Conformational analysis. Part 27.[1] NMR, solvation and theoretical investigation of conformational isomerism in fluoro- and 1,1-difluoro-acetone

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The solvent and temperature dependence of the ^{1}H and ^{13}C NMR spectra of fluoroacetone (FA), 1,1-difluoroacetone (DFA) and 1,1,1-trifluoroacetone (TFA) are reported and the $^4J_{HF}$, $^1J_{CF}$ and $^2J_{CF}$ couplings analysed using *ab initio* calculations and solvation theory.

In FA the energy difference ($E_{cis} - E_{tr}$) between the *cis* (F–C–C=O 0°) and *trans* (F–C–C=O 180°) conformers is 2.2 kcal mol^{-1} in the vapour, decreasing to 1.0 kcal mol^{-1} in CCl$_4$ solution and to −0.6 kcal mol^{-1} in the pure liquid.

In DFA the conformational equilibrium is between the less polar *cis* (H–C–C=O 0°) and a *gauche* conformation (H–C–C=O 104°). The energy difference ($E_g - E_{cis}$) is +0.8 kcal mol^{-1} in the vapour, decreasing to 0.1 kcal mol^{-1} in CCl$_4$ solution and to −0.9 kcal mol^{-1} in the pure liquid.

The vapour state energy difference for FA compares well with that calculated (2.8 kcal mol^{-1} at MP4/6–31G*). DFA calculations at this level gave only one minimum in the potential surface corresponding to the *cis* form. A minimum for the *gauche* conformer was only found when solvation was included in the *ab initio* calculations, or at much larger basis sets (6-311++G).**

The conformer couplings obtained show that the $^4J_{HF}$ coupling (F–C–C–CH$_3$) is proportional to $\cos^2\theta$, where θ is the F–C–C–C dihedral angle. The $^1J_{CF}$ and $^2J_{CF}$ couplings also show a pronounced orientation dependence which could be of particular utility in those cases where other couplings are not present.

Introduction

The interaction between vicinal fluorine and oxygen atoms continues to intrigue both experimentalists and theoreticians after more than two decades of investigations.

The interaction between vicinal fluorine and singly-bonded oxygen (F–C–C–O), the *gauche* effect,[2] has been the subject of numerous investigations including a recent paper in this series.[3] This investigation noted the considerable difference between the monofluoro (CH$_2$F) and difluoro (CHF$_2$) substituents, in that there appeared to be no *gauche* effect for the CHF$_2$ group. A definitive theoretical reason for this has yet to be given.

Here we consider the vicinal interaction between fluorine and doubly-bonded oxygen of the carbonyl group (*i.e.* F–C–C=O). Again this interaction has been investigated for many years. The original authoritative investigation in this area was the clear demonstration that the microwave spectrum of CH$_2$FCOF showed the existence of the *cis* (F–C–C=O 0°) and *trans* (F–C–C=O 180°) conformers, and not the expected *cis* and *gauche* forms[4] [Fig. 1(*a*), R = F].

Further evidence for the predominantly twofold potential in these systems came from investigations on fluoroacetic acid,[5] fluoroacetyl chloride[6] and fluoroacetone,[7] in all of which the equilibrium was shown to be between *cis* and *trans* forms. The microwave spectrum of fluoroacetone was originally interpreted as arising from *cis* and *gauche* forms,[8] but later Durig *et al.*[7] using IR, Raman and *ab initio* calculations at the 6.31G* level showed that the equilibrium was between the *cis* and *trans* forms. They were not able to accurately determine the vapour state energy difference, but obtained a value of 1.2 kcal mol^{-1} in favour of the *cis* conformation for the pure liquid.

The pronounced twofold potential appears to be restricted to the fluorine substituent, as comparable investigations of monochloro and bromo acid esters,[9,10,11] acid halides,[12,13] aldehydes[14] and ketones[15,16] have been interpreted on the basis of interconverting *cis* and *gauche* conformers.

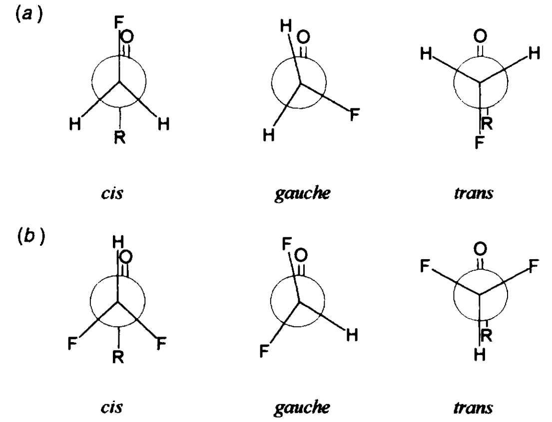

Fig. 1 Possible conformers of (*a*) fluorocarbonyl compounds and (*b*) 1,1-difluorocarbonyl compounds

Much less attention has been given to the dihalosubstituted compounds. Detailed IR and Raman studies of the difluoro, dichloro and dibromo acid halides by Woodward and Jonathan[17] led the authors to conclude that the equilibrium was between the *cis* and *gauche* forms in the acid chlorides, but this was not the case for the dichloroacetyl fluoride for which the results were more consistent with interconverting *gauche* and *trans* forms. Subsequently Durig and co-workers[18] investigated the same compounds and concluded that the equilibrium was between the *cis* and *gauche* forms in all cases. NMR studies of the dichloro and dibromo acetaldehydes also were interpreted on the basis of interconverting *cis* and *gauche* forms.[19]

Shapiro and co-workers[20,21] examined both the solvent and the temperature dependence of the ^{1}H and ^{19}F NMR spectra of a series of fluoroketones including fluoroacetone (FA) and 1,1-difluoroacetone (DFA). Although the existence of two or more interconverting conformers in FA and DFA was evident from their data, they could not determine the conformations present with the data available.

