		Obs.	Calc.	Obs.	Calc.
cis,cis-1,3,5-Cyclohexanetriol (**26**)	1,3,5ax	3.70	3.77	3.33	3.36
	2,4,6eq	2.22	2.13	1.96	1.70
	2,4,6ax	1.24	1.31	0.97	1.18
	OH	–	–	4.49	4.33
myo-Inositol (**27**)	1,3	3.54	3.63	3.14	3.36
	2	4.07	3.94	3.72	3.67
	4,6	3.64	3.68	3.37	3.41
	5	3.27	3.48	2.93	3.22
	OH(1,3)	–	–	4.51	4.25
	OH(2)	–	–	4.55	4.42
	OH(4,6)	–	–	4.31	4.35
	OH(5)	–	–	4.46	4.35
1,3,5-*O*-Methylidine-*myo*-inositol (**28**)	1,3	4.25	4.28	3.95	3.98
	2	4.28	4.23	4.01	3.96
	4,6	4.59	4.42	4.28	4.15
	5	4.34	4.29	4.07	3.99
	CH	5.61	5.47	5.46	5.32
	OH(2)	–	–	5.32	4.75
	OH(4,6)	–	–	5.48	4.73
chiro-Inositol (**29**)	1,6	4.03	3.94	3.65	3.67
	2,5	3.77	3.78	3.42	3.51
	3,4	3.60	3.64	3.26	3.37
	OH(1,6)	–	–	4.36	4.47
	OH(2,5)	–	–	4.03	4.25
	OH(3,4)	–	–	4.15	4.34
Quebrachitol (**30**)	1	4.27	4.15	3.87	3.88
	2	3.40	3.17	3.10	2.88
	3	3.62	3.89	3.38	3.61
	4	3.60	3.63	3.29	3.36
	5	3.75	3.82	3.43	3.55
	6	4.06	3.98	3.68	3.72
	OMe	3.47	3.43	3.41	3.32
	OH(1)	–	–	4.60	4.73
	OH(3)	–	–	4.39	4.56
	OH(4)	–	–	4.41	4.36
	OH(5)	–	–	4.26	4.36
	OH(6)	–	–	4.62	4.53
allo-Inositol (**31**)	1	4.03	3.94	4.08[b]	–
	2	4.03	3.91	3.88	–
	3	3.92	3.92	3.99	–
	4	4.06	3.94	4.04	–
	5	4.06	3.93	3.95	–
	6	3.92	3.77	3.74	–

[a] This work.

[b] d_4-MeOD at −40 °C, OH protons exchange with MeOD.

Table 4. Observed vs calculated ^{1}H,^{1}H coupling constants (Hz) of cyclohexane-1,3,5-triol and inositols in D_2O and DMSO solution[a]

Molecule		Obs.		
		D_2O	DMSO	Calc.
cis,cis-1,3,5-Cyclohexanetriol	^3J(1a,2e)	4.2	4.3	3.0
	^3J(1a,2a)	11.5	11.5	11.2
	^2J(2e,2a)	−11.5	−11.4	−12.5
	^4J(2e,4e)	1.5	–	1.3
	^3J(1a,OH)	–	4.7	–
myo-Inositol	^3J(1a,2e)	2.9 (2.8)	2.8	2.8
	^3J(3a,4a)	10.0 (9.9)	9.6	9.7
	^3J(4a,5a)	9.3 (9.2)	9.1	9.7
	^3J(1,3-OH)	–	4.3	–
	^3J(2,OH)	–	3.4	–
	^3J(4,6-OH)	–	5.6	–
	^3J(5,OH)	–	4.0	–
1,3,5-*O*-Methylidine-*myo*-inositol	^3J(1e,2a)	1.8	1.7	2.2
	^3J(3e,4e)	4.2	4.6	4.3
	^3J(4e,5e)	3.8	3.6	4.3
	^4J(1e,5e)	1.7	1.7	1.3
	^5J(CH,2a)	1.1	1.3	–
	^3J(2,OH)	–	6.2	–
	^3J(4,6-OH)	–	5.8	–
chiro-Inositol	^3J(1e,2a)	2.7 (3.0)	2.4	3.0
	^3J(1e,6e)	3.4 (3.2)	3.8	3.8
	^3J(2a,3a)	9.9 (9.5)	9.5	9.8
	^3J(3a,4a)	9.5 (9.5)	8.9	9.9
	^3J(1,6-OH)	–	4.1	–
	^3J(2,5-OH)	–	5.6	–
	^3J(3,4-OH)	–	3.8	–
Quebrachitol	^3J(1e,2a)	3.4	3.0	2.8
	^3J(2a,3a)	9.7	9.5	10.0
	^3J(3a,4a)	9.8	9.2	9.9
	^3J(4a,5a)	9.6	9.0	9.7
	^3J(6a,6e)	3.7	3.8	3.3
	^3J(6e,1e)	3.6	3.5	3.9
	^3J(1,OH)	–	3.8	–
	^3J(3,OH)	–	4.1	–
	^3J(4,OH)	–	4.6	–
	^3J(5,OH)	–	5.4	–
	^3J(6,OH)	–	3.5	–
allo-Inositol	^3J(3e,4e)	3.5[b]	–	3.9
	^3J(2a,3e)	3.5	–	3.1
	^3J(1e,2a)	3.0	–	3.1
	^3J(1e,6a)	2.8	–	3.1
	^3J(4e,5a)	3.0	–	3.1
	^3J(5a,6a)	10.3	–	9.7

