Conformational Analysis. Part 22.[1] An NMR and Theoretical Investigation of the *gauche* Effect in Fluoroethanols

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The ABCX NMR spectrum of the C·CH(OH)·CH$_2$F fragment of 1-(4-bromophenyl)-2-fluoroethanol (BPFE) in eight solvents of different polarities was recorded and fully analysed. ^{13}C and NOE measurements confirmed the assignment of the prochiral methylene protons. The AA'BB'XX'R NMR spectrum of 1,3-difluoropropan-2-ol (DFP) was completely analysed in four solvents of different polarities. The couplings showed little solvent dependence except for D$_2$O solution.

From these analyses the conformer populations and hence relative energies of the possible conformers of these molecules were obtained. In BPFE, the *gt* rotamer in which fluorine is *gauche* to the hydroxy and *trans* (*anti*) to the phenyl group is favoured in all solvents but the rotamer energies are very dependent on the solvent. Δ*E* (*gg* − *gt*) varies from 1.6 kcal mol^{-1} in CCl$_4$ to 0.5 kcal mol^{-1} in DMSO, and Δ*E* (*tg* − *gt*) varies from 1.0 to 0.5 kcal mol^{-1} in the same solvents.† In DFP three populated conformers were found, two with a *trans–gauche* arrangement of the fluorine atoms and one with a *gauche–gauche* arrangement.

Ab initio MO calculations at the 6-31G level correctly predict the conformer energies except that the *gauche vs. trans* F···O orientation is calculated to be 1–2 kcal mol^{-1} less stable than observed. Other theoretical studies show that including polarisation functions does not affect this general result. It is suggested that C–F bond shortening in the *trans* orientation may contribute to the higher energy of this form and this would also explain the fact that the *gauche* effect is not observed for the comparable CHF$_2$ group.

The attraction of two vicinal electronegative atoms, the '*gauche* effect', has been a long-standing problem in theoretical conformational analysis.[2] This effect is present in olefins,[3,4] ethanes [5,6] and cyclohexanes [7] with vicinal electronegative atoms, particularly oxygen and fluorine. Pople elegantly summarised this problem in discussing the stability of (*Z*)- *vs.* (*E*)-1,2-difluoroethene.[8] The electrostatic repulsion of the fluorine atoms destabilises the *cis* olefin with respect to the *trans* form by *ca.* 2 kcal mol^{-1}. What interaction is therefore responsible for the observed greater stability of the *cis* olefin by 1.1 kcal mol^{-1}? Pople suggested that the stabilisation was due, in part, to F···F attraction in the *cis* isomer and partly to the greater correlation energy of the *cis* isomer. The greater stability of *gauche* with respect to *trans* 1,2-difluoroethane has also been suggested as due to correlation effects.[5] Intriguingly the *gauche* effect appears to be only present for 1,2-disubstituted compounds as 1,1,2-trifluoroethane and 1,1,2,2-tetrafluoroethane do not show the *gauche* effect, the *trans* conformers being more stable than the *gauche* forms by 1.1 and 1.2 kcal mol^{-1}. To date this has no theoretical explanation, apart from a pioneering molecular mechanics calculation by Abraham and Stolevick (*vide infra*).[9]

Similarly in 2-fluoroethanol OH···F hydrogen bonding was invoked to explain the predominance of the *gauche* form,[6] though Abraham and Monasteros showed that acetylation of the hydroxy group has little effect on the conformer energies in solution.[10]

There have been many attempts to explain these phenomena theoretically. Pople showed that (*Z*)-1,2-difluoroethene was indeed more stable than the (*E*)-isomer at the Hartree–Fock (HF) level, though by only 0.2 kcal mol^{-1} at the 6-311G level.[8] Wolfe *et al.* using the STO-3G basis set obtained good agreement with the experimental geometries of the fluoroethenes,[3] but could not reproduce the greater stability of (*Z*)-1,2-difluoroethene. Subsequently Dixon *et al.* using a double ζ plus polarisation function on carbon calculated the *cis vs. trans* energy difference as −0.13 kcal mol^{-1} (*cf.* the observed value of −0.93 kcal mol^{-1}), but noted that calculations using the 3-21G basis set were less satisfactory.[4]

Hirano *et al.* used a variety of basis sets in their calculations of 1,2-difluoroethane.[5] They could reproduce the experimental geometry with the 6-31G** basis set, but the only basis set at the HF level to give the *gauche* form more stable than the *trans* was the STO-3G one. Second-order Møller–Plesset (MP) perturbation was necessary to reproduce this stability, and the best energy difference they obtained was −0.3 kcal mol^{-1} with the MP2/6-311G** (*cf.* the observed value of −0.9 kcal mol^{-1}).