Here we extend Shapiro's NMR studies by recording the ^{13}C and in part ^{19}F spectra of FA, DFA and TFA, and show that the $^1J_{CF}$ and $^2J_{CF}$ couplings as well as the $^4J_{HF}$ coupling are sensitive to the F–C–C=O orientation. The use of *ab initio* plus solvation calculations allows us to define both the interconverting conformers in FA and DFA and also to obtain the conformer energy differences. In FA, the existence of *cis* and *trans* conformers is confirmed, whereas in DFA the *cis* and *gauche* forms are in equilibrium, even though the *gauche* form is not predicted by *ab initio* theory.

Theoretical

The *ab initio* calculations were performed using the GAUSSIAN 92 program.[22] This includes a solvation routine in which the dipole reaction field of the molecule is added to the quantum-mechanical Hamiltonian.[23]

Solvation calculations using the MODELS program[24] 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 ($E_A{}^V$) and in any solvent ($E_A{}^S$) of dielectric constant ε is given by eqn. (1),

$$E_A{}^V - E_A{}^S = k_A x/(1 - lx) + 3h_A x/(5 - x) + bf[1 - \exp(-bf/16RT)] \quad (1)$$

where $x = (\varepsilon - 1)/(2\varepsilon + 1)$, $1 = 2(n_D{}^2 - 1)/(n_D{}^2 + 2)$, $b = 4.30\ (a^{\frac{3}{2}}/r^3)(k_A + 0.5h_A)^{\frac{1}{2}}$ and $f = [(\varepsilon - 2)/(\varepsilon + 1)/\varepsilon]^{\frac{1}{2}}$ 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 ($E_A{}^S - E_B{}^S$), the energy difference in any solvent S of given dielectric, in terms of ΔE^V ($E_A{}^V - E_B{}^V$) 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,[24] including the halocyclohexanones.[25] 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.[26]

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) dielectric constant can appreciably affect the value of the energy difference obtained.

It has been shown[24] that 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) by eqn. (3).

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

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

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,[24] thus it cannot be ignored in any accurate determination of conformer energies.

Fluoroacetone

The geometry of this molecule was optimised at the recommended MP2/6-31G* level.[23] Two stable conformers were found, the *cis* and *trans* forms, in agreement with the results of Durig *et al.*[7] (note Durig *et al.* nomenclature is the reverse of the nomenclature used here) and the geometries and relative energies are given in Table 1. Comparison of these with those of ref. 7 shows only small changes, but the introduction of electron correlation does give a better fit with the microwave geometries.[8] *E.g.* r(C=O) and r(C–F) are 1.222 and 1.398 Å in the predominant *trans* isomer in the vapour, which compare with the calculated values of 1.191 and 1.366 Å in ref. 7 and with 1.226 and 1.394 Å (Table 1). Also the calculated energy difference ($E_{cis} - E_t$) is reduced from 3.3 kcal mol^{-1} with the 6-31G* basis set[7] to 2.9 kcal mol^{-1} adding MP2 and 2.8 kcal mol^{-1} at the MP4 level.

The *ab initio* dipole moments are 0.76 to 1.31 D (*trans*) and 2.69 to 4.33 D (*cis*) depending on the basis set used, and the *trans* value compares reasonably with the microwave value[8] of 1.12 D. Using the *ab initio* geometries, the CHARGE routine gave dipole moments of 0.97 D (*trans*) and 4.18 D (*cis*). Lumbroso *et al.*[27] estimated values of 4.29 (4.17) D for the *cis* form and 1.03 (0.94) D for the *trans* form from dipole moment measurements of octyl fluoride and butan-2-one in CCl_4 and (in parentheses) benzene. These are all reasonably consistent, thus the CHARGE partial atomic charges may be used with confidence in the MODELS solvation calculations. The values of the parameters required to calculate the solvation energy from eqn. (1) are given in Table 2. The refractive index and molar volume were calculated in the program.

1,1-Difluoroacetone

To our knowledge there has been no previous theoretical study of the conformations of this molecule, though Choi and Boyd[28] calculated equilibrium structures of all fluorinated acetones at the 4-31G* level.

When the molecular geometry was optimised at the MP2/6-31G* level, only one stable conformer, the *cis* form (H–C–C=O 0°) was found. The *trans* form is at a maximum in the potential surface and there is merely a change in the slope near the *gauche* form. Increasing the size of the basis set led to a gradual flattening of the relaxed potential energy surface around the *gauche* form (H–C–C=O *ca.* 70 to 120°), until a minimum is found with the 6-311++G** basis set. At the Hartree–Fock level the energy difference between this minima and the global mimina ($E_g - E_{cis}$) is 1.98 kcal mol^{-1}, reducing to 1.89 kcal mol^{-1} optimising with electron correlation (MP2). However, this minimum is poorly defined and larger calculations, beyond the scope of this work, are necessary to accurately determine this *ab initio* vapour phase minima.

