Conformational analysis. Part 28.[1] OH ··· F hydrogen bonding and the conformation of *trans*-2-fluorocyclohexanol

Raymond J. Abraham,[a] Timothy A. D. Smith[a] and W. Anthony Thomas[b]

[a] *Department of Chemistry, The University of Liverpool, PO Box 147, Liverpool, UK L69 3BX*
[b] *Roche Products Ltd., PO Box 8, Welwyn Garden City, Herts., UK AL7 3AY*

The ^1H and ^{13}C NMR spectra of *trans*-2-fluorocyclohexanol 1 and the methyl ether 2 have been obtained in a variety of solvents and temperatures. From the low-temperature spectra the proportions of the ax–ax and eq–eq conformers were obtained by direct integration together with the vicinal HH couplings of the 2-proton in the dominant eq–eq conformer. From these results the conformer populations and energies in a variety of solvents are given.

In 1 ΔG(aa–ee) varies from 1.5 kcal mol^{-1} (1 cal = 4.184 J) in non polar solvents (*e.g.* CCl_4) to *ca.* 1.2 kcal mol^{-1} in very polar solvents (acetone), whereas in 2 the corresponding values are 0.4 and 1.0 kcal mol^{-1}. The proton donor solvents $CDCl_3$ and CD_2Cl_2 are exceptions due to preferential CH ··· O hydrogen bonding in the eq–eq form.

These figures are explained by solvation theory, which also provides the vapour state free energy differences of 1.6 kcal mol^{-1} 1 and 0.1 kcal mol^{-1} 2. In 1 ΔS is zero and ΔH equals ΔG but in 2 values of ΔS of 2.0 cal mol^{-1} K^{-1} and of ΔH of 1.1 kcal mol^{-1} in non polar media and 0.7 kcal mol^{-1} for the vapour are obtained. These values may be compared with those calculated by *ab initio* theory at the 6-31G*(MP2) level of 1.1 kcal mol^{-1} 1 and −0.75 kcal mol^{-1} 2. In both cases the eq–eq conformer is more stable than predicted, by 0.5 and 1.5 kcal mol^{-1}.

Comparison of the conformer energies with those obtained from the ΔG values for the monosubstituted cyclohexanes gives the OH ··· F hydrogen bonding attraction in the eq–eq conformer as 1.6 kcal mol^{-1} whilst the *gauche* OMe ··· F interaction is neutral, neither repulsive nor attractive. These figures support previous theoretical interpretations that the gauche form of 2-fluoroethanol is predominant due to OH ··· F hydrogen bonding and show also that the previous discrepancy between experimental measurements in the condensed phase and theory is due to solvation.

Introduction

The strength, if any, of the intramolecular hydrogen bond between vicinal hydroxy and fluorine atoms has been a source of controversy for many years and the simplest molecule with this interaction, 2-fluoroethanol, has been the subject of numerous experimental and theoretical investigations. Recent theoretical investigations have attempted to resolve this problem. Wiberg and Murcko[2] calculated the energy of the various conformers with different orientations of the OH group at the MP3/6-311++G** level. The GG conformer was more stable than the *trans* (TT) conformer by 2.3 kcal mol^{-1} but the *gauche* (GT) conformer with the hydroxy hydrogen antiparallel to the C–C bond pointing away from the fluorine atom was 0.6 kcal mol^{-1} higher in energy than the TT conformer. They concluded that the H ··· F interaction was best modelled as a coulombic term and their results indicate the absence of any *gauche* effect between oxygen and fluorine. Dixon and Smart[3] using a triple Z basis set plus polarisation functions obtained relative energies for the GG, GT and TT forms of 0.0, 1.9 and 2.0 kcal mol^{-1} and concluded that the stability of the GG form is 'almost entirely due to hydrogen bonding with the *gauche* effect contributing only 0.1 kcal mol^{-1}'.

The experimental data for 2-fluoroethanol does not completely support these results. In the gas phase the *gauche* conformer is so predominant that there is little evidence for the *trans* conformer, the latest ED study giving ΔG_{g-t} = 2.7 (+1.8, −1.5) kcal mol^{-1} [4] and concluding that 'it was not possible to obtain a reliable measure of the internal hydrogen bond'. In the pure liquid and solution NMR,[5] IR[6] and Raman[7] spectroscopic studies gave energy differences of 1.0–2.0 kcal mol^{-1} in favour of the *gauche* form and these results were interpreted as due to an internal hydrogen bond. However, acetylation of the OH group, which removes the hydrogen bond, made little difference to the conformation in solution[8] and analysis of the hydroxy proton chemical shift with concentration in CCl_4 does not support the existence of a strong hydrogen bond.[9] Also the OH and CF bonds in the stable *gauche* (GG) conformer are parallel (*cf.* Fig. 1g$^-$) with an H ··· F distance of 2.42 Å,[10] only 0.1 Å less than the sum of the van der Waals radii which is not the recommended geometry for a hydrogen bond.

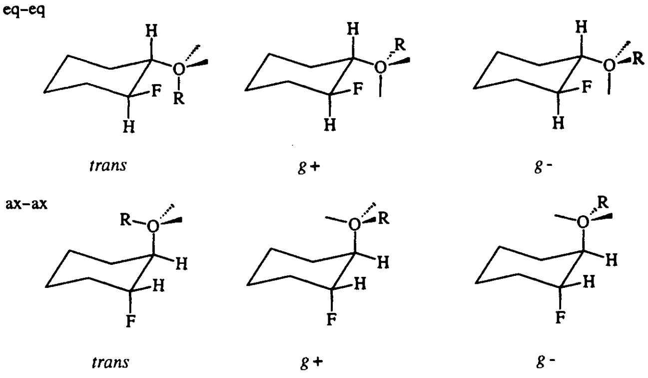

Fig. 1 Possible conformations of *trans*-2-fluorocyclohexanol (**1**, R = H) and the methyl ether (**2**, R = Me)

The experimental data is not definitive. Variable-temperature studies of such dipolar compounds in any medium except the gas phase and non-polar solvents are subject to a correction term due to the variation of the solvent dielectric constant with temperature, which can be as much as 0.5 kcal mol^{-1} (see later).[11] Also the individual conformers for such molecules cannot be observed directly by NMR spectroscopy and thus the determination of the conformer energies by NMR spectroscopy is limited by the estimates made for the values of the couplings in the individual conformers.