Wiberg *et al.*[6a] examined the conformational isomerism in 2-fluoroethanol using various basis sets. They optimised the geometries at the 6-31G* level, and obtained values of Δ*E*(*g* − *t*) ranging from −1.2 to −2.9 kcal mol^{-1} using HF, MP2 and MP3 perturbations, which compare well with the experimental value of −2.7 kcal mol^{-1}, though again it was not the highest level of theory which gave the best answer. They also calculated the energy of the *gauche* isomer when the hydroxy proton was directed away from the fluorine atom (*i.e.*, ∠CCOH = 180°) thus removing any possible hydrogen bond. In this case ΔE_{g-t} was +0.1 to +1.2 kcal mol^{-1} depending on the basis set used. Examination of the energy profile for rotation about the C–O bond suggested that the hydroxy H--F interaction is primarily electrostatic in nature. More recent calculations on fluoroethanol by Dixon and Smart[6b] with a triple ζ basis set augmented by polarisation functions gave similar results. They concluded that 'the stability of the *gauche* form is almost entirely due to hydrogen bonding and the *gauche* effect contributes only *ca.* 0.1 kcal mol^{-1}.'

We note that all the theoretical calculations tend to underestimate the *gauche* effect, and furthermore they have not provided a definitive answer to Pople's original question.

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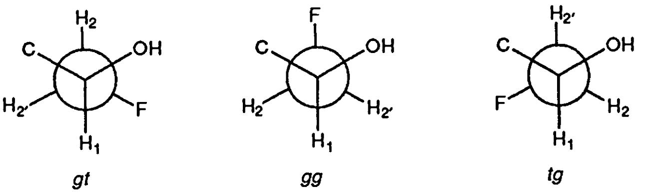
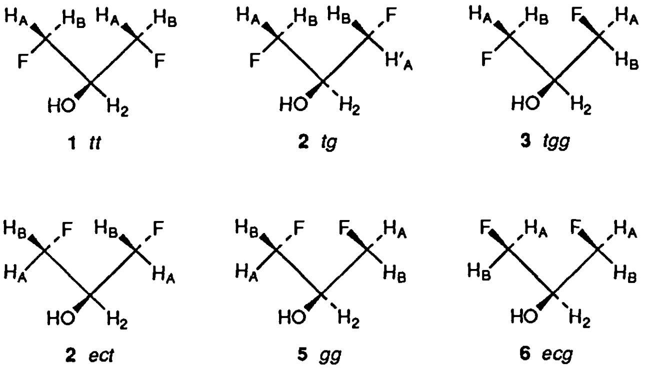
† 1 kcal mol^{-1} = 4.18 kJ mol^{-1}.



gt *gg* *tg*

Fig. 1 Newman projections of the C^1–C^2 rotamers of BPFE and DFP



1 *tt* 2 *tg* 3 *tgg*

2 *ect* 5 *gg* 6 *ecg*

Fig. 2 The possible conformations of DFP

Clearly further experimental and theoretical investigations are necessary in order to provide a satisfactory explanation for the *gauche* effect. The absence of any simple explanation for the *gauche* effect is responsible for the virtual complete absence of any comprehensive molecular mechanics investigation of these compounds. Abraham and Stolevik[9] considered the rotational barriers and conformer energies of a variety of fluoroalkanes and suggested a novel F • • • F potential to explain the experimental data, but since this pioneering investigation to our knowledge there has been no systematic MM investigation of any fluoro-compounds.

Although the pharmaceutical applications of fluoro-compounds is now one of the growth areas of molecular pharmacology,[11] there is still a lack of experimental data on simple fluoro-compounds, particularly alcohols and this provided much of the impetus for this series of investigations. We have shown recently, in examining the conformations in solution of fluoro sugars[12] and cyclohexane-1,3-diol,[1] how the F • • • OH interaction has little effect on the molecular conformation in solution, in contrast to the OH • • • OH interaction.

Here we present the conformational analysis of two substituted fluoroethanols 1-(4-bromophenyl)-2-fluoroethanol (BPFE) and 1,3-difluoropropan-2-ol (DFP) by NMR spectroscopy in a variety of solvents from which both the conformational energies in the gas phase and the influence of solvent can be obtained. This experimental data is compared with both molecular mechanics and *ab initio* calculations. In BPFE, there are three distinct conformations about the OC–CF bond (Fig. 1), whilst DFP has six non-equivalent conformations (Fig. 2) providing an additional test of the theory. The only related investigations are electron diffraction studies of 2-fluoroethanol 1-fluoropropan-2-ol, which was shown to exist predominantly as the *gt* isomer,[13] and the analysis of the NMR spectrum of 1-phenyl-2-fluoroethanol.[14] In neither case was any energetic data derived. The structure of 1,3-difluoropropane has been determined by electron diffraction,[15] and vapour phase conformer populations of C_2 63%, C_1 27%, C_s 10% and C_{2v} 0% were found. The nomenclature refers to the symmetry group of the conformer. The conformers in which the C–F bonds are eclipsed (C_s) and in which they are *trans–trans* (C_{2v}) were also found to be of high energy by MM and MO calculations. Shapiro *et al.*[16] have analysed the NMR spectra of a number of fluorinated acetones and some qualitative structural information was obtained. The $^4J_{FF}$ couplings in these molecules are noteworthy as the values of this coupling can vary from − 10 to + 81 Hz. Both the F–F distance (the through space effect) and the relative orientation of the C–F bonds contribute to the values of this coupling.[17]

