Proton chemical shifts in NMR. Part 12.[1] Steric, electric field and conformational effects in acyclic and cyclic ethers

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The proton resonance spectra of tetrahydropyran, at room temperature and −85 °C where the ring inversion is slow on the NMR timescale, 2-methoxy-, 3-methyl- and several 4-substituted tetrahydropyrans, 2-methyl-1,3-dioxolane and the rigid cyclic ethers 7-oxabicyclo[2.2.1]heptane and 1,8-cineole have been recorded and completely analysed.

These results together with literature data on acyclic and cyclic ethers (1,3- and 1,4-dioxane, dioxolane, 4-oxa-5α-androstane *etc.*) have allowed the determination of the oxygen substituent chemical shifts (SCS) in these systems. This data set consisting of 78 proton chemical shifts in 17 compounds has been used to test the application of a previous theoretical model of proton chemical shifts to these compounds.

It is shown that the model gives a very good account of the proton chemical shifts in these systems. The ether oxygen SCS are due to both steric and electrostatic terms, the steric term predominating at short distances (*e.g.* in the 1,3-diaxial interactions in methoxycyclohexanes).

Conformational isomerism in these compounds has also been investigated. Low temperature NMR gave ΔG (eq–ax) +1.0 kcal mol^{-1} for 4-hydroxy-THP. Analysis of the couplings in the $CHCH_2OH$ side chain of 2-(hydroxymethyl)-THP has shown that the preferred conformer is *gt* in both chloroform and acetone solvents.

Introduction

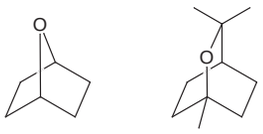
Ethers and alcohols are of very considerable practical and theoretical importance in chemistry and commerce. Yet although the effect of the electronegative oxygen atom on proton chemical shifts has been known for *ca.* five decades[2] a definitive analysis of oxygen substituent chemical shifts (SCS) in proton spectra has not been performed to date despite a number of investigations.[3a–c,4] Zurcher[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 oxasteroids but did not consider any steric contributions.

The major reason for the absence of any systematic investigation is simply the divalent nature of the oxygen atom which gives an additional degree of freedom when compared to monovalent substituents. For example, the SCS of the hydroxy group may well be dependent on the position of the hydroxy proton. The CH–OH coupling in alcohols shows that the OH proton is usually not in a single orientation but may have a preferred conformation.[5] However the precise populations of the different conformers cannot be estimated accurately. For these reasons we have restricted this initial investigation of oxygen SCS to ethers. Even in ethers the conformational mobility caused by the oxygen atom produces considerable problems. The only simply acyclic ethers that exist in one conformation are dimethyl ether and methyl *tert*-butyl ether. Methyl ethyl ether has two populated conformers, diethyl ether four and the number of conformations of more complex ethers (*e.g.* diglyme, 2-methoxyethyl ether) is prohibitive for any quantitative calculation.

Thus we have selected mainly cyclic ethers of known conformation. The proton chemical shifts in 1,3- and 1,4-dioxanes and their methyl derivatives have been obtained in a number of previous investigations.[6–9] In contrast the tetrahydropyran (THP) ring system has been mainly studied in investigations of the substituent $\Delta G°$ values by low temperature ^{13}C NMR.[7,10] The proton spectrum of THP (**1**) has been recorded at low temperature by a number of investigators,[11–15] but the full assignment has not been given. Gatti *et al.*[11] decoupled H3/H4 and observed the H2 AB pattern at 100 MHz. Lambert *et al.*[12] examined deuterated analogues and reported the $\Delta G^{\ddagger}$ and coupling data, but no chemical shift data. Late work by Lambert *et al.*[13] and a detailed study by Canuel and St.-Jacques,[14] again on deuterated THP, excluded the H3 and H4 chemical shifts. These analyses were in different solvents, CD_3OD–$CHClF_2$ and CS_2, with the former only giving $\Delta(\delta eq - \delta ax)$ values. Eliel *et al.*[15] determined $^2J_{HH}$ and $^3J_{HH}$ and the *R* values obtained indicated that the THP ring was not flattened relative to cyclohexane. They also gave data for monosubstituted THPs but as unassigned multiplets of overlapping groups of protons. A more recent study by Chu and True[16] at 500 MHz assigned the room temperature ^1H chemical shifts as H3 δ 1.657 and H4 δ 1.549 despite an apparent peak intensity of 1 : 2. Thus even the combined published data does not provide a full assignment.

We give here the complete assignment of the proton spectrum of THP (**1**), at room temp. and below coalescence, the 3-methyl- (**2**), 2-(hydroxymethyl)- (**3**), 2-methoxy- (**4**), 4-hydroxy- (**5**), 4-(4′-hydroxybenzyl)- (**6**) THPs and THP-4-carboxylic acid (**7**), 2-methyl-1,3-dioxolane (**8**) and two cyclic ethers of known conformation, 7-oxabicyclo[2.2.1]heptane (7-oxanorbornane) (**9**) and 1,8-cineole (**10**).