[a] This work; Ref. 17 in parentheses.

[b] In d_4-methanol at −40 °C.

Fig. 5, which compares the ^{1}H spectrum of *chiro*-inositol with that of quebrachitol, the 2-*O*-methyl derivative. Methylation of the equatorial 2-OH group gives a 0.37 ppm shift of the α-proton H-2 to low frequency. For the β-protons H-1 shifts to high frequency by 0.25 ppm whereas H-3 is unchanged. The remaining protons are unaffected. Note the different chemical shift scales in Fig. 5(a) and (b). The effect of methylation on the ^{1}H chemical shifts of four inositols (*scyllo, myo, chiro* and *epi*) has been studied previously[17] and explained in terms of the possible orientations of the methoxy group. No modelling studies or calculations were given.

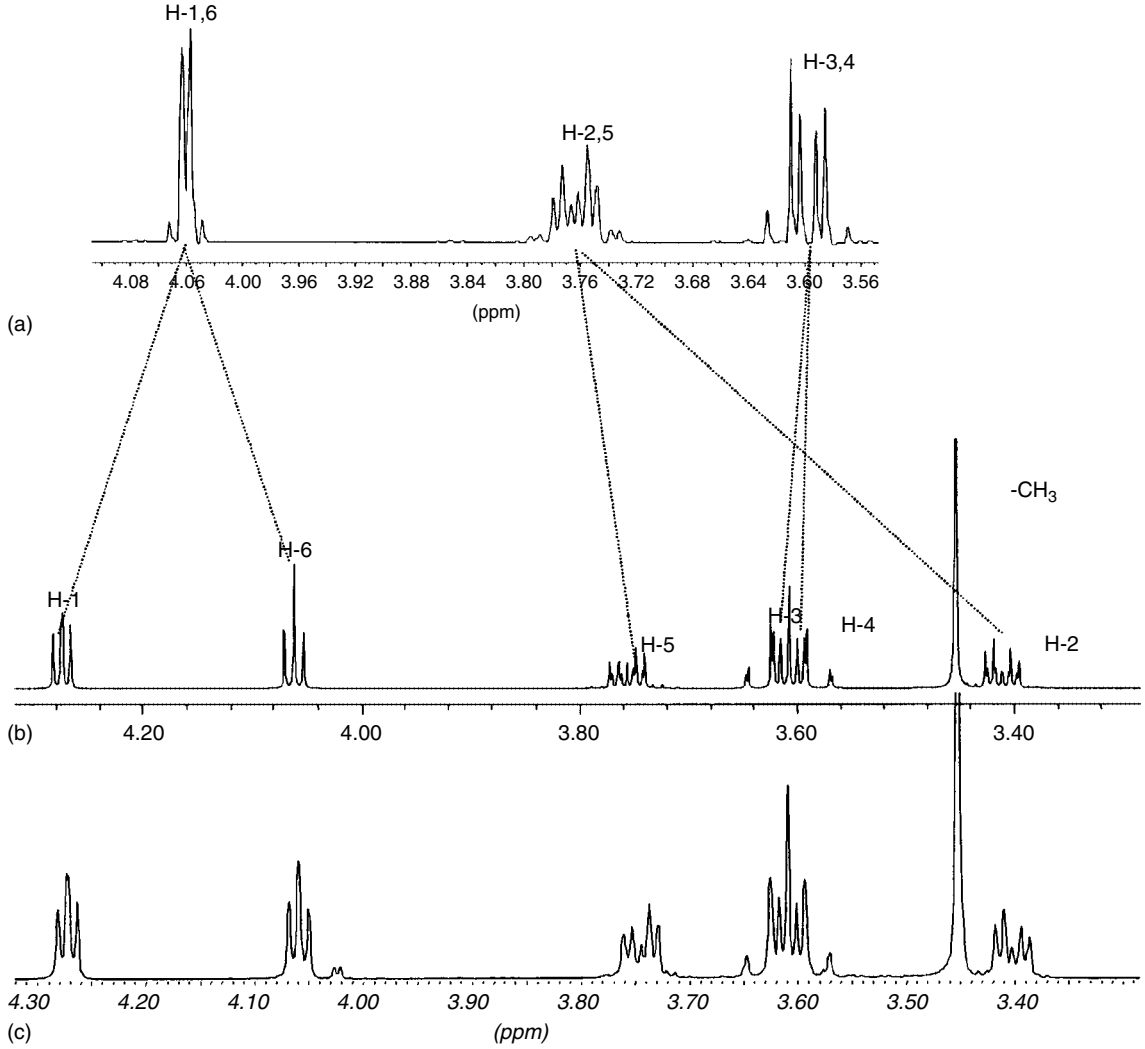


Figure 5. ^{1}H NMR spectrum of (+)-*chiro*-inositol (a) and the simulated (b) and the observed (c) ^{1}H NMR spectra of quebrachitol in D_2O.

In the CHARGE routine, both short- and long-range effects need to be included to calculate these shifts. The short-range electronic effects include the γ (H.C.C.OH) effect and for the ethers H.C.C.OC and H.C.O.C effects. The dependence of the H.C.C.OH SCS on the H.C.C.O dihedral angle is shown in Fig. 6 for the five compounds in Table 1 containing the C.CH_2.CH(OH).C fragment. The general Eqn (6) which includes one-, two- and threefold functionalities was used to simulate these values.

$$\gamma(\mathrm{SCS}) = A_0 + \sum_{n=1-3} \mathrm{A}_n \cos n\phi \qquad (6)$$