Theoretical

The modelling studies were carried out using the commercial molecular mechanics packages PCMODEL[18] and NEMESIS[19] and the *ab initio* calculations using the GAUSSIAN90 package.[20] The combination of molecular modelling and *ab initio* calculations was used in order to maximise the computational efficiency as follows. For both PFE† and DFP there are a number of possible orientations of the hydroxy proton for each of the conformations shown in Figs. 1 and 2. Thus PFE has nine and DFP 18 possible conformations. The modelling calculations were performed on all these conformations in order to determine the preferred orientation of the OH proton for each of the conformations of Figs. 1 and 2. In most cases this preferred orientation is well defined, *e.g.* if the vicinal fluorine and oxygen atoms are in a *gauche* orientation the strongly preferred orientation of the OH proton is that with the OH bond parallel to the CF bond, giving maximum electrostatic stabilisation. In those cases where the OH orientation is more degenerate (*i.e.* where the fluorine and oxygen are in a *trans* orientation) all the conformations were optimised.

The optimisations were then performed at the 6-31G basis set level. The recommended basis set for geometry optimisations is the 6-31G* basis set.[6,8] In some preliminary calculations the 6-31G basis set gave almost identical geometries to the 6-31G* set and we therefore used the computationally less demanding basis set. Even at the 6-31G* level the experimental bond lengths are not particularly well reproduced in these systems. For example in *gauche* fluoroethanol the optimised[6] (and observed)[21] C–F, C–C, C–O and O–H bond lengths are 1.378 (1.395), 1.509 (1.513), 1.397 (1.418) and 0.948 (0.966) Å respectively. (Note that a 0.03 Å change in a bond length is equivalent to *ca.* 0.3 kcal mol^{-1} change in the energy.[19]) Thus we preferred to retain the experimental bond lengths given above, together with the standard C–H bond length (1.09 Å) and C–C–H angles and the geometry of the benzene ring (C–C 1.397, C–H 1.083 Å, $\angle$CCC 120°). The remaining bond and dihedral angles were optimised for each conformation and the results summarised in Tables 1 and 2.

For both molecules the optimised geometries show, as expected, no large deviations from idealised geometries, with the possible exception of the C–O–H angle. This is in all cases *ca.* 113° somewhat larger than the experimental value in methanol (108.5°)[21] and the calculated value in fluoroethanol (108.5–110.5°).[6] Unfortunately every experimental determination of the geometry of fluoroethanol assumes the value of this angle to be 108.5°.

The central C–C–C angle shows some variations about the 'unstrained' value of 112.5° in propane,[21] as expected but no other bond angles change appreciably from the tetrahedral values apart from the C–C–O angles in the *tg* conformer of DFP. The stable orientation of the OH proton is always obtained from the rule given previously, *i.e.* the O–H and C–F bonds are parallel whenever the vicinal oxygen and fluorine atoms are in a *gauche* orientation. This rule is obeyed for all the conformations of both molecules studied and provides an immediate means of identifying the stable conformation for

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† Note that the theoretical calculations are for 1-phenyl-2-fluoroethanol (PFE).

Table 1 6-31G Geometries and energies for PFE

Parameter	*gt*	*gg*	*tg*
∠FCCC	180.2	−70.0	64.0
∠HOCA	177.3[a]	184.2[b]	178.9[c]
∠C^2C^1CC	97.8	61.4	86.9
∠C^2C^1C	110.8	113.6	112.9
∠CCF	108.4	109.1	109.0
∠C^2C^1O	109.0	108.7	103.1
∠$C_{Ar}CO$	109.1	112.4	112.5
∠COH	112.4	113.3	113.8
E_{rel}/kcal mol^{-1}	0.0	3.3	0.2
μ/D	1.86	2.20	2.46

[a] A = C_{Ar}. [b] A = H. [c] A = C^2.

Table 2 6-31G Geometries and energies for DFP

Parameter	*tt*	*tg*	*tgg*	*ect*	*gg*	*ecg*
∠F^1CCC	178.4	177.8	180.4	−65.8	64.4	66.0
∠$CCCF^2$	164.8	59.5	−44.1	65.8	60.9	−66.0
∠HOCH	53.0	63.0	68.1	180.0	161.9	180.0
∠CCC	111.4	112.3	111.8	115.1	112.6	114.1
∠F^1CC	108.0	107.9	107.8	110.4	107.9	109.5
∠CCF^2	109.3	109.0	109.7	110.4	108.7	109.5
∠C^1C^2O	108.1	110.6	110.1	108.5	110.7	109.6
∠OC^2C^3	108.1	104.4	107.1	108.5	108.4	109.6
∠COH	113.1	113.3	113.1	115.0	113.0	112.0
E_{rel}/kcal mol^{-1}	4.3	0.0	2.3	7.5	0.7	4.5
μ/D	2.90	0.55	2.77	3.53	0.80	3.82

molecules like DFP where there is more than one vicinal fluorine atom. For the two cases where there is no fluorine *gauche* to the OH (*tg* in Fig. 1 and *ect* in Fig. 2), the HCOH dihedral is 180° but this orientation is not so strongly preferred. These conformations are of low population (see later).

Experimental

DFP was obtained from Fluorochem. The solvents were obtained commercially, stored over molecular sieves and used without further purification.