Alternatively, inclusion of the solvation routine in the GAUSSIAN calculations (at the HF/6-31G* level) now shows two distinct minima, for a *cis* and a *gauche* (H–C–C=O 104°)

Table 1 Observed and calculated geometries of fluoroacetone and 1,1-difluoroacetone

	Fluoroacetone			1,1-Difluoroacetone	
	trans		*cis*	*cis*	*gauche*
Parameter	obs.^{a}	calc.^{b}	calc.^{b}	calc.^{c}	calc.^{d}
r(C=O)	1.222	1.226	1.223	1.188	1.187
r(C–C)	1.507	1.521	1.521	1.525	1.529
r(C–Me)	1.507	1.504	1.512	1.505	1.506
r(C–F)	1.398	1.394	1.381	1.341^e	1.338
r(C_{Me}–H)^e	1.085	1.092	1.092	1.084^e	1.084^e
r(C–H)	1.095	1.094	1.097	1.076	1.080
∠C–C=O	118.38	118.38	121.30	118.68	116.09
∠Me–C=O	121.40	124.17	123.35	124.59	124.40
∠F–C–C	110.68	111.30	110.60	109.09	109.75^e
∠H–C–C	112.90	109.26	109.73	111.76	111.78
∠H–C_{Me}–C^e	110.17	110.10	109.80	109.48^e	110.00^e
θ(X–C–C=O)	180.0	180.0	0.0	0.0	103.68
E^f	—	−291.533 60	−291.528 98	−389.665 68	—
$E_{rel}{}^g$		0.00	2.90		
Dipole mom.^{h}	1.12	1.31	4.33	1.16	3.72

^{a} Microwave, from ref. 8. ^{b} MP2/6-31G*. ^{c} 6-31G*. ^{d} 6-31G*/solvation (ε = 20.7). ^{e} Averaged values. ^{f} /Hartrees. ^{g} /kcal mol^{-1} (1 cal = 4.184 J). ^{h} /D.

Table 2 Parameters for reaction-field calculations

		Dipole mom.^{a}	k^b	h^b	n_D	V_M	l
Fluoroacetone	*cis*	4.18	8.77	0.20	1.3572	72.32	0.4383
	trans	0.97	0.471	7.42			
1,1-Difluoroacetone	*gauche*	3.15	4.60	2.84	1.3230	78.17	0.4002
	cis	0.83	0.319	5.85			

^{a} /D. ^{b} /kcal mol^{-1}.

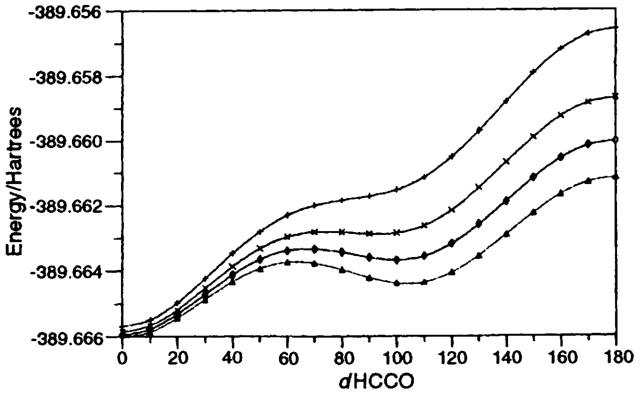

Fig. 2 Rigid rotor potential energy surface for the *cis* rotamer of CHF_2COCH_3 at the HF/6–31G* level at different values of the medium dielectric constant: (+) vapour; (×) 2.24, CCl_4; (◆) 4.81, chloroform; (▲) 20.70, acetone

conformer. As expected the minimum for the more polar *gauche* conformer deepens with increasing solvent dielectric constant. Fig. 2 shows the energy profiles for CCl_4, chloroform and acetone solutions. In all cases the energy at 180° is a maximum ($E_{tr} - E_{cis}$ *ca.* 5.6 kcal mol^{-1} in the vapour phase), thus we may confidently conclude from these results that the conformational equilibrium in DFA is between the *cis* and *gauche* equilibrating conformers. The calculated geometries for these conformers are given in Table 1. The calculated dipole moments from the *ab initio* results vary from 0.65 to 1.16 D (*cis*) and 2.24 to 3.72 D (*gauche*) depending on the basis set, with a smaller variation (*ca.* 0.4 D) for the *gauche* form with dielectric constant. These compare well with the corresponding values of 0.83 D and 3.15 D respectively from the CHARGE 4 program using the calculated 6-31G* geometries. The solvation parameters for the *cis* and *gauche* conformers, using the geometries of Table 1 are given in Table 2.

Experimental

Fluoroacetone and 1,1,1-trifluoroacetone were obtained from Fluorochem Ltd. and 1,1-difluoroacetone prepared by literature procedures.[20] The solvents were obtained commercially, stored over molecular sieves and used without further purification.