These limitations in the NMR studies can be overcome by observing the analogous cyclohexane derivatives as the individual conformers may be observed directly at low temperatures and conformationally fixed analogues are available and this approach has been used successfully recently. Bakke *et al.*[12] studied by NMR 2-fluoroethanol, the methyl ether and *trans*-4-*tert*-butyl-*cis*-2-fluorocyclohexanol as a conformationally fixed analogue. They noted the predominance of the *gauche* conformer in 2-fluoroethanol but from the similar conformation of the methyl ether they concluded that an intramolecular hydrogen bond was not important for the stability of the *gauche* conformer which was due mainly to the *gauche* effect. They also obtained definitive evidence from the CH–OH coupling in the *tert*-butyl(fluoro)cyclohexanol that the orientation of the OH proton was with the OH parallel to the C–F bond, as indicated by theory.

Zefirov *et al.*[13] in a pioneering investigation studied a series of *trans*-1,2-disubstituted cyclohexanes, including *trans*-2 fluorocyclohexanol and the methyl ether by ^{1}H and ^{13}C NMR spectroscopy. They obtained the conformer populations by direct integration of the ^{13}C signals at low temperature and by measurements at room temperature of the line width of the ^{1}H peaks using *tert*-butyl derivatives as standards. They noted that neither of these methods is precise, as ^{13}C intensities are known to be unreliable and line width measurements with 'estimated' standards are subject to considerable uncertainties.

We shall show that these uncertainties may be completely overcome and present here a definitive NMR investigation of *trans*-2-fluorocyclohexanol **1** and its methyl ether **2**. The conformer energies are obtained directly by integration of the ^{1}H spectra at low temperatures and these spectra also provided accurate values of the conformer couplings of the major (eq–eq) conformer, which may be used together with the observed couplings at room temperature to give precise values of the conformer energies in any solvent. We obtain from these analyses definitive values of both the *gauche* effect and the OH ··· F hydrogen bond strength in this molecule.

Theoretical

The molecular geometries were obtained from *ab initio* calculations (GAUSSIAN 92).[14] Solvation calculations using the MODELS program[11] were also performed. In this treatment, the solvation energy of a molecule is given by including both the dipole and quadrupole reaction fields and also a direct dipole–dipole term to take account of the breakdown of the Onsager reaction-field theory in very polar media. On this basis the solvation energy of any molecule in state A, *i.e.* the difference between the energy in the vapour ($E^V{}_A$) and in any solvent ($E^S{}_A$) of relative permittivity ε is given by eqn. (1),

$$E^V{}_A - E^S{}_A = k_A x/(1 - lx) + 3h_A x/(5 - x) + bf\{1 - e^{-bf/16RT}\} \quad (1)$$

where $x = (\varepsilon - 1)/(2\varepsilon + 1)$, $l = 2(n_D{}^2 - 1)/(n_D{}^2 + 2)$, $b = 4.30(a^{3/2}/r^3)(k_A + 0.5\ h_A)^{1/2}$ and $f = \{(\varepsilon - 2)/(\varepsilon + 1)/\varepsilon\}^{1/2}$ for $\varepsilon > 2$ and is zero otherwise, n_D is the solute refractive index, T is the temperature (K), k_A and h_A are $\mu_A{}^2/a^3$ and $q_A{}^2/a^5$, μ_A and q_A being the dipole and quadrupole moments of molecule A and a the solute radius. r is the solute–solvent distance and is taken as $a + 1.8$ Å. The solute radius is obtained directly from the molar volume (V_M) of the solute by the equation $V_M/N = 4\pi a^3/3$ where N is Avogadro's number. The molar volume can be obtained from the density of the pure liquid, if known or directly in the program from additive atomic volumes. Similarly the solute refractive index may be inserted if known or calculated directly from additive contributions.

For a molecule in state B a similar equation is obtained differing only in the values of k_B and h_B. Subtraction of the two equations gives the experimentally required quantity ΔE^S ($E^S{}_A - E^S{}_B$), the energy difference in any solvent S of given permittivity, in terms of ΔE^V ($E^V{}_A - E^V{}_B$) and calculable or measurable parameters.

This theory has been given in detail previously and shown to give an accurate account of the solvent dependences of a variety of conformational equilibria,[11] including the halocyclohexanones.[15] In the early applications of this theory the dipole and quadrupole moments of the molecules (*i.e.* parameters k and h) were calculated by placing point dipoles along the appropriate bonds. This has now been replaced by the more accurate and computationally simpler procedure of calculating these parameters directly from the partial atomic charges in the molecule, calculated from the CHARGE routine.[16]

An important factor in the determination of the conformational equilibrium between two conformers of very different dipole moments is that the temperature dependence of the pure liquid (or solvent) relative permittivity can appreciably affect the value of the energy difference obtained. The true value of the free energy difference at any temperature [$\Delta H(t)$] is related to that obtained using the Van't Hoff eqn. (2),

$$\mathrm{d}\ln K/\mathrm{d}\,(1/t) = -\Delta H^\circ/R \quad (2)$$

by eqn. (3).

$$\Delta H(t) = \Delta H^\circ + T(\mathrm{d}H/dt) \quad (3)$$

The correction factor $T(\mathrm{d}H/\mathrm{d}t)$ has been shown to be as much as 0.5 kcal mol^{-1} for moderately polar solutes and solvents,[1,11] thus it cannot be ignored in any accurate determination of conformer energies.

Molecular conformations and energies

In both the eq–eq and ax–ax conformers of **1** and **2** the OR group has three possible orientations, the *trans*, g^+ and g^- forms where the designation refers to the H–C–O–R dihedral angle (Fig. 1). The geometries of all the possible conformations of **1** and **2** were minimised using GAUSSIAN 92 at the recommended[17] 6-31G* basis set at the Hartree-Fock (HF) and MP2 levels and the resulting energies relative to the most stable forms are given in Table 1, together with the calculated dipole moments from the CHARGE program using the 6-31G* geometries and the values of the solvation energy (E^V–E^S) from eqn. (1).