^{1}H, ^{19}F and ^{13}C NMR spectra were obtained on Bruker AMX 400 and AM 400 spectrometers. Spectra were of 10 mg cm^{-3} solutions (^{1}H, ^{19}F) and *ca.* 100 mg cm^{-3} (^{13}C) with a probe temperature of *ca.* 25 °C (Me_2SO 40 °C). A [$^2H_6$]acetone capillary was used as the deuterium lock signal for the CCl_4 solution. All ^{1}H NMR measurements were referenced to Me_4Si as an internal reference. ^{13}C NMR were referenced to the deuteriated solvent peak. ^{19}F NMR spectra were referenced externally to CF_3CO_2H or $CFCl_3$.

Typical conditions for ^{1}H NMR spectra obtained on the AM 400 and AMX 400 are given in ref. 1. Broadband proton-decoupled and gated proton-decoupled ^{13}C spectra were obtained on the AMX 400. Typical conditions were 20 000 transients; 64 K data points; 5.0 µs (60° flip angle); 17000 Hz sweep width; 2 s acquisition time; zero-filled to 256 K data points for a 0.06 Hz per point digital resolution. An exponential multiplication (LB = 2.0 Hz) was applied to improve signal to noise.

A ^{1}H NOE difference experiment was carried out on the AMX 400 spectrometer using the 'NOEMULT' automated program[23] with 8 transients; 2 dummy scans; 256 cycles; 2 on-resonance irradiation points (*ortho-* and *meta*-protons); *l*4 = 100; *d*1 = 30 ms; *d*12 = 20 ms; *d*20 = 50 ms; irradiation power level = 90 dB; 5 600 Hz sweep width; 4 K data points and 0.4 s acquisition time. An exponential window function LB = 2.0 Hz was used and the FID was zero-filled to 32 K data points for a digital resolution of 0.3 Hz per point.

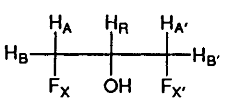

Fig. 3 Nomenclature used for the DFP spin system

The synthesis of BPFE was achieved in two steps from the starting compound 2,4′-dibromoacetophenone (Sigma).

4′-Bromo-2-fluoroacetophenone.—A suspension of 2,4′-dibromoacetophenone (0.973 g, 3.5 mmol, 278 g mol^{-1}) in 2.5 cm^3 of triethylamine trishydrofluoride reagent (University of Birmingham Chemistry Dept.) was heated in N_2 under reflux at 120 °C for 2 h. TLC indicated a reaction. An excess of saturated sodium hydrogen carbonate solution was added and the product extracted into diethyl ether. The ether solution was dried (sodium sulfate); removal of diethyl ether left 388 mg of an orange crystalline material (51% yield).

1-(*4-Bromophenyl*)-*2-fluoroethanol*.—The ketone (198 mg, 217 g mol^{-1}, 0.91 mmol) dissolved in freshly distilled tetrahydrofuran (THF) (3 cm^3) was cooled in an ice bath. $NaBH_4$ (65 mg, 1.7 mmol, 37.83 g mol^{-1}) was added carefully to the stirred solution. The reaction mixture was left at room temp. for several hours. A ^{1}H NMR spectrum of the reaction mixture established that the fluorohydrin had been formed. The THF was evaporated, glacial acetic acid added to the residue, the product extracted into methylene chloride, washed with 1 mol dm^{-3} HCl and then dilute sodium hydrogen carbonate solution. Evaporation of the solvent yielded the fluorohydrin (186 mg, 0.85 mmol, 93% yield).

Spectral Analysis and Assignments.—The iterative analyses of the NMR spectra were carried out using the LAOCOON[24] and PANIC851[25] programs.

(*a*) *BPFE*. The CH–CH_2F group of BPFE is an ABCX spin system. The iterative calculations on the proton spectra had RMS errors < 0.08 Hz and probable errors < 0.1 Hz. The observed and simulated ^{1}H NMR spectra of the CH–CH_2F group of BPFE in CD_2Cl_2 are given in ref. 26. The prochiral H-2 and -2′ are assigned on the basis of the relative magnitudes of $J_{1,2}$ and $J_{1,2'}$. We assign the signal with the smaller splitting as H-2′, so that $J_{1,2} > J_{1,2'}$. In the eight solvents of this study H-2′ occurs downfield of H-2, Table 3. This assignment is supported by the magnitude of $^3J_{C,F}$ in $CDCl_3$ solution of 8.1 Hz, which is indicative of a *trans* F/C orientation as in rotamer *gt* (Fig. 1)[27] and the NOE experiment. This experiment was performed on BPFE in CCl_4 and provided strong evidence of the preponderance of rotamer *gt*. Irradiation of the *ortho* phenyl protons results in an NOE of H-2, -2′ and -1. That the NOE of H-2 is similar in size to that of H-2′ is to be expected if rotamer *gt* is highly populated (an NOE of H-2 far greater than that of H-2′ would be expected if rotamer *tg* was preferred). The through space distances predicted by PCMODEL for rotamer *gt* are *ortho*-H ⋯ H-2 = 2.6, *ortho*-H ⋯ H-2′ = 3.4 and *ortho*-H ⋯ H-1 = 2.4 Å, all within the '3.5 Å' limit usually quoted for an NOE.[28]

(*b*) *DFP*. The DFP spin system is an AA′BB′XX′R spin system (Fig. 3). The R spectrum of the H-2 resonance is essentially a triplet of quintets centred at *v*(R) from which first-order values for *J*(XR), *J*(AR) and *J*(BR) are provided by the splittings.