The values of the parameters A_{0-n} were obtained by a least mean square fit of the observed shifts using the Chap8 program.[42] This showed that only the one- and twofold potentials were required; the coefficient of the threefold term was zero. Figure 6 shows that the calculated curve gives a good description of the OH SCS. It is of some interest that although the minimum SCS occurs at a 0° dihedral angle, the largest SCS occurs for a dihedral angle of ca 120°. This angle dependence has not been recognized hitherto and it would be of some interest to determine the theoretical basis

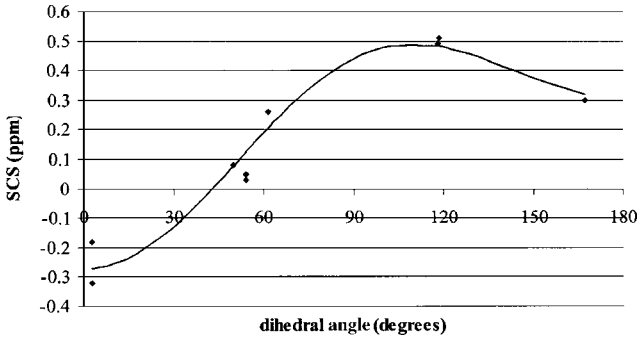


Figure 6. SCS of the OH group in the C.CH_2.CH(OH).C fragment vs the H.C.C.O dihedral angle.

for this result. It was also found that the *gem*-diols needed to be treated separately so the H.C(OH).C(OH) fragment was separately parametrized using a similar equation. Following the treatment given earlier, the only long-range effect is the oxygen steric effect, which was parametrized together with the γ effects. The oxygen steric coefficient [Eqn (2)] was found to differ in the alcohols, ethers and 1,2-diols with values of a_s of 85,136 and 26 Å^6, respectively.

The result of this parametrization is shown in the calculated shifts in Tables 1–3. For the alcohols the 150 chemical shifts are reproduced with an r.m.s. error of 0.0759 ppm. The 1,2-diols and the inositols also gave 150 separate shifts, which are reproduced with an average error of 0.0789 ppm. This excludes the OH chemical shifts, which have larger errors due to possible inter- and intramolecular hydrogen bonding (see later). Note that in D_2O the OH chemical shift for any molecule is set for convenience in CHARGE equal to the water value of 4.70 ppm.