These plus previous literature results provide sufficient data for an analysis of oxygen SCS based on a previous theoretical model of proton chemical shifts.[1] This model has been applied successfully to a variety of saturated hydrocarbons[1,17] and their halogen[18] and carbonyl[19] derivatives. We shall show that this model provides a quantitative treatment for ether oxygen SCS



9 **10**

and that these are due to electric field and steric effects of which the steric effect is the major contributor.

Theory

As the theory has been detailed previously[1,17] only a brief summary of the latest version (CHARGE5) is given here. The theory distinguishes between substituent effects over one, two and three bonds which are attributed to the electronic effects of the substituents and longer range effects due to the electric fields, steric effects and anisotropy of the substituents. The CHARGE scheme calculates the effects of atoms on the partial atomic charge of the atom under consideration, based upon 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 an α effect from atom J given by the difference in the electronegativity of atoms I and J, a β effect from atom K proportional to both the electronegativity of atom K and the polarisability of atom I, and a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L. The important carbon γ effect (*i.e.* C.C.C.H) is parametrised separately and is given by a simple cos θ dependence where θ is the C.C.C.H dihedral angle. There are also routines for the methyl γ effect and for the decrease in the γ effect of the electronegative oxygen and fluorine atoms for CX_2 and CX_3 groups.

The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using eqn. (1).

$$\delta_{\text{charge}} = 160.84q - 6.68 \quad (1)$$

The effects of more distant atoms on the proton chemical shifts are due to steric, anisotropic and electric field contributions. H · · · H steric interactions were found to be shielding and X · · · H (X = C, F, Cl, Br, I) interactions deshielding according to a simple r^{-6} dependence [eqn. (2)].

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

Furthermore any X · · · H steric contributions on a methylene or methyl proton resulted in a push–pull effect (shielding) on the other proton(s) on the attached carbon.

The effects of the electric field of the C–X bonds (X = H, F, Cl, Br, I, C=O) were calculated from eqn. (3) where A_Z was determined as 3.67×10^{-12} esu (63 ppm au) and E_Z is the component of the electric field along the C–H bond.

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

For anisotropic groups the magnetic anisotropy contribution was calculated from the McConnell equation involving the anisotropies of the magnetic susceptibilities of the group. It was only necessary to invoke this term for the unsaturated carbonyl group. The other groups investigated so far (C–X, X = H, F, C, Cl, Br, I) did not require this term and we will assume that this term is not significant for ether oxygen SCS (see later).

These contributions were then added to the shifts of eqn. (1) to give the calculated shift of eqn. (4).

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anisotropy}} + \delta_{\text{el}} \quad (4)$$

To apply the above theory to the ethers considered here the only addition necessary is the calculation of the electric field of the ether oxygen. The electric field for a univalent atom (*e.g.* fluorine) is calculated as due to the charge on the fluorine atom and an equal and opposite charge on the attached carbon atom. 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 E_Z in eqn. (3). This procedure is both simpler and more accurate than the alternative calculation using bond dipoles.

For the ether oxygen two possible models were attempted. In the first the electric fields due to the charge on the oxygen atom and of both the attached carbon atoms were calculated at the proton in question. The carbon atoms each have a positive charge equal to half the oxygen charge. An alternative procedure was to calculate the electric field due to the ether oxygen atom and a dummy atom placed midway between the attached carbon atoms with an equal and opposite charge. As the coefficient in eqn. (3) is known the electric field is given immediately without any further parametrisation. In practice the latter model gave better agreement with the observed data and this model is given here.

The steric effect of the oxygen atom is not known and therefore a value of the coefficient a_S in eqn. (2) for oxygen must be determined. This and the associated push–pull coefficient are the only additional parameters required in order to apply the theory to the more distant protons in ethers. The vicinal (H.C.C.X) effects are treated separately in CHARGE and for ethers an explicit H.C.C.O term equal to 0.20 cos θ was required (see later).

Experimental

THP (**1**), 3-methyl-THP (**2**), 2-(hydroxymethyl)-THP (**3**), 2-methoxy-THP (**4**), 4-hydroxy-THP (**5**), 2-methyl-1,3-dioxolane (**8**), bicyclo[2.2.1]heptane (**9**) and 1,8-cineole (**10**) were obtained from Aldrich. 4-(4-Hydroxybenzyl)-THP (**6**) and THP-4-carboxylic acid (**7**) were kindly donated by Zeneca Pharmaceuticals. **3** was distilled prior to use. The solvents were obtained commercially, stored over molecular sieves and used without further purification.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX400 spectrometer operating at 400.14 MHz for proton and 100.63 MHz for carbon. Spectra for **2** were also recorded on a Bruker DRX 600 spectrometer. Spectra were recorded in 10 mg cm^{-3} solutions (^{1}H) and *ca.* 50 mg cm^{-3} (^{13}C) with a probe temperature of *ca.* 25 °C in $CDCl_3$ and referenced to TMS unless otherwise stated. Typical ^{1}H conditions were 128 transients, spectral width 3300 Hz, 32k data points, giving an acquisition time of 5 s and zero-filled to 128k to give a digital resolution of 0.025 Hz.

The 2D experiments were performed on the AMX400 and Bruker DRX-600 instruments using the standard Bruker COSY-DQF and HXCO-BI pulse sequences.[20] The geometries of the compounds investigated were obtained by geometry optimisations using the GAUSSIAN94 programme at the RHF/6-31G* level.[21] Full details of these optimisations and geometries are given in ref. 22. The GAUSSIAN94 calculations were performed on the University of Liverpool central computing facility, and the CHARGE5 computations were performed on a PC.