The spectrum required extensive trial and error fitting plus the observation of the C-13 satellites in both the ^{1}H and ^{19}F spectra to obtain precise agreement between the observed and calculated spectrum. The observed and calculated ^{1}H spectra are shown in Fig. 4. Note that the observed spectrum has been given slightly too much apodisation, resulting in the negative dip in parts of the spectrum. This was necessary to obtain the

Table 3 Coupling constants (Hz) and chemical shifts (δ) in 1-(4-bromophenyl)-2-fluoroethanol in solution

Solution	δ_1	δ_2	$\delta_{2'}$	J_{12}	$J_{12'}$	$J_{22'}$	J_{1F}	J_{2F}	$J_{2'F}$
$CFCl_3$[a]	4.635	4.252	4.287	9.0	2.6	−9.5	14.2	48.5	47.5
CCl_4	4.857	4.242	4.376	8.41	3.36	−9.40	13.00	48.44	46.75
$CDCl_3$	4.971	4.381	4.481	8.00	3.38	−9.57	14.2	48.27	46.69
CD_2Cl_2	4.978	4.369	4.478	8.01	3.23	−9.65	14.66	48.23	46.66
Ac[b,d]	4.954	4.390	4.459	7.01	3.69	−9.43	15.3	48.14	47.17
MeOD	4.879	4.383	4.438	7.07	3.82	−9.56	15.84	48.08	47.13
MeCN	4.952	4.429	4.504	7.12	3.64	−9.61	16.48	48.01	47.05
Me_2SO[c]	4.818	4.361	4.416	6.69	3.97	−9.40	16.85	47.90	47.23
D_2O	5.037	4.542	4.615	7.20	3.35	−9.99	18.02	47.75	46.81

[a] Ref. 14. [b] OH signal obscured by the hydroxy signal. Iteration on H-2 and -2′ only. [c] 313 K. [d] δ_F −304.0.

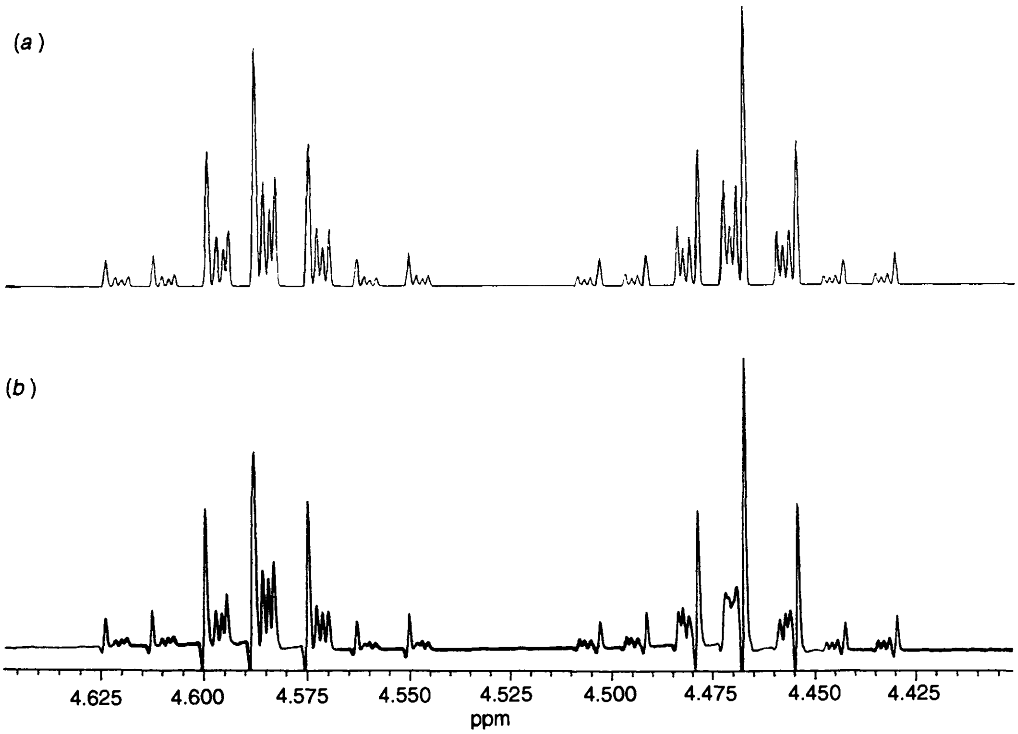

Fig. 4 The calculated (*a*) and observed (*b*) AA′BB′ part of the spectrum of DFP in $CDCl_3$ solution at 400 MHz