The excellent agreement of the observed and calculated shifts is strong support for the model used in the calculations and for the assumptions made of no magnetic anisotropy and no electric field effects for the OH group. Previous theoretical and experimental investigations have shown no support for significant magnetic anisotropies of single bonds. Pople[43] concluded there was no theoretical evidence for C—C bond anisotropy and Williamson and Asakura[44] successfully analysed ^{1}H chemical shifts in proteins without including any magnetic anisotropy for the single bonds, although there was significant anisotropy from the C═O double bond and also from the N—CO partial double bond. Indirect support for the absence of any electric field contribution from the OH groups comes from the identical chemical shifts of the compounds investigated in $CDCl_3$ and D_2O. A significant electric field effect from the OH group would have been expected to produce different shifts in the two solvents, as any electric field in D_2O solution would be much reduced from the corresponding field in $CDCl_3$ owing to the much greater solvent permitivity in D_2O (80 vs 4.6).

DMSO solvent effects

The data in Tables 1–3 show that the ^{1}H shifts in DMSO differ considerably from those in the other solvents. This is true not only for the OH proton, which is found at a different region in the spectrum in $CDCl_3$ (ca 1.6 ppm) and DMSO (ca 4.4 ppm), but also for other protons. For example, the CH_2 protons α to the hydroxy group show solvent shifts of ca 0.3–0.4 ppm, which is too large to be neglected in any shift calculation. Hence the effect of DMSO on the ^{1}H chemical shifts needs to be considered explicitly. This has been done in the CHARGE model by including a subroutine for DMSO solvent. We consider here only the alcohol solvent shifts; the solvent shifts for a wide range of solute molecules will be given elsewhere.[45] In this subroutine, the solvent shift $\Delta\delta$ (DMSO − $CDCl_3$) is modelled in the same manner as the ^{1}H shifts are calculated. Thus the effects of the OH and OR substituents are separated into one-bond (α), two-bond (β) and three-bond (γ) effects together with their long-range (>three-bond) effects. These separate effects are determined from the experimental data in Tables 1–3 and the resulting solvent shift added to the calculated ^{1}H shift for any proton in $CDCl_3$ solvent. The three-bond γ effect (H.C.C.OH) showed a dihedral angle dependence and this was modelled by a simple $\cos\phi$ function. Also for compounds containing a number of hydroxy or ether groups it was found that there was a saturation effect, i.e. any proton α to a hydroxy group would experience a large solvent shift due to this group (ca 0.27 ppm) but would not experience a β or γ effect from additional OH groups. Similarly, the effect of a number of long-range OH groups was not additive and the long-range solvent effect was only included for the first OH group. These effects were included in the coding.

The resulting calculated shifts in DMSO are compared with the observed shifts in Tables 1–3. It can be seen that this simple routine gives reasonable agreement with the observed shifts for the molecules studied here. The average error (observed − calculated shifts) of all the DMSO data in Table 1 is 0.070 ppm (excluding the labile OH protons). Even for these labile protons the average error is only 0.094 ppm. The chemical shift range of the OH protons studied here in $CDCl_3$ solution is ca 1–4 ppm, probably due to the concentration dependence of intermolecular O—H···O hydrogen bonding. For example, the chemical shift of the OH proton in ethanol varies from 5.3 ppm in the pure liquid to 1.1 ppm in dilute $CDCl_3$.[10b] This concentration dependence is so large that these protons cannot be used for diagnostic purposes. However, the range of the OH shifts in DMSO solvent is much less, which raises the possibility that these protons could be used for predictive purposes. An interesting example of this is the chemical shifts for the C(2) and C(4,6) OH protons of 1,3,5-*O*-methylidene-*myo*-inositol (**28**) in DMSO (Table 3). They are ca 1 ppm to higher frequency than the other OH shifts and this is reproduced to some extent by the calculated shifts. Detailed examination of the calculated output shows that the conformer obtained from the modelling has an intramolecular hydrogen bond between the diaxial OH substituents on C(4) and C(6) and also a bifurcated hydrogen bond between the C(2)OH and the C(1) and C(3) axial ether groups. A hydrogen bond between the diaxial OH groups was observed in the x-ray structure of the solid[22] and the authors suggested that the same hydrogen bond was present in DMSO solution from the temperature dependence of the OH chemical shifts (-3.76×10^{-3} ppm $^\circ C^{-1}$). The observed temperature dependence for the C(2)OH (-7.5×10^{-3} ppm $^\circ C^{-1}$) was, however, characteristic of a solvated OH group.