Assignments

Tetrahydropyran (1). The room temperature ^{1}H spectrum of THP in 50 : 50 v/v $CDCl_3$–$CFCl_3$ consists of three multiplets at δ 3.632, 1.637 and 1.568 of integration 2 : 1 : 2, assigned as H2, H4 and H3 respectively. At −85 °C all proton chemical shifts are resolved with no change observed to −95 °C. The H2 protons were at low field, and H3 and H4 distinguished by integration. Assignment of axial or equatorial was based upon the splitting patterns of the protons.

3-Methyltetrahydropyran (2). The H2 and H6 protons are to low field and the methyl doublet at δ 1.69. The COSY plot

Table 1 ^{1}H chemical shifts (δ) and H–H couplings (Hz) in THP (**1**), 3-methyl-THP (**2**), 2-(hydroxymethyl)-THP (**3**), 2-methoxy-THP (**4**), 4-hydroxy-THP (**5**), 4-(4-hydroxybenzyl)-THP (**6**), THP-4-carboxylic acid (**7**) and 2-methyl-1,3-dioxolane (**8**)

	δ_H									
Proton	**1**[a]	**5**[a]		**2**[b]	**3**[b]	**4**[b]	**5**[b]	**6**[b]	**7**[b]	**8**[b]
		eq-OH	ax-OH							
2ax	3.439	3.407	3.836	2.971	3.437	—	3.444	3.340	3.457	4.987
2eq	3.997	4.029	3.75[c]	3.801	—	4.517	3.962	3.954	3.990	—
3ax	1.682	1.579	*d*	1.686	1.323	1.60	1.566	1.315	1.803	—
3eq	1.566	1.915	*d*	—	1.53[e]	1.732	1.904	1.551	1.885	—
4ax	1.493	3.751	—	1.114	1.51[e]	1.816	3.860	1.692	2.593	3.857 (*syn*)
4eq	1.860	—	4.229	1.810	1.856	1.55	—	—	—	3.993 (*anti*)
5ax				1.618	1.56[e]	1.60				3.857 (*syn*)
5eq				1.563	1.56[e]	1.55				3.993 (*anti*)
6ax				3.316	3.463	3.856				
6eq				3.860	4.012	3.522				
CH_3				0.805		3.405				1.384
CH_2					3.569 3.507[f]			2.470		
Ph								6.750 7.006		

	H–H couplings				
	5	**6**[h]	**7**	**8**	
$^2J_{2ax2eq}$	−11.29	−11.81	−11.58	$^2J_{HH}$	−7.74
$^2J_{3ax3eq}$	−13.21	−13.39	−13.60	$^3J_{cis(AA')}$	7.04
$^3J_{2ax3ax}$	9.85	11.87	10.86	$^3J_{trans(AB')}$	6.12
$^3J_{2ax3eq}$	2.68	2.15	2.69	$^3J_{cis(BB')}$	7.46
$^3J_{2eq3ax}$	4.01	4.53	4.26	$^3J_{(Me,H)}$	4.83
$^3J_{2eq3eq}$	4.45	*g*	3.00		
$^3J_{3ax4ax}$	9.03	11.48	10.82		
$^3J_{3eq4ax}$	4.43	3.75	4.32		

[a] In $CDCl_3$–$CFCl_3$ at −85 °C. [b] In $CDCl_3$ at rt. [c] Obscured by H4ax of eq-OH. [d] Obscured by respective eq-OH protons. [e] *cf.* ^{13}C–^{1}H correlations. [f] Non-degenerate CH_2 group. [g] Long range 'W' couplings complicating 2eq and 3eq patterns. [h] Compound **6**, benzyl group δ (CH_2) 2.470, Ph 2, 6H 7.006; 3,5H 6.750, couplings J_{23} 8.14, J_{24} 2.65, $J_{3,5}$ 2.47, J_{25} 0.45, $J(CH_2,H_o)$ 0.53, $J(CH_2,H4ax)$ 7.19.

shows a connection from the methyl peak to H3ax which is on the low field side of the multiplet at *ca*. δ 1.48 to 1.75. This was distinguishable at 600 MHz as an axial pattern, and correlates to the low field axial proton at δ 3.00 (H2ax), which in turn assigns H2eq at δ 3.80. The two remaining low field protons are thus H6ax δ 3.32 and H6eq δ 3.80. H6ax strongly correlates to the centre of the multiplet at δ 1.62, which at 600 MHz is an axial pattern, indicating H5ax. The lone axial proton at δ 1.11 shows large couplings to both H3ax and H5ax assigning this as H4ax. H4ax correlates strongly to an equatorial proton at δ 1.81 which is assigned as H4eq. The high field side of the multiplet at δ 1.56 is thus H5eq. These assignments were confirmed by an HMQC experiment with the ^{13}C assignments of Eliel *et al.*,[15] and are given in Table 1.