Table 4 Spectral parameters for 1,3-difluoropropan-2-ol in solution

Solvent	δ(HA)	δ(HB)	δ(HR)	δ(F)	*J*(AR)	*J*(BR)	*J*(AB)
CCl_4	3.658	3.658	3.236				
$CDCl_3$	4.540	4.512	4.128	−236.2	4.42	5.35	−9.79
CD_3OD	4.450	4.416	3.981	−233.1	4.46	5.35	−9.72
Me_2SO[a]	5.211	5.178	4.716	−229.9	4.46	5.36	−9.61
D_2O	4.604	4.549	4.177	−233.5	3.74	5.55	−10.13
Solvent	*J*(AX)	*J*(BX)	*J*(AX′)	*J*(BX′)	*J*(XR)	*J*(XX′)	RMS
$CDCl_3$	46.97	46.93	1.53	1.32	18.53	1.2	0.049
CD_3OD	47.31	47.30	1.46	1.40	19.04	1.2	0.033
Me_2SO	47.29	47.33	1.45	1.42	19.80	—	0.075
D_2O	46.62	47.07	1.67	0.80	21.46	0.7	0.067

[a] For H-2 signal in Me_2SO, 3*J*(2,OH) = 5.3 Hz.

best resolution and did not affect at all the subsequent analysis. This spin system is analogous to the simple AA′XX′ spin system in that the spectrum is insensitive to the relative signs of $J_{AA'}$ and $J_{XX'}$. The observed spectrum is dependent on the relative signs of J_{AX} and J_{BX} and $J_{AX'}$ and $J_{BX'}$. This is demonstrated clearly in Fig. 5 where the AA′BB′ spectrum is calculated for various combinations of the relative signs of the AX and BX couplings. The spectrum shows unambiguously that the relative signs of all these couplings are the same, and as the geminal HF couplings J_{AX} and J_{BX} are known to be positive the analysis confirms that all the HF couplings in this molecule are positive. The NMR parameters obtained from the analyses of this spectrum in a range of solvents of differing polarity are given in Table 4. Note that in CCl_4 solution the chemical shift ν(A) − ν(B) becomes so