The increase in the δ value for the OH groups is due to steric effects from the neighbouring oxygen atoms. The oxygen steric coefficient (a_s) used is a general one for any OH group which is determined mainly by the numerous O···HC interactions. Clearly, better agreement could be obtained by parametrizing this for O—H···O bonds, but more data are required to do this accurately. However, this does illustrate the potential usefulness of accurate ^{1}H chemical shift predictions for DMSO solution in monitoring intramolecular hydrogen bonds.

^{1}H,^{1}H coupling constants

The ^{1}H,^{1}H coupling constants obtained by iterative analysis of the inositol spectra are given in Table 4. The values for *myo*-inositol and *chiro*-inositol in D_2O solution reported are in good agreement with the first-order values given previously.[17] These couplings can give information on the molecular conformations provided that the corresponding couplings in the distinct conformers can be determined. One of the most useful modifications of the original Karplus $\cos^2\phi$ equation is the Haasnoot, de Leeuw and Altona[46]

equation (henceforth HLA), which is installed in PCMODEL. This equation is a function of the electronegativity of the substituents, the H—C—C—H torsion angle and the orientation of each substituent relative to the coupled protons. In a recent investigation,[47] it was noted that the ^{1}H,^{1}H coupling constants calculated with this equation for the $C_4.C_5$ fragment in *cis*- and *trans*-cyclopentane-1,2-diol were much larger than the observed values. An alternative equation was derived for the $C.CH_2.CH_2.C$ fragment in five- and six-membered rings using a simple form of the Karplus equation[48] with accurate experimental couplings of molecules in known conformations to give Eqn (7), and this equation is implemented in the CHARGE routine.

$$^3J(\mathrm{H,H}) = 11.16\cos^2\phi - 1.28\cos\phi + 0.77 \qquad (7)$$

This equation has been further developed to include the effects of electronegative substituents on the ^{1}H,^{1}H coupling constants. These have an orientational effect which is largest for a *trans* (*anti*) arrangement of the H.C.C.X fragment.[51] This has been included in the CHARGE routine using compounds of known conformation to parametrize the equation. A selection of the results is given in Table 5 with the corresponding values from the HLA equation. It can be seen that both methods give generally good agreement in these cases.

The ^{1}H,^{1}H coupling constants in the distinct conformers of the inositols calculated from the present routine are given together with the observed couplings in Table 4. Comparison of the observed with calculated couplings shows immediately that they are essentially identical. This confirms unequivocally that these molecules in both D_2O and DMSO solution are in the single conformations shown earlier (Fig. 2).

Previous investigations have concluded that the CH—OH coupling also has a similar orientation dependence.[6,52,53] However, in contrast to the CH—CH couplings, the CH—OH coupling has an intrinsic solvent[6] and temperature[52] dependence. The coupling in methanol varies from 5.16 Hz in pure methanol to 5.58 Hz in cyclohexane.[6] Using these figures, we modified Fraser *et al.*'s $\cos^2\phi$ equation[53] to give Eqn (8) for DMSO solution.

$$^3J(\mathrm{HC,OH}) = 10.0\cos^2\phi - 1.5\cos\phi \qquad (8)$$

Table 5. Observed and calculated ^3J(H,H) couplings in C.CHX.CHX.C fragments in *trans*-2,3-dimethyl-1,4-dioxane (I)[49] and 4-fluoro-α-D-glucopyranose (II)[50]

		Vicinal ^3J(H,H) couplings (Hz)		
			Calculated	
Compound	Protons	Observed	CHARGE	HLA
I	5ax-6ax	11.5	11.4	10.6
	5ax-6eq	2.7	2.6	2.9
	5eq-6eq	0.6	1.0	0.5
II	1eq,2ax	3.5	2.7	4.0
	2ax,3ax	9.7	9.9	8.7
	3ax,4ax	8.8	9.6	8.0
	4ax,5ax	9.9	10.5	9.3

The calculated values of J_{trans}, J_{gauche} and J_{av}, the free rotation value, from Eqn (8) are 11.5, 1.75 and 5.0 Hz, respectively, (cf: the observed value for ethanol in DMSO of 5.0 Hz[6]) and these will be used as the basis to evaluate the observed couplings in the inositol derivatives.