2-(Hydroxymethyl)tetrahydropyran (3). The low field equatorial pattern at δ 4.01 is assigned as H6eq. The remaining low field protons are in an overlapping multiplet of two axial protons and an AB type pattern. From the COSY correlations H6eq defines H6ax at δ 3.46, leaving H2ax at δ 3.44, and the AB pattern as non-degenerate CH_2 protons at *ca*. δ 3.53. H2ax correlates strongly to an axial pattern at δ 1.32 assigning this as H3ax. The lone equatorial pattern at δ 1.86 correlates to H3ax and H6eq ('W' coupling), but not H6ax, and is thus H4eq. The remaining protons (H3eq/H4ax/H5ax/H5eq) form a strongly overlapping multiplet at δ 1.50 to 1.57. Correlations to H3ax and H4eq show H3eq δ 1.53 and H4ax δ 1.51 to be at the high field end of this multiplet. H5ax and H5eq form a complex second order pattern centred at δ 1.56. These assignments were confirmed by an HET-CORR experiment with the ^{13}C assignments of C2 δ 78.40, C3 δ 27.46, C4 δ 22.98, C5 δ 26.01, C6 δ 68.32 and CH_2OH δ 66.22. The hydroxy proton position varied on successive experiments between δ 2.1 and 2.3, but was distinctive as a doublet of doublets.

2-Methoxytetrahydropyran (4). The H2 and H6 protons are immediately assigned and the remaining protons assigned by the COSY connections of H2e/H3e and H4ax/H3e with no correlations of H4ax to H2,6. H3e and H4a can be clearly distinguished at 400 MHz but the remaining protons are closely coupled and their chemical shifts are only accurate to 0.01 ppm.

4-Substituted tetrahydropyrans. The room temperature spectra of **5**, **6** and **7** can be immediately assigned and the spectral data is given in Table 1. For **6** the aromatic spectrum was analysed using the LAOCOON software[23] on the hydroxy decoupled spectrum to give an rms of 0.090 Hz (and probable errors of 0.024 to 0.042 Hz), and the chemical shifts and couplings in Table 1.

2-Methyl-1,3-dioxolane (8). The A_2B_2 spectrum of the ring protons has been analysed previously at 60 MHz[24] but at this frequency only 16 of the 24 theoretically allowed transitions were observed and it was necessary to assume $J_{AA'} = J_{BB'}$. At 400 MHz all the allowed transitions were resolved and thus all the couplings could be obtained by iterative analysis. The results are given in Table 1; the rms error (LAOCOON) was 0.009 Hz with probable errors of 0.003 Hz (couplings) and 0.009 Hz (chemical shifts). Note that the assignment of the H4,5 protons (*syn* and *anti* with respect to the methyl group) cannot be obtained from the analysis but was made from the calculated shifts (see later).

7-Oxabicyclo[2.2.1]heptane (9). The CH_2 protons occur at δ 1.69 and 1.15, and the CH proton at δ 4.56. The low field methylene proton was assigned as *exo* since it showed the largest coupling to the methine proton (shown by decoupling the CH proton).

1,8-Cineole (10). The methyl resonances at δ 1.24 (C_{Me} δ 28.8) and δ 1.05 (C_{Me} δ 27.5) of integration 2 : 1 are assigned to 10/11-Me and 9-Me respectively. The multiplet at δ 1.41 consists of sets of overlapping triplets or quartets (J ~1.2 Hz) and with an integration of one proton is H4 (C4 δ 32.8). From the COSY

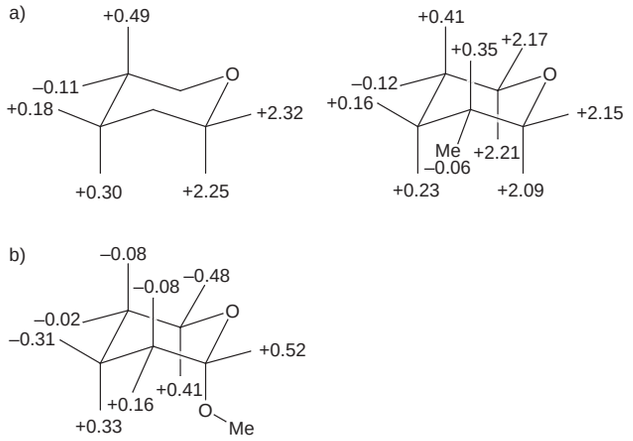


Fig. 1 (a) Oxygen ring SCS for **1** and **2**, and (b) SCS of the 2-methoxy group in **4**

plot H4 couples to the multiplet at δ 1.5 (4 protons) and δ 2.0 (2 protons), but not at δ 1.7 (2 protons) which is thus a C2 proton. From the HET-CORR the C_3 (δ 22.7) has protons at δ 1.5 and 2.0, and C_2 (δ 31.4) at δ 1.5 and 1.7. The assignment of the protons for C3 can be made on the basis of the coupling from H4 to δ 2.0 (3x) $\gg$ δ 1.5 (3n). This assignment is consistent with that in bornanes with the *exo* proton to low field of the *endo* protons.[1] The multiplet pattern at δ 1.66 is similar to 3x and could tentatively be assigned as 2x, although the pattern at δ 1.5 is not obviously *endo* or *exo*. Consideration of chemical shifts might suggest δ(*exo*) > δ(*endo*) yet in 1,4-cineole[25] the opposite was found from lanthanide induced shift (LIS) analysis.