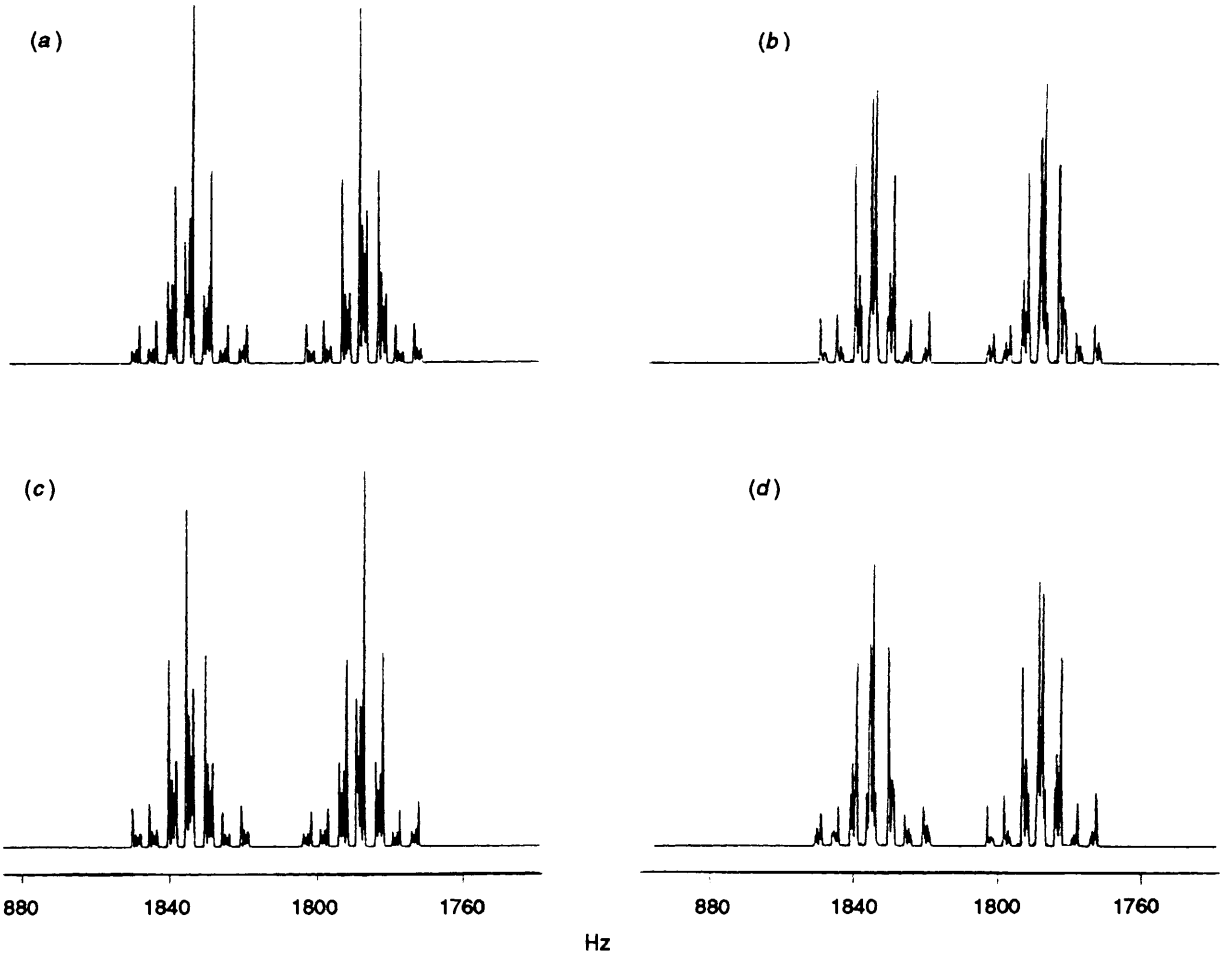

Fig. 5 Calculated spectra for the AA'BB' signals of DFP in $CDCl_3$ which show the dependence of the AA'BB' pattern upon the relative signs of the $J_{H,F}$ couplings. (*a*) *J*(AX') and *J*(BX') negative; (*b*) *J*(AX') positive, *J*(BX') negative; (*c*) *J*(AX') and *J*(BX') positive (matches the observed spectrum); (*d*) *J*(AX') negative, *J*(BX') positive.

Table 5 Vicinal HH and HF couplings Hz in the C•CH(OH)•CH_2F fragment

	Conformer		
Coupling	*gt*	*gg*	*tg*
J_{12}	10.2	−0.2	5.0
$J_{12'}$	2.3	2.2	10.2
J_{HF}	13.4	35.8	7.3

Table 6 Rotamer populations P_{ij}(%) and relative rotamer energies E_{ij} kcal mol^{-1} in 1-(4-bromophenyl)-2-fluoroethanol

Solvent	P_{gt}	P_{gg}	P_{tg}	E_{gt}	E_{gg}	F_{tg}
Vapour[a]	86	2	12	0.0	2.2	1.2
CCl_4	75	5	15	0.0	1.6	1.0
$CDCl_3$	72	10	15	0.0	1.2	0.9
CD_2Cl_2	73	12	13	0.0	1.1	1.0
Acetone	60	17	20	0.0	0.8	0.7
Methanol	60	18	21	0.0	0.7	0.8
MeCN	62	19	18	0.0	0.7	0.8
Me_2SO	56	22	22	0.0	0.5	0.5
D_2O	64	23	13	0.0	0.6	1.0

[a] Values obtained by extrapolation.

small that the spectrum is deceptively simple and only the sums of the AX and BX couplings can be obtained. The rms errors from these analyses were *ca.* 0.05 Hz and the probable errors all < 0.016 Hz. Further details can be found in ref. 26.

Conformational Analysis.—The data in Tables 3 and 4 may now be used to deduce the conformations of the molecules in solution. These can be obtained from the standard eqn. (1)

$$J_{obs} = \sum_{i=1,3} n_i J_i \qquad (1)$$

$$1 = n_1 + n_2 + n_3$$

provided the couplings in the individual conformers are known and also the assignments of the methylene protons. Eqn. (1), when used for the C•CH(OH)•CH_2F fragment, gives four equations in the three unknowns n_{1-3} as there are two vicinal HH and one vicinal HF coupling. This means that the system is over-determined and therefore given sufficient data the observed couplings may be used to obtain the individual rotamer couplings as well as the populations. This approach has recently been used by us,[29] in an analysis of the solvent dependence of the conformational equilibrium of a number of fluorosugars containing the above fragment together with the data for BPFE. The collective data for five compounds over 16 solutions in all gave a total of 64 equations in 54 unknowns (*i.e.* the rotamer populations in the 16 solutions and the nine unknown rotamer couplings), thus the system is over-determined and the rotamer couplings and populations for each solution can be obtained from a simple least-mean square-fit analysis. Full details are given in ref. 29. This analysis gave the values of the rotamer couplings of Table 5 and the rotamer populations and energies of Table 6 for BPFE.

The conformational analysis of DFP is more complex than that of PFE as there are six non-equivalent conformers (Fig. 2). Thus eqn. (1) now becomes four equations in six unknowns and is therefore indeterminate. The corresponding equation for the $^4J_{FF}$ coupling may be included, in which the values of the coupling in the individual conformers are taken from ref. 17(*c*). This still gives only five equations in the six unknown conformer populations and therefore other data need to be included.

In contrast to BPFE the observed couplings in DFP show little dependence on the solvent, indeed they are identical for all the solvents studied except for D_2O (Table 4). This suggests that the results of the *ab initio* calculations, which are of course vapour phase calculations may be used to simplify this analysis. Table 2 shows that conformers **1** (*tt*), **4** (*ect*) and **6** (*ecg*) are of high energy (>4 kcal mol^{-1}) compared to the most stable conformer and will therefore have negligible populations at room temp. Removing these conformations gives five equations in the three remaining unknowns which are immediately solvable. There are two possible assignments of the prochiral methylene protons. The assignment of Table 4 and Fig. 2 gives much better solutions and is the one used here. This results in conformer populations for conformers **2** (*tg*), **3** (*tgg*) and **5** (*gg*) of *ca.* 35, 45 and 20% in all solvents except D_2O for which the corresponding results are 25, 65 and 10%. This gives relative conformer energies of 0.2, 0.0 and 0.5 kcal mol^{-1} for all solvents except D_2O, for which the values are 0.6, 0.0 and 1.1 kcal mol^{-1} respectively.