The *ab initio* calculations show clearly that in (1ee) the only significantly populated conformer is the g^- form, the other conformations being of much higher energy (> 3 kcal mol^{-1}). The increased solvation energy of these more polar forms does not compensate for the intrinsically higher energy. Thus, we will henceforth only consider the g^- form of the eq–eq conformer. In the ax–ax conformer the position is not so clear cut as although the g^- form is again predicted to be the most stable conformer, the g^+ form is only slightly higher in energy (*ca.* 0.5 kcal mol^{-1}). The *trans* form is again of somewhat higher energy. In these rotamers the solvation energies are comparable despite the difference in the dipole moments, due to the compensating effect of the quadrupole term [eqn. (1)]. For simplicity, we will again consider in the subsequent analysis only the g^- form, though it should be emphasised that there may be significant amounts of the g^+ conformer present.

In **2** the situation is more complex. In both the eq–eq and

Table 1 Conformer energies, dipole moments and solvation energies for **1** and **2**

	Conformer	θ(H-C-O-R)	E_{Rel}/kcal mol^{-1} HF	MP2	Dip. Mom. (D)	E_{Solv}/kcal mol^{-1} $\varepsilon = 2.2$	20.7
1							
	trans	180.9	3.45	3.58	3.25	1.10	2.81
Eq–eq	$g+$	−51.8	2.99	3.33	3.12	1.18	2.98
	$g-$	63.1	0.00	0.00	1.48	0.36	0.91
	trans	199.8	2.86	2.33	2.44	0.66	1.68
Ax–ax	$g+$	−47.7	1.79	1.49	1.41	0.69	1.68
	$g-$	62.0	1.34	1.11	2.04	0.64	1.60
2							
Eq–eq	*trans*	163.7	4.18	4.21	2.77	0.74	1.89
	$g+$	−28.5	1.30	2.16	2.54	0.75	1.89
	$g-$	32.4	0.30	0.75	1.69	0.39	0.98
	trans	—	>5	>5	—		
Ax–ax	$g+$	−27.4	0.49	0.59	1.26	0.48	1.17
	$g-$	41.5	0.00	0.00	1.65	0.44	1.10

ax–ax conformers the *trans* form is of high energy and may be neglected (the GAUSSIAN iteration for the ax–ax form iterated to the g^+ form, indicating no minimum in the energy profile. PCMODEL[18] iterated to a conformer of > 10 kcal mol^{-1} higher energy than the stable form). The g^+ and g^- forms are of comparable energy in both the eq–eq and ax–ax conformers but the solvation energy of the conformers is very different. In the eq–eq conformer the g^+ form will become relatively more populated in polar solvents due to its much larger solvation energy but in the ax–ax conformer the solvation energies of the g^- and g^+ forms are very similar and the g^- form will be the major form in all solvents. In the subsequent analysis, for simplicity, we will consider only the eq–eq (g^+) and ax–ax (g^-) forms though significant amounts of the other *gauche* forms will undoubtedly be present.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX 400 spectrometer with probe temperature 25 °C operating at 400.14 (^{1}H) and 100.63 MHz (^{13}C). Spectra were of *ca.* 10 mg ml^{-1} solutions using $SiMe_4$ as internal reference. [$^2H_{12}$]-Cyclohexane was used as the deuterium lock signal for the CCl_4 and $CFCl_3$ solutions at room temp., CD_2Cl_2 for the $CFCl_3$–CD_2Cl_2 solution at −110 °C and [$^2H_8$]toluene for the $CFCl_3$–CS_2 solution at −110 °C. All solvents were stored over molecular sieves prior to use. Typical conditions were; ^{1}H spectra 128 transients, accumulated into 32 K data points with a pulse width of 12.5 μs (80° flip-angle), sweep width of *ca.* 2500 Hz and acquisition time (AT) of *ca.* 4.5 s. The FID was zero filled to 256 K data points giving a digital resolution of 0.019 Hz/point. The spectral integrations were performed using the integration facility of the Bruker UXNMR software package.[19] ^{13}C spectra 1024 transients, accumulated into 32 K data points with a pulse width of 3.4 μs (40° flip-angle), a sweep width of *ca.* 20 000 Hz and AT of 1 s. The FID was zero filled to 256 K data points giving a digital resolution of < 0.16 Hz per point.

For the ^{1}H–^{1}H-COSY experiment a COSYDFTP[20] pulse program was used. Typical conditions were 128 transients, accumulated into 1 K data points with 512 experiments, with a pulse width of 12.5 μs (80° flip-angle), sweep width of *ca.* 2500 Hz and AT of 0.2 s. The FID was zero filled to 2 K data points (F2) 1 K data points (F1). Solutions were of *ca.* 30 mg ml^{-1} of sample. The low-temperature spectra were recorded using the above conditions for the various spectra (^{1}H, ^{13}C and COSY), the probe was re-tuned at *ca.* 30 °C changes in temperature and the temperature calibrated directly by a thermocouple.

trans-2-Fluorocyclohexanol 1

Cyclohexene oxide (2.02 g, 20.6 mmol) was reacted for 12 h with 20 cm^3 of $NEt_3 \cdot 3HF$ with stirring under a N_2 atmosphere at 90 °C. The reaction was followed by TLC (eluent 20% ethyl acetate : 80% light petroleum 40–60 °C). The reaction mixture was allowed to cool, washed with 4 x 50 cm^3 of saturated sodium hydrogen carbonate solution (with great care); extracted with ethyl acetate (4 x 50 cm^3). The organic extracts were combined, and washed with brine (2 x 50 cm^3) and dried over magnesium sulfate. The solvent was filtered, and removed *in vacuo*. The crude product (1.69 g) was distilled under reduced pressure (55 °C at 0.1 mmHg). Yield of pure product 1.50 g (62%). Elemental analysis, calc. C (60.99%); H (9.38%); F (16.08%); O (13.54%); obs. C (60.16%); H (9.51%). *m*/*z*, M^+ = 118; MH − F^+ = 100.