The assignments of **9** and **10** were confirmed by their LIS using Yb(FOD)$_3$. For **9** the assignment of the *exo* proton to low field was confirmed by the greater LIS than the *endo*, since the *exo* proton is closer to the lanthanide at the oxygen binding site. For **10** the assignments of 2x with the largest methine proton LIS shift, and 3x with a LIS greater than 3n, are confirmed.

Results

The low temperature chemical shift differences (δeq − δax) of **1** derived from the data in Table 1 are in good agreement with the literature values, *e.g.* H2 0.558 *cf.* 0.55,[11] 0.50,[13] 0.527,[14] 0.563;[16] H3 −0.116, *cf.* −0.074;[14] and H4 0.367 *cf.* 0.32.[13] δH3ax > δH3eq in contrast to H2 and H4 (Table 1) and the general cyclohexane rule of δeq > δax. This may explain why the average δH4 is greater than δH3 at room temperature against the assignment of Chu and True.[16]

For **2** ΔG° (eq–ax) is 1.44 kcal mol^{-1},[15] thus *ca.* 6% of the axial form is present at room temperature. This is sufficiently small that the resultant oxygen ring substitution shift should be relatively unaffected by the minor conformer. Note that δH5ax > δH5eq confirming an orientational oxygen γ effect.

It is of interest to consider the oxygen SCS in these systems in more detail and Fig. 1 shows the oxygen ring substitution effects of **1** relative to cyclohexane, **2** relative to methylcyclohexane[1,17] and also the SCS of the 2-methoxy group in **4**. In THP the β effect of the oxygen atom on H2ax and H2eq is +2.1 to +2.3 ppm and non-orientational. The γ effect is strongly deshielding on H3ax (+0.4 to +0.5 ppm) but shielding on H3eq (*ca.* −0.1 ppm). This orientational effect is also seen in 1,3-dioxanes where the ring substitution shifts of 4-methyl-1,3-dioxane (Table 2) *vs.* methylcyclohexane[1] on H5ax is +0.83 ppm and for H5eq −0.28 ppm. Here the effect of two oxygen atoms would appear roughly additive. Finally, the long range oxygen effect on H4 is deshielding at +0.15 to +0.3 ppm, with the greatest effect on the axial proton.

The oxygen ring substitution effect of 7-oxanorbornane *versus* norbornane[17] may be compared with the results for THP (**1**). For the methine proton the oxygen shift of +2.37 ppm is in accord with the β THP protons. The oxygen SCS of +0.22 ppm (H*exo*) and −0.01 ppm (H*endo*) again show the orientational oxygen SCS, although less pronounced than for THP.

Even more remarkable are the SCS of the 2-methoxy group in 2-methoxy-THP [Fig. 1(b)]. The 2-methoxy group is predominantly axial [ΔG°(eq–ax) is *ca.* −0.8 kcal mol^{-1}][10] as shown in Fig. 1. The values of the methoxy SCS are confirmed by the similar data for the *trans*-2-methoxy-4-methyl-THP (Table 2) in which due to both the substituent groups being in their favourable confirmation the molecule is entirely in the conformation with equatorial methyl and axial methoxy. The corresponding values for the 2-methoxy SCS at the 6ax and 6eq protons are +0.38 and −0.34 ppm.[10]

These data together with the other data in Table 2 provide a rigorous test of the application of the theoretical model to these compounds. The six-membered ring compounds in Table 2 all exist predominantly in one chair conformation but the five-membered rings of THF and 1,3-dioxolane exhibit pseudorotation. For THF both the O-envelope (C_2) and half-chair (C_S) conformations were considered. (At the 6-31G* level of theory the C_S conformer was favoured by 0.39 kcal mol^{-1}). The *ab initio* calculations for dioxolane iterated preferentially to the C_S conformation which was used in the calculations. However the calculations for the 2-methyl-1,3-dioxolane gave an envelope conformation with C_2 out of the plane of the other ring atoms. The calculated shifts for the 2-methoxy-THP derivatives are given for the axial conformation of the methoxy group. In this conformation there are only two populated conformations of the methoxy methyl group as the conformer with the methyl over the THP ring (*i.e.* with the H.C$_2$.O.Me dihedral *ca.* 180°) is very unfavourable. The calculations for the two *gauche* conformers (H.C$_2$.O.Me dihedral) are given in Table 2, although the rotamer with ∠O.C.O.Me of −64° is preferred over ∠O.C.O.Me of 145° at RHF/6-31G* calculations by 4.0 kcal mol^{-1}.

As previously mentioned the electric field effect is given directly by eqn. (3); thus only the steric coefficient a_S [eqn. (2)] and the push–pull coefficient need to be determined. The data in Fig. 1 suggest that the push–pull coefficient for the methoxy group should be *ca.* −1.0 and this was confirmed in the calculations together with the appropriate value of a_S for oxygen as 100.0.