^1H and ^{13}C NMR spectra were obtained on a Bruker AMX 400 spectrometer operating at 400.14 MHz for proton and 100.63 MHz for carbon. Spectra were of *ca.* 10 mg cm^{-3} solutions (^1H) and *ca.* 100 mg cm^{-3} (^{13}C) with a probe temperature of *ca.* 25 °C. [$^2H_{12}$]Cyclohexane was used as the deuterium lock signal for the CCl_4 solution and [$^2H_8$]toluene external lock was used for the $CFCl_3$ solution and the pure liquid. The ^1H and ^{13}C spectra were all referenced to Me_4Si. Typical conditions were; proton spectra 64 transients, spectral width 3100 Hz with 32K data points, giving an acquisition time of 5 s and zero filled to 128 K to give a digital resolution of 0.025 Hz. Proton-decoupled carbon spectra were obtained with typical conditions 4000 transients, 7.0 μs (80° flip angle), 5 s pulse delay, spectral width 25 000 Hz with 64 K data points giving an acquisition time of 2 s and zero filled to 256 K for a 0.12 Hz digital resolution.

The spectra were all first-order and the coupling constants and chemical shifts taken directly from the spectra. These are given in Tables 3, 4 and 5. The temperature dependence of the proton spectrum of DFA was recorded in non-polar and polar solvents and these data are given in Table 6.

Where the NMR data overlap, our results are in complete agreement with those of Shapiro *et al.*[20] In several solvents the separate spectrum of the hydrate was observed in small amounts in the DFA spectrum. This was easily identified and distinguished from that of the ketone. Typical parameters for the hydrate are as follows. CHF_2-$C(OH)_2$-CH_3 in [$^2H_6$]-acetone, H-1 5.579 ppm, H-3 1.369 ppm, C-1 116.30 ppm, C-2 93.31 ppm, C-3 21.87 ppm, $^2J_{HF}$ 56.27 Hz, $^4J_{HF}$ 1.73 Hz, J_{CF} 246.79 Hz, $^2J_{CF}$ 24.27 Hz and $^3J_{CF}$ 1.04 Hz.

In methanol solution the separate spectrum of the methyl acetal CH_2F-C(OH)OMeCH_3 was observed for FA. This was

Table 3 Chemical shifts (ppm) and couplings (Hz) in CH_2FCOCH_3

Solvent	ε	H-1	H-3	C-1	C-2	C-3	$^2J_{HF}$	$^4J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	2.24	4.656	2.218	84.58	203.01	25.24	48.19	4.68	185.7	22.10
$CDCl_3$	4.81	4.792	2.253	85.70	205.62	26.42	47.74	4.32	184.9	20.42
CD_2Cl_2	8.93	4.801	2.183	85.28	204.44	25.33	47.60	4.03	184.1	19.32
[$^2H_6$]Acetone	20.7	4.931	2.135	85.77	203.99	25.31	47.45	3.76	181.0	18.01
CD_3OD	32.7	4.891	2.150	86.08	206.43	25.25	47.41	3.77	181.7	18.00
[$^2H_6$]DMSO	46.7	4.986	2.079	84.94	203.54	25.06	47.13	3.53	179.4	16.23

Table 4 Chemical shifts (ppm) and couplings (Hz) in CHF_2COCH_3

Solvent	ε	H-1	H-3	C-1	C-2	C-3	$^2J_{HF}$	$^4J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	2.24	5.565	2.302	109.68	195.10	22.36	54.44	1.34	253.3	27.67
$CDCl_3$	4.81	5.667	2.342	109.76	197.38	23.40	54.10	1.45	252.2	27.32
CD_2Cl_2	8.93	5.710	2.320	110.29	197.73	23.94	53.95	1.52	251.7	26.26
Pure liquid	20.2	5.826	2.310	111.18	199.14	23.87	53.74	1.58	249.9	26.02
[$^2H_6$]Acetone	20.7	6.077	2.326	110.89	197.98	24.24	53.65	1.62	248.8	25.41
CD_3NO_2	35.9	5.904	2.331	111.44	199.61	24.49	53.50	1.65	249.5	25.21
CD_3CN	37.5	5.916	2.287	110.94	198.82	24.73	53.51	1.65	248.7	25.17
[$^2H_6$]DMSO	46.7	6.228	2.289	109.60	197.68	24.50	53.28	1.72	248.2	24.54

Table 5 Chemical shifts (ppm) and couplings (Hz) in CF_3COCH_3

Solvent	ε	H-3	C-1	C-2	C-3	$^4J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	2.24	2.388	115.35	186.70	23.10	0.94	291.3	36.3
$CDCl_3$	4.81	2.431	116.07	189.33	24.40	0.95	291.3	36.4
CD_2Cl_2	8.93	2.421	116.28	189.60	24.45	0.97	291.4	36.0
[$^2H_6$]Acetone	20.7	2.510	116.49	189.77	24.08	0.98	291.3	35.2
CD_3NO_2	35.9	2.475	116.99	191.19	24.22	1.00	291.3	35.4
[$^2H_6$]DMSO	46.7	2.487	115.19	189.32	24.12	0.99	292.3	34.7