1-Methoxy-2-fluorocyclohexane 2

To 2-fluorocyclohexanol **1** (0.498 g, 4.2 mmol) was added 20 cm^3 of anhydrous THF. To this solution was added 0.27 g (11.2 mmol) of sodium hydride in small portions over a period of about 20 min with stirring. This was continued until no more effervescing took place. To this was added a solution of 1.00 g (7.0 mmol) of MeI in 80 cm^3 of anhydrous THF. The reaction mixture was then fitted with a reflux condenser and refluxed at 80 °C for 6 h and followed by TLC (eluent: 30% ethyl acetate : 70% light petroleum 40–60 °C). The mixture was allowed to cool and quenched with 50 cm^3 of water (to remove any excess NaH). The mixture was filtered and the filtrate washed with 10 cm^3 of diethyl ether. The filtrate was further extracted with 3 x 50 cm^3 of diethyl ether; the organic extracts were combined, washed with 2 x 50 cm^3 portions of water, and dried over magnesium sulfate. The solvents were removed *in vacuo*. The crude product was distilled under reduced pressure (35 °C at 2 mmHg). Yield of very volatile pure product 0.20 g (36%). Elemental analysis, calc. C (63.61%); H (9.91%); F (14.37%); O (12.10%); found C (63.20%); H (9.99%). *m*/*z*, M^+ = 132; MH − F = 114.

Results

Spectral assignments and analysis

The assignment of the ^{1}H NMR spectrum of **1** was obtained by a ^{1}H–^{1}H COSY experiment and that of **2** followed directly. The ^{13}C NMR spectrum of **1** was assigned by comparing the observed chemical shifts with those calculated from substituent effects[21] and also from the magnitudes of the $^nJ_{CF}$ coupling constants[22] (n = 1, 2, 3 or 4). Again, the assignment of the ^{13}C spectrum of **2** directly followed. The ^{1}H chemical shifts together

Table 2 (*a*) Proton chemical shifts (δ) and (*b*) couplings (Hz) for *trans*-2-fluorocyclohexanol **1**

(*a*) Solvent	**1a**	**2a**	**3a**	**3e**	**4a**	**4e**	**5a**	**5e**	**6a**	**6e**	OH
CCl_4	3.52	4.13	1.41	2.03	1.25	1.73	1.25	1.68	1.25	1.95	2.28
$CFCl_3$	3.51	4.12	1.41	2.04	1.26	1.73	1.26	1.68	1.26	1.96	2.22
$CDCl_3$	3.64	4.27	1.45	2.10	1.27	1.76	1.27	1.71	1.27	2.02	2.36
Acetone	3.54	4.20	1.41	2.00	1.28	1.67	1.28	1.67	1.28	1.89	4.10
CD_3CN	3.52	4.12	1.42	2.01	1.27	1.68	1.27	1.63	1.27	1.90	3.79
$(CD_3)_2SO$	3.41	4.17	1.35	1.94	1.16	1.59	1.16	1.55	1.16	1.76	5.00
$CFCl_3$[a]	3.44	4.09	1.30	1.98	1.18	1.65	1.18	1.62	1.18	1.89	5.24
Acetone[a,e]	3.53	4.22	1.38	2.01	1.24	1.68	1.24	1.60	1.24	1.88	5.25

(*b*) Solvent	$J_{1a\text{-}2a}$	$J_{2a\text{-}3a}$	$J_{2a\text{-}3e}$	$J_{2a\text{-}F}$
CCl_4	8.14	10.60	4.77	51.02
$CFCl_3$[b,f]	8.21	10.70	4.80	51.15
$CDCl_3$[f]	8.40	10.97	4.91	51.37
CD_2Cl_2	8.36	10.92	4.90	51.42
[$^2H_6$]Acetone[c,f]	7.96	10.21	4.68	50.76
CD_3CN[c]	8.13	10.41	4.73	50.93
$(CD_3)_2SO$	8.01	10.24	4.67	50.71
$CFCl_3$[a]	8.63	11.01	4.96	51.18
[$^2H_6$]Acetone[d]	8.66	11.04	4.90	51.34

[a] 183 K. [b] 293 K. [c] $J_{1a\text{-}OH}$ was 4.11 (CD_3CN), 4.58 (Me_2SO), 4.09 (acetone). [d] 183 K ee conformer. [e] aa Conformer, δ (2e) 4.565. [f] Extra splittings of *ca.* 0.5 to 1 Hz were observed for $CFCl_3$, $CDCl_3$ and acetone.

Table 3 (*a*) ^{13}C chemical shifts (*δ*) and (*b*) ^{13}C–^{19}F coupling constants (Hz) for **1**

(*a*) Solvent	C1	C2	C3	C4	C5	C6
CCl_4	72.56	95.63	29.95	23.36	23.26	31.10
[$^2H_6$]Acetone	71.66	95.52	30.03	22.89	22.91	32.05
$(CD_3)_2SO$	71.03	95.62	30.10	22.92	22.95	32.49
Acetone[a]	72.17	96.57	30.41	23.41	23.28	32.36

(*b*) Solvent	C1-F	C2-F	C3-F	C4-F	C5-F	C6-F
CCl_4	18.76	174.43	17.89	10.24	1.90	6.54
[$^2H_6$]Acetone	18.47	174.12	18.15	9.97	1.73	6.68
$(CD_3)_2SO$	18.05	173.94	17.96	9.97	1.99	6.93
Acetone[a]	17.00	173.91	17.45	11.32	2.01	7.97

[a] 193 K, ee conformer.

with the couplings of the H2a proton of **1** in a range of solvents, including that of the ee conformer at 183 K $CFCl_3$ and acetone are presented in Table 2. The H2a proton was always well resolved, in contrast to H1a and the rest of the protons. The numbering of the protons (a = axial, e = equatorial) is taken from the dominant eq–eq conformer (Fig. 1). The coupling constants were obtained from an iterative analysis (LAOCOON III[23]) of the H2a resonance in **1** treating this as a five-spin system, *i.e.* including only nuclei coupled to this proton. The chemical shifts of the protons which couple to H2a (H1a, 3a and 3b) are well separated (Table 1) thus this is a weakly coupled spin system. The iteration gave rms errors of <0.02 Hz with probable errors of 0.05 Hz for the coupling constants.