The observed *vs.* calculated shifts for a range of ethers is given in Table 2 and it is of some interest to consider these results. The general agreement of the observed *vs.* calculated shifts is very good and the great majority of the observed shifts are reproduced to better than 0.1 ppm. The agreement is particularly striking for the chair conformations of THP and 1,3-dioxane with an overall rms error (observed *vs.* calculated shifts) of <0.05 ppm. In both cases the calculations reproduce all the oxygen SCS very well and in particular the low field shift of the axial proton with respect to the corresponding equatorial proton in 3a *vs.* 3e (THP) and 5a *vs.* 5e (3-methyl-THP and 1,3-dioxanes) is strikingly reproduced. The only significant discrepancy for these compounds is H4ax for which the calculated shift is *ca.* 0.2 ppm too low.

The agreement between the observed and calculated shifts, though reasonable, is not as good in the case of the boat structures of 7-oxanorbornane and 1,8-cineole. This may well be due to the fact that the proton shifts in the parent hydrocarbons of norbornane and bicyclo[2.2.2]octane are not as well reproduced as those of cyclohexanes in this theoretical model and these discrepancies may well carry over to the oxygen analogues, *e.g.* the observed shift of the bridgehead proton in norbornane is to low field of the calculated value (δ 2.19 *vs.* 1.95)[1] and the difference is similar to the observed–calculated shift of H1 in 7-oxanorbornane (Table 2). However even in these cases the model does provide a basis for estimating the proton shifts in these compounds and indeed the correct order of the proton shifts is given in every case.

Table 2 Observed *vs.* calculated proton chemical shifts (δ) of acyclic and cyclic ethers

Molecule		Experimental[a]	CHARGE5	Molecule		Experimental[a]	CHARGE5
Dimethyl ether	Me	3.24[b]	3.31	1,4-Dioxane	CH_2	3.70[c]	3.85
Methyl *tert*-butyl ether	Me	3.22[c]	3.43	1,3,5-Trioxane	CH_2	5.00[b] 5.15[c]	4.93
	Bu^t	1.19	1.27	2,4,6-Trimethyl-1,3,5-trioxane	CH	5.05[g]	4.59
Tetrahydrofuran	α-CH_2	3.83[c]	3.80(C_2), 3.84(C_S)		Me	1.40	1.37
	β-CH_2	1.85	1.58(C_2), 1.54(C_S)	1,3-Dioxane	2-H	4.84[c]	4.85
Tetrahydropyran	2e	4.00	3.99		4-H	3.90	3.73
	2a	3.44	3.44		5-H	1.78	1.75
	3e	1.57	1.54	2-Methyl-1,3-dioxane	2e (Me)	1.15[h]	1.29
	3a	1.68	1.65		2a (CH)	4.50	4.59
	4e	1.86	1.80		4e	3.95	4.17
	4a	1.49	1.25		4a	3.61	3.52
3-Methyl-THP	2e	3.80	3.92		5e	1.23	1.44
	2a	2.97	3.10		5a	1.95	2.12
	3e (Me)	0.81	0.86	4-Methyl-1,3-dioxane	2e	5.05 4.89[i]	5.19
	3a (CH)	1.69	1.85		2a	4.71 4.55	4.53
	4e	1.81	1.77		4e (Me)	1.24 1.17	1.27
	4a	1.11	0.87		4a (CH)	3.73 3.61	3.59
	5e	1.56	1.56		5e	1.48 1.38	1.42
	5a	1.62	1.64		5a	1.76 1.69	1.67
	6e	3.86	3.99		6e	4.09 4.02	4.15
	6a	3.32	3.47		6a	3.71 3.58	3.53
2-Methoxy-THP	2e (CH)	4.52	4.79[d] 4.68[e]	2-Methyl-1,3-dioxolane	2 (Me)	1.38	1.30
	2a (OMe)	3.41	3.37 3.32		2 (CH)	4.99	4.75
	3e	1.73	1.77 1.72		4,5 (*anti*)	3.99	3.99
	3a	1.60	1.53 1.41		4,5 (*syn*)	3.86	3.79
	4e	1.55	1.53 1.53	7-Oxanorbornane	H1 (CH)	4.56	4.17
	4a	1.82	1.74 1.75		H*exo*	1.69	1.86
	5e	1.55	1.57 1.57		H*endo*	1.44	1.30
	5a	1.60	1.64 1.62	1,8-Cineole	2*exo*	1.66	2.00
	6e	3.52	3.64 3.61		2*endo*	1.50	1.28
	6a	3.86	4.19 4.21		3*exo*	2.02	1.90
trans-2-Methoxy-4-methyl-THP	2e (CH)	4.64[f]	4.76[d] 4.70[e]		3*endo*	1.50	1.32
	2a (OMe)	3.30	3.38 3.33		H4 (CH)	1.41	1.38
	3e	1.67	1.73 1.69		9-Me	1.05	1.18
	3a	1.24	1.17 1.05		10/11-Me	1.24	1.19
	4e (Me)	0.87	0.87 0.87	1,3-Dioxolane	α-CH_2	4.90[c]	5.02
	4a (CH)	1.88	1.95 1.97		β-CH_2	3.88	3.89
	5e	1.52	1.54 1.53				
	5a	1.23	1.28 1.26				
	6e	3.53	3.66 3.63				
	6a	3.70	4.18 4.20				

[a] This work unless stated. [b] Ref. 26. [c] Ref. 27. [d] O.C.O.Me dihedral angle −64°. [e] O.C.O.Me dihedral angle 145°. [f] Ref. 8. [g] Ref. 28. [h] Ref. 4. [i] Ref. 5.