Table 6 Temperature dependence of the HF couplings in 1,1-difluoroacetone

	$CFCl_3$		$CDCl_3$		[$^2H_6$]Acetone	
T/°C	$^2J_{HF}$	$^4J_{HF}$	$^2J_{HF}$	$^4J_{HF}$	$^2J_{HF}$	$^4J_{HF}$
40			54.15	1.44	53.71	1.59
20	54.59	1.31	54.09	1.45	53.65	1.62
0	54.56	1.31	54.03	1.47	53.59	1.64
−20	54.54	1.31	53.98	1.48	53.52	1.66
−30	54.52	1.30				
−40	54.50	1.27	53.87	1.50	53.45	1.70
−50	54.49	1.28	53.81	1.50		
−60	54.44	1.29			53.37	1.73

of some interest in that the prochiral H-1 protons become non-equivalent in the acetal giving an ABX pattern and molecular parameters as follows. H-1A 4.231 ppm, H-1B 4.126 ppm, H-3 1.344 ppm, C-1 86.52 ppm, C-2 97.27 ppm, C-3 21.40 ppm, $J_{A,B}$ −9.35 Hz, $J_{H1A,F}$ 47.6 Hz, $J_{H1B,F}$ 47.3 Hz, $^1J_{CF}$ 175.3 Hz, $^2J_{CF}$ 18.0 Hz, $^3J_{CF}$ 1.52 Hz.

The IR spectra were recorded with a Perkin-Elmer model 1720-X FTIR spectrometer, using a 1.00 mm sodium chloride cell for dilute (*ca.* 1 mg cm^{-3}) solutions, with the solvent as background when recording the solute spectrum, and in the gas phase in a 10 cm pathlength cell.

Results

The NMR data of Tables 3–6, together with that of Shapiro *et al.*,[20] can now be used with the results of the theoretical calculations given earlier to determine the conformational equilibrium in these molecules.

Although the use of $^3J_{HH}$ couplings in conformational investigations is well established,[1] this is not the case for the HF and CF couplings measured here. Thus, it is first necessary to determine how much of the observed variation of the couplings is due to changes in the conformer populations and how much to an intrinsic solvent dependence.

This can be partly answered by comparing the observed changes in FA and DFA (Tables 3 and 4) with those of TFA (Table 5) in which there is only one possible conformer. The $^4J_{HF}$ coupling in TFA is essentially independent of solvent, thus the large change in this coupling in FA ($4.7 \longrightarrow 3.5$ Hz) and the appreciable but smaller change in DFA ($1.3 \longrightarrow 1.7$ Hz) may be reasonably attributed to changes in the conformer populations. A similar situation is observed for the $^1J_{CF}$ coupling, but the $^2J_{CF}$ coupling does show a significant intrinsic solvent dependence in TFA ($36.3 \longrightarrow 34.7$ Hz) which is, however, much less than the observed variation in FA ($22.1 \longrightarrow 16.2$ Hz), but is appreciable compared to the change in DFA ($27.7 \longrightarrow 24.5$ Hz).

An alternative method of isolating the changes in the couplings due to population changes is simply to plot one variable against another. If the changes are solely due to population changes, the plots are linear.[1] This procedure shows that, both for FA and DFA, $^4J_{HF}$ and $^2J_{CF}$ plots are accurately linear (corr. coeffs. > 0.99) but this is not the case for the $^1J_{CF}$ coupling (corr. coeffs. 0.95 and 0.97 respectively). Thus, we will consider initially only the $^4J_{HF}$ and $^2J_{CF}$ couplings. It is of interest to note that the large changes observed in the ^1H and ^{13}C chemical shifts also do not correlate at all with the couplings, showing that other factors apart from the conformer populations, are dominating the nuclear chemical shifts.

Fluoroacetone

The NMR data in Table 3 and ref. 20 together with the measurement of the energy difference in the pure liquid may be combined with the solvation calculations given earlier to provide a detailed account of the conformational equilibrium in this compound, which may be described in terms of the *cis* and *trans* conformers [eqn. (4)].

Table 7 Conformer energy differences (kcal mol^{-1}) and observed and calculated couplings in fluoroacetone and 1,1-difluoroacetone

	Fluoroacetone			1,1-Difluoroacetone		
		$^4J_{HF}$/Hz			$^4J_{HF}$/Hz	
Solvent	$E_{cis} - E_{tr}$[a]	calc.	obs.	$E_g - E_{cis}$[b]	calc.	obs.
CCl_4	1.04	4.73	4.68	0.11	1.30	1.34
CS_2	0.85	4.65	4.68[c]	—	—	—
$CDCl_3$	0.25	4.35	4.32	−0.35	1.48	1.45
CD_2Cl_2	−0.24	4.04	4.03	−0.62	1.56	1.52
Pure liquid	−0.63	3.82	3.89[c]	−0.91	1.61	1.58
[$^2H_6$]Acetone	−0.75	3.77	3.76	−0.92	1.62	1.62
CD_3CN	−1.12	3.63	3.66[c]	−1.13	1.65	1.65
DMSO	−1.27	3.59	3.53	−1.23	1.67	1.72

[a] With $\Delta E^V = 2.2$ kcal mol^{-1}. [b] $\Delta E^V = 0.8$ kcal mol^{-1}. [c] Ref. 20.

$$\begin{aligned} J_{obs} &= n_{cis}J_{cis} + n_{tr}J_{tr} \\ l &= n_{cis} + n_{tr} \\ n_{cis}/n_{tr} &= \exp(-\Delta E/RT) \\ \Delta E &= E_{cis} - E_{tr} \end{aligned} \quad (4)$$