In *cis*-1,3,5-cyclohexanetriol, the OH groups are, as expected, all equatorial in DMSO solution. The CH—OH coupling (4.71 Hz) is identical with that for *cis*-1,3-cyclohexanediol[12] (4.70 Hz) and close to the free rotation value (5.0 Hz). There is no evidence of intramolecular hydrogen bonding.

In *myo*-inositol (**27**), only the C(2)(OH) is axial and the CH—OH coupling for this OH group is low (3.4 Hz, Table 4). This implies a favoured *gauche* orientation which is immediately understandable as the *trans* arrangement of the HC—OH moiety would result in the OH hydrogen facing into the ring producing steric repulsions with the axial C4,6 hydrogens. Hence the low value of this coupling is due to steric effects and not to any intramolecular hydrogen bonds. Note that the value of this coupling in *cis*-4-*tert*-butylcyclohexanol is even lower (3.0 Hz),[6] presumably reflecting the increased rigidity of this cyclohexane ring.

In contrast, the CH—OH couplings for the axial C(4,6)OH groups in 1,3,5-methylidene-*myo*-inositol (**28**) are larger than average (5.8 Hz,) implying a favoured *trans* orientation of the OH groups, and this supports the proposed existence of a 1,3-diaxial intramolecular H-bond in this compound. Note that only one of the two equivalent OH groups can be hydrogen bonded at any time, hence the maximum value of this coupling is $(J_t + J_g)/2$, i.e. 6.1 Hz The equatorial C_2 OH group also has a large coupling (6.2 Hz) and again this favoured *trans* orientation supports the previous suggestion based on the OH chemical shifts of an intramolecular H-bond between this hydrogen and the neighbouring axial C(1,3) ether oxygen atoms.

In (+)-*chiro*-inositol (**29**), the axial C(1,6)OH couplings are less than the free rotation value and the *trans* HC—OH conformer has again 1,3 steric repulsions. However, the equatorial C(3,4) OH groups also have low values of the CH—OH coupling which cannot be due to 1,3-diaxial effects, and this may imply intramolecular H-bonding between the vicinal OH groups in a diequatorial conformation.

The axial C(1,6)H groups in quebrachitol (**30**) all have CH—OH couplings which are less than J_{av} and the remaining couplings are close to J_{av}, showing that there is no evidence for any intramolecular hydrogen bonding in this compound.

To provide a further test for any intramolecular hydrogen bonding, the temperature dependence of the OH groups in DMSO was measured. From Ref. 22, a temperature coefficient of ca -3.6×10^{-3}ppm °C^{-1} is typical for an OH participating in intramolecular hydrogen bonding. The values obtained from plots of δ(OH) vs temperature (from 30 to 70 °C) for *chiro*-inositol in DMSO were for OH(1,6), (3,4) and (2,5) -6.28, -7.35 and -7.31×10^{-3}ppm °C^{-1}, respectively. A similar experiment for quebrachitol gave values of -7.18, -7.63, -8.10, -8.04 and -6.54×10^{-3}ppm °C^{-1} for OH-1, -3, -4, -5 and -6, respectively. All these values are characteristic of OH protons that are not intramolecularly H-bonded.

CONCLUSIONS

The ^{1}H chemical shifts of the alcohols and ethers investigated are identical for $CDCl_3$ and D_2O solution, provided that the conformational profile of the solute is the same in both solvents. The chemical shifts in both solvents were analysed using the CHARGE model. An accurate prediction of the observed shifts was obtained by parametrizing only the electronic (= three bonds) and steric effects. No anisotropy (C—O, O—H) or OH electric field effects were included.

The ^{1}H shifts in DMSO solution differ considerably from the other solvents and they were incorporated into the CHARGE model by the addition of a DMSO solvation subroutine, based on the CHARGE model.

Complete analysis of the ^{1}H spectra of the inositols gave the ring ^{1}H,^{1}H coupling constants and these conformed the proposed conformations of these molecules.

The OH chemical shifts and CH—OH couplings in DMSO solution are shown to provide useful conformational information with respect to the CH—OH orientation and any intramolecular hydrogen bonding in these molecules.

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