The good agreement between the observed and calculated shifts over this diverse range of compounds is strong support for our original decision to neglect any C–O bond anisotropy contributions and this is also in accord with Zurcher's earlier conclusions.[3a]

The theoretical interpretation of these SCS on the basis of the present theory is of some interest. The oxygen γ effect is deshielding for a *gauche* O.C.C.H orientation and shielding for a *trans* orientation, in contrast to the carbon γ effect which is shielding for a *gauche* C.C.C.H orientation and deshielding for the *trans* orientation. Thus the large differences in the oxygen γ effects shown in H3ax *vs.* H3eq in THP *etc.* are due to the replacement of the carbon at C1 by the oxygen atom. The consequent replacement of the carbon γ effect by the oxygen γ effect gives rise to the observed oxygen SCS.

The oxygen SCS at the more distant H4 proton (and H4 and H6 in 1,3-dioxane) are also due to the replacement of the CH_2 group interactions by the oxygen atom. In this case the interactions concerned are the steric and electric field terms and these have much less orientation dependence in these systems. Both terms are quite small at these protons, *e.g.* for H4 of THP the steric interactions with the oxygen atom are 0.03 and 0.08 ppm respectively for H4e and H4a and the corresponding electric field contributions are 0.13 and 0.12 ppm. The alternative model in which positive charges were placed on the carbon atoms attached to the oxygen atom gave generally smaller effects and poorer agreement with the observed shifts.

In contrast the steric term and the associated push–pull contribution dominate the SCS of the axial 2-methoxy group, *e.g.* for H4a the calculated contributions are 0.32 (steric) and 0.17 ppm (electric field) and these well reproduce the observed shifts. There are similar calculated values for H6a but here the calculated shift is somewhat larger than the observed shift.

As a further check on the accuracy of these calculations Table 3 gives the calculated δ values for 4-oxa-5α-androstane and also the comparable values for the parent 5α-androstane from which the calculated SCS can be obtained to compare with the observed SCS from ref. 4. The agreement is very good and again the vicinal equatorial proton in the tetrahydropyran ring (2α in Table 3) shows an upfield SCS. The only disagreement between the observed and calculated SCS occurs for the 1α and 6 protons. The 1α proton is exactly analogous to H4a of THP and the 6 protons in 5α-androstane are part of a complex unresolved multiplet with the 4 protons and thus the observed SCS will not be known very accurately.[1]

Conformational Analysis

4-Hydroxy-THP (5)

The value of $^3J_{2ax3ax}$ of 9.85 Hz in **5** (Table 1) suggested a significant percentage of the axial OH conformer at room temperature (*cf.* 11.87 Hz for **6**) and this was confirmed by a low temperature experiment. Integration of H4ax in $CDCl_3$–$CFCl_3$ at −85 °C gave 8.5% of the axial conformer which gives

$\Delta G°$(eq–ax) = 1.02 kcal mol^{-1}. This is almost identical to the $\Delta G°$ value of the hydroxy group in cyclohexane[8] (1.04 kcal mol^{-1}) showing clearly that there is no OH · · · O interaction in this molecule.

2-(Hydroxymethyl)-THP (3)

Compound **3** is a model for the $CH_2OH \cdots O$ interactions in sugars such as D-glucose and derivatives. The non-degeneracy of the methylene protons of the CH_2OH fragment in **3** suggests an interaction between the hydroxy group and the THP ring oxygen, causing energy differences between the three staggered rotamers (*gg*, *gt* and *tg* using the nomenclature of ref. 29, see Fig. 3). The chemical shifts and couplings of this fragment in both a non-polar solvent ($CDCl_3$) and a polar solvent ([$^2H_6$]-acetone) obtained from the LAOCOON analysis are given in Table 4. From the two couplings ($^3J_{A,2ax}$ and $^3J_{B,2ax}$) it is possible to calculate the relative populations of the three rotamers from eqns. (5) and (6) if the couplings in the individual conformers are known.

$$J_{obs} = \Sigma_{i=1,3}\, n_i\, J_i \quad (5)$$

$$\Sigma_{i=1,3}\, n_i = 1 \quad (6)$$

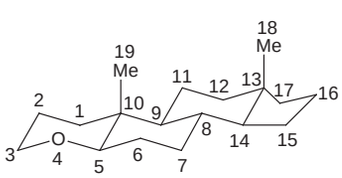
The conformer couplings derived from PCModel calculations[30] on the HF/6-31G* geometries[21] (Scheme 1) are compared to the values using the equations of ref. 31 (Scheme 2) in Table 5, along with their resultant populations. The consistency between the two schemes is encouraging, although Scheme 2 appears to give more realistic values of the *tg* conformer. In chloroform the *gt* conformer is favoured over the *gg* form in about a 2 : 1 ratio, with almost none of the *tg* form present. In both the *gg* and *gt* conformers the possibility of intramolecular hydrogen bonding between the hydroxy proton and the ring oxygen exists, as shown in Fig. 4. From *ab initio* calculations at the MP2/6-31G* level the OH · · · O distance for the *gg* form is 2.728 Å and for the *gt* conformer is 2.714 Å, suggesting for the latter isomer this interaction may be larger. This could account for some of the preference for the *gt* form.