The value of $^4J_{HF}$ in the pure liquid (3.89 Hz)[20] gives with the data of Table 3 an interpolated value of 16.8 for the pure liquid dielectric constant, somewhat less than that deduced in analogous fashion previously.[20]

The energy difference ($E_{cis} - E_{tr}$) in the pure liquid was determined as −1.19 (±0.15) kcal mol^{-1} from Raman spectroscopy,[7] but this value has to be corrected for the $T(dH/dt)$ term [eqn. (3)]. Assuming that the temperature dependence of the pure liquid dielectric constant is similar to that of acetone,[29] the MODELS calculations give $T(dH/dt)$ equal to *ca.* 0.5 kcal mol^{-1}. Thus, the true energy difference in the liquid is *ca.* −0.7 kcal mol^{-1}.

The variable-temperature NMR data[20] show that the $^4J_{HF}$ coupling increases with increasing temperature in acetonitrile (3.49 $\longrightarrow$ 3.69 Hz) and methylene chloride (3.96 $\longrightarrow$ 4.10 Hz) solutions, but decreases with increasing temperature in CCl_4 solution (4.73 $\longrightarrow$ 4.59 Hz). These results indicate that the conformer energy difference is *ca.* 0 in moderately polar solvents and also that the average coupling $(J_{cis} + J_{tr})/2$ is between 4.10 and 4.59 Hz.

With these considerations the solvent data in Table 3 and ref. 20 may be used with the solvation theory to search for the best solution for both the conformer energy difference and the values of J_{cis} and J_{trans}.

This gave values of ΔE^V of 2.2 kcal mol^{-1}, ΔE^L −0.6 kcal mol^{-1}, J_{cis} 3.4 Hz and J_{tr} 5.0 Hz and the solution energy differences and couplings of Table 7. The rms error of the (obs. − calc.) couplings is 0.05 Hz over all the data of Table 7, which is equivalent to an error in the ΔE values of 0.04 kcal mol^{-1}.

The values of the remaining couplings in the two conformers may be obtained directly from the previously noted linear relationships between the couplings in Table 3. This gives for the $^1J_{CF}$, $^2J_{CF}$ and $^2J_{HF}$ couplings in the *cis* isomer 179.6, 16.2 and 47.1 Hz and for the *trans* isomer 188.0, 23.5 and 48.4 Hz, respectively. These values will be considered subsequently.

1,1-Difluoroacetone

The NMR data in Tables 4 and 6 and that of ref. 20 can now be combined with the solvation calculations in an analogous manner to that of fluoroacetone, though in difluoroacetone there is no measured value of the energy difference in any state.

The GAUSSIAN calculations show clearly the presence of two conformers in solution, the *cis* and *gauche* forms, and thus the equilibrium in this compound is described in terms of these conformers [eqn. (5)].

$$\begin{aligned} J_{obs} &= n_{cis}J_{cis} + n_gJ_g \\ l &= n_{cis} + n_g \\ n_g/n_{cis} &= 2\exp(-\Delta E/RT) \\ \Delta E &= E_g - E_{cis} \end{aligned} \quad (5)$$

Note the statistical weight of two for the *gauche* conformer, with two mirror image forms. Also we note that the value of $^4J_{HF}$ in the pure liquid (1.58 Hz) is essentially the same as that in acetone solution, thus we will take the pure liquid dielectric constant to be equal to that of acetone (20.2).

The variable-temperature studies (Table 6) show that the $^4J_{HF}$ coupling decreases with increasing temperature in $CDCl_3$ and acetone solution but slightly increases with increasing temperature in $CFCl_3$ solution. This indicates that the conformer energy is zero in a solvent of dielectric constant between that of $CFCl_3$ (2.44) and $CDCl_3$ (4.71), and also the averaged coupling, which is now $(J_{cis} + 2J_g)/3$, is between 1.31 and 1.44 Hz.

With these restrictions the observed solution NMR data (Table 4 plus ref. 20) can be input with the solvation theory to obtain the best agreement between the observed and calculated couplings. This gives values of ΔE^V 0.80 kcal mol^{-1}, J_g 1.73 Hz and J_{cis} 0.57 Hz and the solution energy differences and couplings of Table 7. Again the rms error of the observed *vs.* calculated couplings is very good (0.033 Hz). The values of the other couplings in the distinct conformers can be obtained from the linear relationships between the couplings to give for the $^1J_{CF}$, $^2J_{CF}$ and $^2J_{HF}$ couplings values of 247.9, 24.5 and 53.3 Hz (*gauche*) and 264.8, 34.6 and 56.8 Hz (*cis*) respectively.

Although the solvation model gives a complete account of the observed NMR data on the basis of an equilibrium between the *cis* and *gauche* forms in all the solvents studied, in view of the GAUSSIAN results (earlier) that suggest that only the *cis* conformer is present in the vapour at the MP2/6-31G* level, it was felt that additional experimental evidence on this equilibrium would be useful.