The ^{13}C NMR spectra were also recorded in a number of solvents for **1**, and the chemical shifts and the ^{13}C–^{19}F coupling constants are presented in Table 3.

Low-temperature studies were performed on **1** in $CFCl_3$ and in [$^2H_6$]acetone. The two separate conformers were observed at *ca.* 183 K in both studies. The integration of the H2a proton peak in acetone solution gave directly the conformer populations but in $CFCl_3$ solution the proportion of the aa conformer was too small to obtain a reliable integration. The analysis of the H2a multiplet in the ee conformer was performed as above. The ^1H chemical shifts, ^{13}C chemical shifts and ^{13}C–^{19}F coupling constants were obtained for **1** in acetone at variable temperatures and are given elsewhere.[24]

Similar experiments were performed for **2** and these results are given in Tables 4 and 5. The low-temperature study was performed on **2** in a 50:50 mixture of $CFCl_3$ and CD_2Cl_2 and also in a 50:50 mixture of $CFCl_3$ and CS_2 as lower temperatures were required to freeze out the two forms for **2** than for **1**. The two forms were observed at *ca.* 163 K. The temperature dependence of the ^1H couplings in the 50:50 mixture of $CFCl_3$ and CD_2Cl_2 is given in Table 6 and that of the ^1H and ^{13}C chemical shifts and ^{13}C–^{19}F coupling constants given elsewhere.[24]

The ^1H and ^{13}C chemical shifts and couplings reported are in agreement with previous data on similar systems,[21] and the ^{13}C–^{19}F couplings very similar to those reported recently for the individual conformers of fluorocyclohexane.[25] These are discussed in more detail elsewhere.[24] The H–H couplings will be analysed in detail subsequently. The value of the H–C–O–H coupling (3.84 Hz at 183 K) is that expected for a *gauche* H–C–O–H fragment as shown in the g^- conformer (Fig. 1).

Conformational analysis

The determination of the conformer populations and relative energies was performed initially by direct integration of the low-temperature spectra for **1** and **2** and subsequently using the observed (averaged) couplings at higher temperatures using the standard eqns. (4).

$$\begin{aligned} J_{AV} &= n_A J_A + n_B J_B \\ n_B/n_A &= e^{(-\Delta G/RT)} \\ n_A + n_B &= 1 \end{aligned} \tag{4}$$

The values of the couplings of the 2a proton in the favoured eq–eq conformer g^- (Fig. 1) are given directly from the low-temperature spectra. However, the corresponding resonance for the ax–ax conformer was an unresolved doublet from which only the $^2J_{(H2a\text{-}F)}$ coupling could be obtained. The couplings in the eq–eq conformer are reasonably well predicted by the PCMODEL program[18] and thus we used this program to calculate the couplings in the ax–ax conformer. Both sets of couplings are given in Table 7. It is important to note that as the conformational equilibrium is heavily biased towards the eq–eq conformer the calculated populations are very dependent on the couplings in this conformer but much less so for the ax–ax

Table 4 (*a*) ^1H chemical shifts (δ) and (*b*) couplings (Hz) for **2**

(*a*) Solvent	1a	2a	3a	3e	4a	4e	5a	5e	6a	6e	OMe
CCl_4	3.12	4.28	1.48	1.95	1.26	1.64	1.26	1.64	1.26	1.86	3.38
$CFCl_3$	3.10	4.25	1.46	1.92	1.23	1.61	1.23	1.61	1.23	1.87	3.36
$CFCl_3/CS_2$	3.08	4.22	1.43	1.93	1.25	1.62	1.25	1.62	1.25	1.85	3.35
Mix[a]	3.15	4.30	1.47	2.00	1.24	1.67	1.24	1.67	1.24	2.00	3.40
$CDCl_3$	3.22	4.39	1.49	2.06	1.25	1.68	1.25	1.68	1.25	2.06	3.48
CD_3CN	3.20	4.32	1.42	2.13	1.25	1.65	1.25	1.65	1.25	2.00	3.37
Acetone	3.18	4.32	1.44	1.98	1.24	1.63	1.24	1.63	1.24	1.98	3.37
Mix[b]	3.19	4.31	1.44	2.22	1.23	1.74	1.23	1.74	1.23	2.12	3.43

(*b*) Solvent	J_{1a-2a}	J_{2a-3a}	J_{2a-3e}	J_{1a-F}
CCl_4	7.02	8.97	4.26	49.59
$CFCl_3$	7.04	9.04	4.28	49.65
$CFCl_3/CS_2$	7.06	9.08	4.30	49.69
$CFCl_3$/DCM[a]	7.62	9.91	4.63	50.21
$CDCl_3$	7.90	10.31	4.78	50.53
[$^2H_6$]Acetone	7.75	9.99	4.66	50.47
CD_3CN	8.01	10.33	4.83	50.72
Mix[b]	8.72	11.35	5.15	51.14

[a] 50:50 mixture of $CFCl_3$ and CD_2Cl_2. [b] 163 K, ee conformer, δ (2e) 4.67.

Table 5 (*a*) ^{13}C Chemical shifts (δ) and (*b*) ^{13}C–^{19}F coupling constants (Hz) for **2**

(*a*) Solvent	C1	C2	C3	C4	C5	C6	OMe
CCl_4	79.94	92.88	28.37	22.27	22.40	29.66	57.42
Mix[a]	81.53	94.76	30.85	23.30	23.43	29.37	57.68
[$^2H_6$]Acetone	81.85	95.20	31.19	23.56	23.66	29.72	57.56
Mix[a,c]	82.06	95.61	31.24	23.7	23.7	29.15	57.27

(*b*)Solvent	C1-F	C2-F	C3-F	C4-F	C5-F	C6-F	OMe-F
CCl_4	19.27	176.88	19.07	8.23	1.60	5.62	2.01
Mix[a]	17.98	176.19	18.47	9.59	1.80	6.38	1.85
[$^2H_6$]Acetone	18.11	175.07	18.31	9.66	1.85	6.50	*b*
Mix[a,c]	15.18	171.41	18.41	*d*	*d*	7.68	*d*

[a] 50:50 mixture of $CFCl_3$ and CD_2Cl_2. [b] No OMe–F coupling observed. [c] 183 K. [d] Broad due to coalescence.