If intramolecular hydrogen bonding is important in determining the rotamers of **3** then in a solvent which can hydrogen bond to the hydroxy group (but not the ring oxygen) the *tg* form should be stabilised. Indeed, in acetone (see Table 5) the *tg* conformer is present at 15–20%, whilst the *gt* form decreases. The *gg* form is approximately the same in both chloroform and acetone solutions.

Table 3 Calculated chemical shifts for 5α-androstane and 4-oxa-5α-androstane and calculated *vs.* observed SCS[a]

	Calculated		SCS	
Proton	Androstane[b]	4-Oxa-androstane	Calc.	Obs.[c]
1α	1.00	1.09	0.09	0.23
1β	1.53	1.69	0.16	0.08
2α	1.57	1.45	−0.12	−0.10
2β	1.44	1.90	0.46	0.44
3α	1.19	3.42	2.23	2.21
3β	1.74	4.08	2.34	2.32
5 (CH)	1.15	3.27	2.12	1.88
6α	1.35	1.95	0.60	0.37
6β	1.40	1.92	0.52	0.21
7α	0.97	0.95	−0.02	0.06
7β	1.94	1.96	0.02	0.05
11α	1.51	1.54	0.03	−0.03
11β	1.34	1.47	0.13	0.05
12α	1.05	1.06	0.01	−0.01
12β	1.60	1.63	0.03	0.00
14 (CH)	0.83	0.83	0.00	−0.03
19-Me	0.80	0.94	0.14	0.15

[a] Protons with SCS <0.01 ppm excluded. [b] *Cf.* Ref. 1. [c] Observed SCS *cf.* 4-oxa-androstan-17-one *vs.* androstan-17-one, ref. 4.



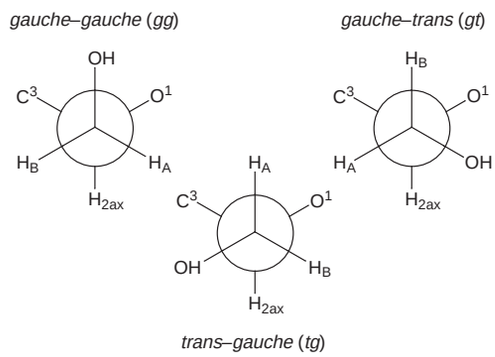


Fig. 3 Three staggered rotamers about the C(2)–C(MeOH) bond in **3**

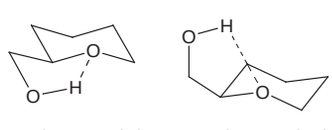


Fig. 4 Possible intramolecular hydrogen bonding (marked with a dashed line) in **3**

Table 5 Conformer couplings (Hz) and populations for the $CHCH_2OH$ fragment of **3**

Conformer		*gg*	*gt*	*tg*
Coupling/Hz				
Scheme 1	*J*(A,2aX)	3.67	2.97	10.68
	J(B,2aX)	0.60	10.73	4.70
Scheme 2	*J*(A,2aX)	2.50	3.10	10.70
	J(B,2aX)	0.60	10.70	5.20
Population (%)				
$CDCl_3$	Scheme 1	34	74	−1
	Scheme 2	31	66	3
[$^2H_6$]Acetone	Scheme 1	36	50	14
	Scheme 2	34	47	19

Table 4 Temperature and solvent effects on the HH couplings (Hz) and ^{1}H chemical shifts (δ) of the $CHCH_2OH$ fragment in **3**

Solvent	*T*/K	δ(2a)	δ(A)	δ(B)	δ(OH)	J_{AB}	$J_{A,2aX}$	$J_{B,2aX}$	$J_{A,OH}$	$J_{B,OH}$	rms
$CDCl_3$	298	3.437	3.569	3.507	2.181	−11.45	3.11	7.38	8.08	4.19	0.053
	233	3.485	3.606	3.543	2.494	−11.62	2.75	7.96	8.61	3.72	0.072
[$^2H_6$]Acetone	288	3.301	3.379	3.441	3.524	−11.26	4.30	6.20	7.02	5.20	0.064
	223	3.293	3.369	3.436	4.270	−11.39	4.26	6.58	7.31	5.25	0.035

In the assignment given in Table 4 we note that the chemical shifts of A and B have reversed order from chloroform to acetone. In the alternative assignment with $\delta(A) > \delta(B)$ and $J_{A,2a} = 6.2$ Hz and $J_{B,2a} = 4.3$ Hz in acetone at 288 K, then using Scheme 1 the calculated populations are $gg = 41\%$, $gt = 21\%$ and $tg = 38\%$. The same trends are seen although the increase in the *tg* and the decrease in the *gt* conformers are more dramatic.

It is interesting to compare the result in **3** of $gt > gg > tg$ with D-glucosides where in general $gg \sim gt \gg tg$. In both cases the *tg* form is small (usually <5% for sugars in polar solvents) and this has been attributed to the destabilisation of the *tg* conformer due to *syn*-diaxial (C6–OR · · · C4–OR) oxygen–oxygen interactions.[32] However in **3** there is no C4-oxygen and thus the stabilisation of the *gt* and *gg* conformers by intramolecular hydrogen bonding is significant, and should also be considered relevant to sugars.

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