Thus, the FTIR spectrum of DFA was recorded in the vapour and pure liquid and the carbonyl band observed in solvents of varying polarity (Fig. 3). In the pure liquid and acetonitrile solution the carbonyl band is a single sharp band at 1754 cm^{-1} of half height width 20 cm^{-1}. In methylene chloride a partially resolved doublet is observed with absorption at 1753 and 1746 cm^{-1}. Similar spectra were observed in CCl_4 and $CHCl_3$ solution, though now the band intensities are reversed. In the vapour a very broad (half height width 55 cm^{-1}) poorly resolved band was observed over the range 1750 to 1780 cm^{-1}. These results are precisely to be expected from the above analysis. Eqn (5) and the data of Table 7 predict 6% of the *cis* form in acetonitrile solution, 15% in methylene chloride, 38% in CCl_4 and 79% in the vapour. Thus, the 1754 cm^{-1} band in solution would appear to be due to the *gauche* isomer and the 1746 cm^{-1} band to the *cis* isomer. This is strong evidence for the occurrence of both conformers in the liquid and vapour phases.

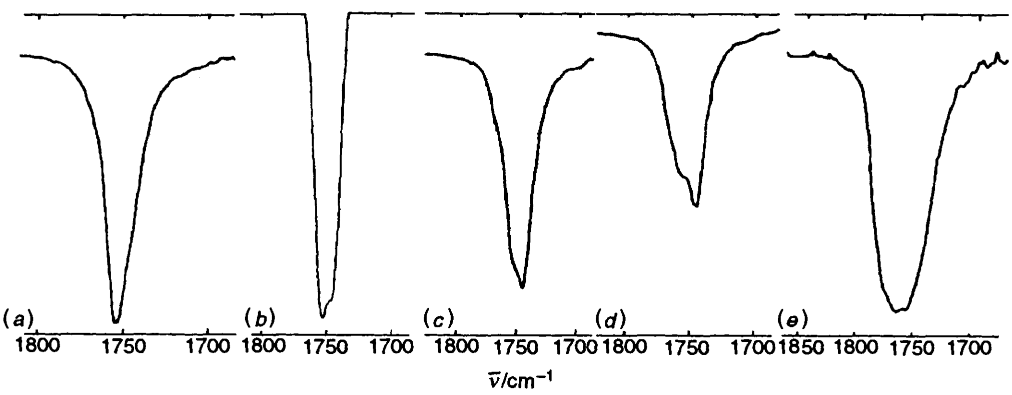

Fig. 3 The carbonyl absorption band in the IR spectrum of DFA in, (*a*) pure liquid, (*b*) CH_2Cl_2, (*c*) $CHCl_3$, (*d*) CCl_4 and (*e*) vapour

Discussion

The NMR and IR experimental data combined with the solvation calculations provide a consistent picture of the conformational equilibrium in the molecules studied here. In FA the equilibrium is between the *cis* and *trans* forms as predicted by theory. The energy difference ($E_{cis} - E_{tr}$) is 2.2 kcal mol^{-1} in the vapour state, which compares well with that calculated theoretically (2.8 kcal mol^{-1}). We note that the true value of the energy difference in the pure liquid (−0.6 kcal mol^{-1}) is quite different from that obtained from Raman spectroscopy (−1.15 kcal mol^{-1})[7] due to the variation of the liquid dielectric constant with temperature.

In DFA the NMR and IR data support an equilibrium between the *gauche* and *cis* forms, with an energy difference ($E_g - E_{cis}$) of 0.8 kcal mol^{-1} in the vapour, reversing to −0.9 kcal mol^{-1} in the pure liquid. These results are only supported by the GAUSSIAN calculations in the vapour state at large basis sets. When solvation was included both the *cis* and *gauche* forms become stable minima in the HF/6-31G* potential surface with a calculated energy difference of *ca.* 1.3 kcal mol^{-1} in CCl_4 solution, decreasing to *ca.* 0.6 kcal mol^{-1} in acetone solution (Fig. 2).

The discrepancy with the theoretical predictions at this 'model chemistry'[23] is of some concern, particularly as the GAUSSIAN calculations are now used routinely in identifying the stable conformers in such systems. For example, recently Veken *et al.*[30] concluded that methyl fluoroacetate and difluoroacetate both existed in the *trans* and *gauche* forms from 6-31G calculations and IR data, even though fluoracetic acid has been shown to occur in the *cis* and *trans* forms by ED experiments.[5] Clearly the question of the accuracy of this basis set in determining such conformational equilibria needs to be addressed.

The problems of *ab initio* theory in reproducing the *gauche* effect are well known.[3] It was observed recently that 6-31G* calculations on 2,6-difluoroacetophenone and 2,6-difluoromethylbenzoate consistently over estimated the repulsive interaction between the *ortho* fluorine substituents and the carbonyl oxygen, resulting in CO-ring torsional angles which were much greater than observed experimentally.[31] This could provide a possible explanation for the discrepancy between theory and experiment observed here. Calculations with larger basis sets and better representation of electron correlation interaction seem to be required to model these systems effectively. However, even the HF/6-311++G** level of theory may be impractical for modest sized systems.

The variations in the nuclear coupling constants in the different conformers are also of some interest. Inspection of the values of the $^4J_{HF}$ couplings in the conformers provides a reasonably consistent picture in that the F–C–C–CH_3 coupling follows an approximate $\cos^2\theta$ dependance, where θ is the F–C–C–C torsional angle. Thus, for θ equals 0 or 180°, the coupling is large (5.0 and 3.4 Hz. respectively), but for θ equals 60° the coupling is much smaller (0.6 Hz). This pattern is followed for all the molecules studied here.