Table 6 ^1H couplings (Hz) for **2** at various temperatures in 50:50 $CFCl_3$:CD_2Cl_2

T/K	J_{1a-2a}	J_{2a-3a}	J_{2a-3e}	J_{2a-F}
293	7.62	9.91	4.63	50.21
283	7.70	10.03	4.68	50.28
273	7.80	10.16	4.72	50.35
263	7.90	10.27	4.76	50.42
243	8.06	10.49	4.84	50.54
163	8.72	11.35	5.15	51.14

Table 7 Obs. and calc. conformer couplings for *trans*-2-fluorocyclohexanol **1** and the methyl ether **2**

Eq–eq	$^3J_{1a-2a}$	$^3J_{2a-3a}$	$^3J_{2a-3e}$	$^2J_{H2a-F}$
1 obs	8.63[a]	11.01	4.96	51.18
	8.66[b]	11.04	4.90	51.34
1 calc[c]	7.8	11.2	4.9	—
2 obs[d]	8.72	11.35	5.15	51.14
2 calc[c]	7.81	11.04	5.07	—
Ax–ax	$^3J_{1e-2e}$	$^3J_{2e-3e}$	$^3J_{2e-3a}$	$^2J_{H2e-F}$
Calc[c,e]	3.74	4.02	1.57	47.50[b]

[a] 203 K in $CFCl_3$. [b] 183 K in [$^2H_6$]acetone. [c] PCMODEL. [d] 163 K in $CFCl_3$–CD_2Cl_2. [e] Same values for **1** and **2**.

couplings. Thus, the use of the calculated couplings for the eq–eq conformer would give quite erroneous results. Indeed, the observed (averaged) value for J_{1a-2a} at room temperature in all the solvents studied (Table 1) is larger than the calculated value of 7.8 Hz, giving an impossible analysis. There is also no intrinsic solvent dependence of the $^3J_{HH}$ couplings as the couplings for the eq–eq conformer are the same in $CFCl_3$ and acetone.

The use of the conformer couplings with the observed averaged couplings gives, from eqn. (1), the populations and relative energies of the conformers and these are given in Table 8 together with the results of ref. 13 (in parentheses). The values in Table 8 are obtained from the J_{1a-2a} and J_{2a-3a} values as these couplings give the best definition of the populations. The accuracy of the populations and energies in Table 8 may be estimated by considering that the probable error in the observed couplings of 0.05 Hz corresponds to a change of 0.05 kcal mol^{-1} in the conformer energies.

Discussion

The results of Table 8 are of considerable interest. The present results agree reasonably well with those of ref. 13, considering the larger uncertainties in the former values and both sets of values show an intriguing variation with solvent. Excluding the hydrogen-bond donor solvents $CDCl_3$ and CD_2Cl_2 which will be considered later, the value of ΔG (ee–aa), the conformational energy at room temperature, varies in **1** from 1.5 kcal mol^{-1} in the non-polar solvents CCl_4 and $CFCl_3$ to *ca.* 1.2 kcal mol^{-1} in the very polar solvents (acetone, Me_2SO, *etc.*). The analogous results for **2** are 0.40 kcal mol^{-1} in the non-polar solvents to *ca.* 1.0 kcal mol^{-1} in the very polar solvents. This, at first sight, remarkable reversal in the variation of ΔG with solvent

Table 8 Conformer populations and observed and calculated energies for **1** and **2**

		trans-2-Fluorocyclohexanol **1**			Methyl ether **2**		
			ΔG/kcal mol^{-1} [a]			ΔG/kcal mol^{-1} [b]	
Solvent	ε	% ax–ax	Obs.	Calc.	% ax–ax	Obs.	Calc.
Vapour	—	—	—	1.77	—	—	0.11
CCl_4	2.24	8.3	1.43 (1.65)[c]	1.50	33.2	0.41 (0.81)[c]	0.41
$CFCl_3$	2.3	6.8	1.55	1.49	32.5	0.43	0.42
$CFCl_3/CS_2$	2.4	—	—	—	32.0	0.45	0.43
$CDCl_3$	4.81	3.0	2.06 (large)[c]	1.30	15.2	1.00 (1.19)[c]	0.64
CD_2Cl_2	8.93	3.7	1.93 (> 1.5)[c]	1.20	20.7[f]	0.78	0.68
[$^2H_6$]Acetone	20.7	12.9	1.13 (1.30)[c]	1.10	18.9	0.85	0.90
CD_3CN	37.5	9.7	1.32 (1.19)[c]	1.01	13.9	1.06 (1.80)[c]	0.99
$(CD_3)_2SO$	46.7	12.2	1.17	0.97	—	—	—
[$^2H_6$]Acetone[e]	30.0	2.5	1.35	—	—	—	—
$CFCl_3/CS_2$[d]	2.5	—	—	—	8.9	0.73	—
$CFCl_3$/DCM[d]	≈10.0	—	—	—	1.7	1.32	—

[a] 298 K. [b] 293 K. [c] Ref. 13. [d] 163 K. [e] 183 K. [f] $CFCl_3/CD_2Cl_2$, $\varepsilon \approx 5.6$.

dielectric constant in **1** and **2** can be explained simply by the solvation theory given earlier and the calculated conformer energy differences for **1** and **2** from the MODELS calculations also given in Table 8. The calculations for simplicity considered only the most stable conformers, *i.e.* for **1** the g^- form for both the eq–eq and ax–ax conformers and for **2** the eq–eq (g^+) and ax–ax (g^-) forms (Fig. 1). The solvation theory gives only $\delta\Delta G$, the change in the conformer free energy with solvent, thus the calculated energies in Table 8 are normalised to the observed values for the non-polar solvents. Inspection of the calculated *vs.* observed conformer energies shows clearly that the observed change in the conformer energy with solvent is well predicted for both **1** and **2**. In **1** the free energy decreases by *ca.* 0.3 kcal mol^{-1} on going from the non-polar to the very polar solvents compared to the calculated value of 0.5 kcal mol^{-1}, whereas in **2** the free energy increases by *ca.* 0.6 kcal mol^{-1}, in exact agreement with the calculated value. Thus, the calculations predict both the trends and also the amount of the solvent variation for both **1** and **2**. In **1** the calculated variation with solvent is rather larger than is observed and this is almost certainly due to the neglect of the other populated forms in the solvation calculations. To include these would be both complex and arbitrary in view of the uncertainty in the actual populations of these forms in solution.