Discussion

The conformer energies of BPFE show a marked dependence on the polarity of the medium (Table 6). There is a linear relationship between the conformer populations and the solvent relative permittivity (excluding D_2O), and this may be used to extrapolate to the vapour state populations and energies, which are also given in Table 6. The large solvent dependence of the conformer energies would not appear to be due to any intermolecular hydrogen bonding, as this should be identical for the *gt* and *gg* forms (Fig. 1). This could preferentially stabilise the *tg* form as the hydroxy proton is less shielded in this form, but this conformer energy shows less change than the *gg* conformer. The dipole moments of the conformers of PFE (Table 1) do not vary sufficiently to explain this solvent dependence, but the corresponding values for BPFE, calculated by NEMESIS[19] are 1.1, 1.7 and 3.3 D for the *gt*, *gg* and *tg* forms, respectively. These are sufficiently different to produce the observed solvent dependence though on this basis the *tg* conformer should have the largest change rather than the *gg* form. Some support for this interpretation comes from the couplings for PFE (Table 3), which give conformer energies of 0.0, 1.5 and 1.7 kcal mol^{-1} for the *gt*, *gg* and *tg* conformers, which are comparable to the vapour phase values for BPFE in Table 6.

In contrast to BPFE, in DFP there is no solvent dependence of the couplings (and therefore conformer energies) apart from D_2O. The lack of any solvent dependence does mean that the observed (solution) values of the conformer energies can be compared with the calculated (*i.e.* vapour state) values.

In PFE the theoretical values of the conformer energies are in reasonable agreement with the observed vapour state values. The *gt* conformer is predicted and observed to be the most stable form and the *gg* conformer is intriguingly of much higher energy. (Note that the experimental value of this relative energy is subject to large errors as there is only a small percentage of this conformer present.) More significant is the difference in the calculated (0.2) *vs.* observed (1.2) relative energy of the *tg* form. We note that this corresponds to the difference between a *gauche* F ··· OH and a *trans* F ··· OH orientation (see later).

In DFP the calculated relative energies for the three stable conformers (*tg*, *tgg* and *gg*, Fig. 2) are 0.0, 2.3 and 0.7 kcal mol^{-1} compared to the observed values of 0.2, 0.0 and 0.5 kcal mol^{-1}. The calculated and observed relative energies of the *tg* and *gg* conformers are in good agreement but the *tgg* conformer is observed to be much more stable than predicted. We are comparing here ΔG (observed) with ΔE (calculated). All three conformers have a statistical weight of two thus the entropy term is the same for them all. Inspection of Fig. 2 shows that the difference between the *tgg* conformer and the *tg* and *gg* ones is simply a *gauche* (O ··· F) interaction *vs.* a *trans* (F ··· O) interaction when no hydrogen bonding is involved. Furthermore the discrepancy in the calculated *vs.* observed conformer energies exactly mirrors that observed for PFE above. The calculations predict the *gauche* F ··· O *vs.* *trans* F ··· O orientation *ca.* 1–2 kcal mol^{-1} less stable than is observed and this is with the inclusion of any OH ··· F hydrogen bonding interaction energy.

This conclusion agrees with the introductory remark that even at the highest level of theory the *gauche* effect appears to be underestimated. It is possible that approximations in our treatment contribute to this discrepancy. Polarisation functions were not included in these calculations and experimental, not optimised bond lengths were used. These may be examined by considering the high level calculations on fluoroethanol.[6] In this molecule three stable conformers were considered, *gg* the observed hydrogen bonded form, *gt* the *gauche* form with the ∠CCOH of 180°, *i.e.* no hydrogen bonding and *tt* the *trans* form. At the 6-31G* level the relative conformer energies (*gg*, *gt*, *tt*) were[6a] given as 0.0, 2.5 and 1.4 kcal mol^{-1} and including polarisation functions (MP3) changed these values to 0.0, 3.0 and 2.3 kcal mol^{-1}. Thus the relative energy of a *gauche vs. trans* (F ··· O) orientation with no hydrogen bonding is 1.1 (RHF) and 0.7 (MP3) kcal mol^{-1}. Dixon and Smart[6b] using a different basis set obtained corresponding values of 0.4 (SCF) and −0.2 (MP2) kcal mol^{-1}. The inclusion of polarisation functions thus makes little difference to these energies.

In the above calculations the optimised C–F bond length varied from 1.378 Å (*gg*) through 1.371 Å (*tt*) to 1.367 Å (*gt*), the most stable conformer having the longest bond length. Even so this is significantly less than the experimental value in the *gg* conformer (1.398 Å). Unfortunately there is no experimental value for the C–F bond length in a *trans* FCCO orientation. A reduction in the C–F bond length in the *trans* orientation giving a higher energy conformer would also serve to explain the reason for the absence of the *gauche* effect in the CHF_2 group. Here the C–F bond is much shorter (1.35 Å) than in the CH_2F group due presumably to the geminal F ··· F interaction, which is far stronger and would therefore override any vicinal F ··· X interaction.

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