The simple physical explanation for this solvation behaviour is that in **1** the most populated ax–ax g^- conformer has a much larger dipole than the eq–eq g^- form, whereas in **2** the eq–eq g^+ conformer has a much larger dipole than the ax–ax g^- form (Table 1) and the conformer with the larger dipole moment is stabilised in solution.

The solvation calculations also allow us to obtain the theoretically important values of the conformer energies in the vapour state. These are given directly in Table 8 from the MODELS calculations but as the calculated solvation energies for **1** are slightly larger than the observed, when this over-estimation is taken into account more realistic values of the vapour state energies are 1.6 for **1** and +0.1 kcal mol^{-1} for **2**. These values are for the free energy differences (ΔG), which are usually assumed to equate to the enthalpy differences (ΔH) as the entropy difference between the conformations is neglected. The precise determination of the free energy differences at very different temperatures in Table 8 allows the determination of both ΔH and ΔS for **1** and **2**. For **1** inspection of the results shows that there is virtually no difference in ΔG with temperature, thus the value of ΔG (above) may be confidently taken to be ΔH. For **2** a quite different scenario is observed. Both the variation of the observed (averaged) couplings with temperature (Table 6) and the direct determination of the equilibrium at different temperatures show that ΔG varies significantly with temperature. The analysis of the couplings of Table 6 gives values of ΔH and ΔS of 1.70 kcal mol^{-1} and 3 cal mol^{-1} K^{-1}, respectively. The direct determination of ΔH and ΔS from the results of Table 8 for the non polar $CFCl_3$–CS_2 solution gives ΔH 1.05 and ΔS 2.0, respectively. The results are in reasonable agreement and the difference in these results is almost certainly due to the variation of ΔH with temperature in the moderately polar $CFCl_3$–CD_2Cl_2 solution. We take the values in the non-polar media as definitive and these together with the extrapolated value of ΔG for the vapour phase gives a value of the ΔH for the vapour as 0.7 kcal mol^{-1}. The increased value of ΔS for **2** compared to **1** could well be due to degeneracy in the various conformational forms of **2**. In **1** the equilibrium is very largely between two stable forms, leeg$^-$ and laag$^-$, whereas in **2** both the ax–ax and eq–eq conformers may have two stable g^- and g^+ forms. Two degenerate ax–ax forms would give a value of ΔS of $R \ln 2$, *i.e.* 1.4 cal mol^{-1} K^{-1}.

The derived energy differences can be compared directly to the theoretical values of ΔE(aa–ee) (Table 1) of 1.2 kcal mol^{-1} for **1** in very reasonable agreement with the observed value and −0.7 kcal mol^{-1} for **2** which is substantially less than the observed value (see below).

These observed energy differences also allow an experimental determination of the magnitude of both the OH ··· F hydrogen bonding in **1** and of the *gauche* effect in **2** by comparing them with the values predicted from the ΔG values of the monosubstituted cyclohexanes. The conformer free energy differences ΔG(ax–eq) for fluoro-, hydroxy- and methoxy-cyclohexane are 0.25, 0.65 and 0.55 kcal mol^{-1} respectively[26] and they are solvent independent apart from the value for the OH group (see below). The above value is for CCl_4 solution. On the basis of simple additivity rules the ax–ax conformer of **1** would be expected to be 0.9 kcal mol^{-1} less stable than the eq–eq conformer and in **2** the corresponding value is 0.8 kcal mol^{-1}. The additional interaction in **1** due to the *gauche* F ··· OH interaction gives rise to a further stabilisation of 0.7 kcal mol^{-1} whereas the *gauche* interaction of the F and OMe in **2** gives rise to a destabilising effect of 0.1 kcal mol^{-1}. This suggests that the *gauche* F ··· OMe interaction is essentially neutral (neither attractive nor repulsive) and that the *gauche* OH ··· F hydrogen bonding interaction is attractive by *ca.* 0.8 kcal mol^{-1}.

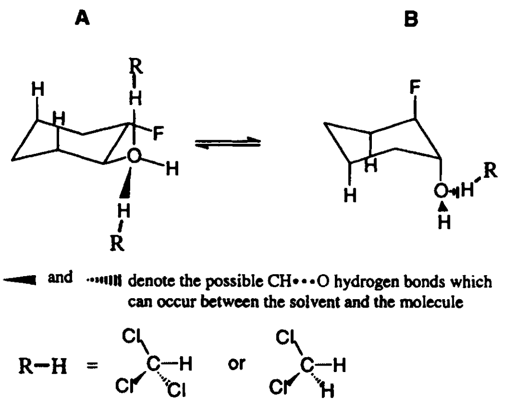

Fig. 2 The probable interaction of $CDCl_3$ (or CD_2Cl_2) with **1** and **2**

Thus, the stability of the eq–eq conformer of **1** and by implication the *gg*$^-$ form of 2-fluoroethanol is due primarily to hydrogen bonding, not to the *gauche* effect and this unequivocally supports the recent theoretical studies quoted above. The discrepancy between the theoretical results and previous experimental results in condensed media is now seen to be largely due to solvation, in that solvation affects the alcohol and ether equilibria in opposing ways.

This is beautifully illustrated by evaluating the equivalent data for acetone solution in analogous manner. The observed ΔG values for acetone (Table 8) of 1.1 and 0.85 for **1** and **2**, respectively, are very close to the predicted values based on the above additivity rules and totally different to the vapour phase results. Clearly solvation plays a key role in both the alcohol and also, more surprisingly, the ether.

The hydrogen-bond donor solvents

In both **1** and **2** the usual smooth trend of ΔG with solvent dielectric constant[11] is not observed, in that in both cases $CDCl_3$ and CD_2Cl_2 are anomalous. In **1** the values of ΔG vary from *ca.* 1.5 kcal mol^{-1} in non-polar solvents to *ca.* 1.2 kcal mol^{-1} in very polar solvents but in $CDCl_3$ and CD_2Cl_2 the ΔG values are 2.1 and 1.9 kcal mol^{-1}, respectively. Similarly, in **2** the ΔG values vary from 0.4 kcal mol^{-1} in non-polar solvents to *ca.* 1.0 in polar solvents and again $CDCl_3$ is anomalous with a ΔG value of 1.0 kcal mol^{-1}. Very similar behaviour has been observed[27,28] in the solvent dependence of the conformer energy ΔG (ax–eq) of cyclohexanol. This is 0.86 kcal mol^{-1} in $CDCl_3$ and 0.65 kcal mol^{-1} in CCl_4 and hydrogen-bond acceptor (HBA) solvents (*e.g.* THF) and this difference was explained as due to the high energy of the *endo* conformation of the OH in axial cyclohexanol (*i.e.* with the hydrogen pointing over the ring). Thus, axial cyclohexanol can only act as a hydrogen-bond donor (HBD). HBA solvents will solvate both the eq and ax conformers equally, giving the same value of ΔG as the inert solvents. In contrast, HBD solvents (*e.g.* $CDCl_3$) will solvate the eq conformer preferentially compared to the ax conformer giving a higher value of ΔG. Protic solvents being both HBA and HBD solvate the eq OH group more readily than the ax OH and again the ΔG values are higher (*e.g.* water *ca.* 1.0 kcal mol^{-1}). This explanation is supported by the similarity between **1** and **2**, which immediately excludes any hydrogen bonding involving the OH as a hydrogen-bond donor as the explanation and is shown schematically in Fig. 2. The $\delta\Delta G$ ($CHCl_3$–CCl_4) is *ca.* 0.6 kcal mol^{-1} for **1** and **2**. This value is much larger than that for cyclohexanol and this could be due to the effect of the vicinal fluorine atom or to the different steric interactions of the OR group in **1** and **2** compared to cyclohexanol.

Acknowledgements

We acknowledge a SERC grant towards the purchase of the Bruker AMX 400 spectrometer, the computer facilities of the University of Liverpool (GAUSSIAN 92) and a SERC/CASE award to T. A. D. S. We wish to thank Mr I. W. A. Whitcombe and Mr J. H. Merrett (Roche Products Limited) for their continued technical and experimental assistance and Mr M. A. Warne for assistance in using the GAUSSIAN program.

References

1 Part 27. R. J. Abraham, A. D. Jones, M. A. Warne, R. Rittner and C. F. Tormena, *J. Chem. Soc., Perkin Trans. 2*, 1996, 533.
2 K. B. Wiberg and M. A. Murcko, *J. Mol. Struct.*, 1988, **163**, 1.
3 D. A. Dixon and B. E. Smart, *J. Phys. Chem.*, 1991, **95**, 1609.
4 J. Huang and K. Hedberg, *J. Am. Chem. Soc.*, 1989, **111**, 6909.
5 K. G. R. Pachler and P. L. Wessels, *J. Mol. Struct.*, 1970, **6**, 471.
6 (*a*) P. Buckley, P. A. Giguere and D. Yamamoto, *Can. J. Chem.*, 1968, **46**, 2917; (*b*) J. R. Durig, P. Klaeboe, G. A. Giurgis, L. Wang and J. Liu, *Z. Phys. Chem.*, 1995, Bd **191**, s23.
7 D. Davenport and M. Schwartz, *J. Mol. Struct.*, 1978, **50**, 259.
8 R. J. Abraham and J. R. Monasterios, *Org. Magn. Reson.*, 1973, **5**, 305.
9 R. C. Griffith and J. D. Roberts, *Tetrahedron Lett.*, 1974, **39**, 3499.
10 *Structure Data of Free Polyatomic Molecules*, ed. K. H. Hellwege, Landolt-Bornstein, vol 7, Springer, New York, 1976.
11 R. J. Abraham and E. Bretschneider, ch. 13, *Internal Rotation in Molecules*, ed. W. J. Orvill-Thomas, Academic, London, 1974.
12 J. M. Bakke, L. H. Bjerkeseth, T. E. C. L. Ronnow and K. Steinsvoll, *J. Mol. Struct.*, 1994, **321**, 205.
13 N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov and S. Wolfe, *Tetrahedron*, 1978, **34**, 2953.
14 GAUSSIAN 92, Revision F.4, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, Gaussian Inc., Pittsburgh PA, USA, 1992.
15 R. J. Abraham and L. Griffiths, *Tetrahedron*, 1981, **37**, 575.
16 R. J. Abraham, G. H. Grant, I. S. Haworth and P. E. Smith, *J. Comp. Aided Mol. Design*, 1991, **5**, 21.
17 J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods: A Guide to Using GAUSSIAN*, Gaussian Inc., Pittsburgh, PA, USA, 1993.
18 PCMODEL v 5.0, Serena Software, 1994.
19 Bruker UXNMR Manual v. 910901. Bruker AM. GmbH, Germany.
20 COSYDFTP automated program, Bruker UXNMR v. 910901.
21 R. J. Abraham, J. Fisher and P. Loftus, *An Introduction to NMR Spectroscopy*, Wiley, Chichester, 1988.
22 D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, London, 1989.
23 S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.
24 T. A. D. Smith, Ph.D. Thesis, Liverpool University, 1996.
25 R. J. Abraham, M. Edgar, L. Griffiths and R. L. Powell, *J. Chem. Soc., Perkin Trans. 2*, 1995, 561.
26 F. A. Carey and P. J. Sundberg, *Advanced Organic Chemistry*, Plenum, New York, Pt. A, 1977.
27 E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, 1965, **87**, 5031.
28 R. J. Abraham, E. J. Chambers and W. A. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1061.

Paper 6/01140C
Received 16*th February* 1996
Accepted 26*th April* 1996