The $^2J_{HF}$ couplings are almost independent of the molecular conformation, but the $^1J_{CF}$ and $^2J_{CF}$ couplings are very dependent on the conformation. The smallest value of both these couplings occurs when the fluorine atom eclipses the carbonyl oxygen. This could suggest possible π contributions to the couplings but it may also be pertinent to note that the calculated C–F bond length changes appreciably with the F–C–C=O angle (Table 1). A similar orientation dependence of these couplings was observed recently in *cis* and *trans* 4-*tert*-butyl-2-fluorocyclohexanone. The *cis* compound with equatorial fluorine has values of 190.6 Hz ($^1J_{CF}$) and 13.6 Hz ($^2J_{CF}$) whereas the *trans* compound with an axial fluorine substituent has very different values of 176.5 and 20.6 Hz, respectively.[32] Further data are required to define the orientation dependence of these couplings. This could be of some interest as these couplings have not previously been used to provide conformational information and this could provide a method of investigating conformational isomerism by NMR for compounds in which there is no appropriate H–H or H–F coupling such as fluoroacetates and amides. These studies are currently being pursued in our laboratories.

Acknowledgements

We acknowledge an SERC grant towards the purchase of the Bruker AMX 400 spectrometer, an industrial studentship from Zeneca (M. A. W.) and the computer facilities of the University of Liverpool (GAUSSIAN 92). Financial support from FINEP (PADCT) and FAPESP (R. R. and C. F. T.) and Oxford Molecular (A. D. J.) is gratefully acknowledged.

References

1 Part 26 R. J. Abraham, P. Leonard, T. A. D. Smith and W. A. Thomas, *Magn. Reson. Chem.*, 1996, **34**, 71.
2 S. Wolfe, *Acc. Chem. Res.*, 1972, **5**, 102.
3 R. J. Abraham, E. J. Chambers and W. A. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 1994, 949.
4 E. Saegebarth and E. B. Wilson, *J. Chem. Phys.*, 1967, **46**, 3088.
5 B. P. van Eijck, G. van der Plaats and P. H. van Roon, *J. Mol. Struct.*, 1972, **11**, 67.
6 J. R. Durig, H. V. Phan, J. A. Hardin and T. S. Little, *J. Chem. Phys.*, 1989, **90**, 6840.
7 J. R. Durig, J. A. Hardin, H. V. Phan and T. S. Little, *Spectrochim. Acta, Part A*, 1989 **45**, 1239.
8 E. Saegebarth and L. C. Krishner, *J. Chem. Phys.*, 1970, **52**, 3555.
9 B. L. Shapiro and D. J. Sardella, *J. Magn. Reson.*, 1970, **3**, 336.
10 G. I. L. Jones and N. L. Owen, *J. Mol. Struct.*, 1973, **18**, 1.
11 P. R. Olivato, D. Klapstein, R. Rittner, E. L. Silva and J. C. D. Lopes, *Can. J. Appl. Spectrosc.*, 1992, **37**, 37.
12 A. Y. Khan and N. Jonathan, *J. Chem. Phys.*, 1969, **50**, 1801.
13 V. I. P. Jones and J. A. Ladd, *J. Chem. Soc. B*, 1970, 1719.

14 G. J. Karabatsos and D. J. Fenoglio, *J. Am. Chem. Soc.*, 1969, **91**, 1124.

15 S. A. Guerrero, J. R. T. Barros, B. Wladislaw, R. Rittner and P. R. Olivato, *J. Chem. Soc.*, *Perkin Trans. 2*, 1983, 1053.

16 (*a*) G. A. Crowder and B. R. Cook, *J. Chem. Phys.*, 1967, **47**, 367; B. R. Cook and G. A. Crowder, *J. Chem. Phys.*, 1967, **47**, 1700.

17 (*a*) A. J. Woodward and N. Jonathan, *J. Mol. Spectrosc.*, 1970, **35**, 127; (*b*) *J. Phys. Chem.*, 1970, **74**, 798.

18 (*a*) J. R. Durig, M. Mamula-Bergana and H. V. Phan, *J. Raman Spectrosc.*, 1991, **22**, 141; (*b*) J. R. Durig, M. Mamula-Bergana and H. V. Phan, *J. Mol. Struct.*, 1991, **242**, 179; (*c*) H. V. Phan, G. A. Guirguis and J. R. Durig, *Spectrochim. Acta*, Part A, 1993, **49**, 1967.

19 (*a*) G. J. Karabatsos, D. J. Fenoglio and S. S. Lande, *J. Am. Chem. Soc.*, 1969, **91**, 3572; (*b*) D. F. Ewing, *J. Chem. Soc.*, *Perkin Trans. 2*, 1972, 701.

20 B. L. Shapiro, C. K. Tseng and M. D. Johnston, Jr., *J. Magn. Reson.*, 1973, **10**, 65.

21 (*a*) B. L. Shapiro, H.-L. Lin and M. D. Johnston, Jr., *J. Magn. Reson.*, 1973, **9**, 305; (*b*) B. L. Shapiro, W. A. Thomas, J. L. McClanahan and M. D. Johnston, Jr., *J. Magn. Reson.*, 1973, **11**, 355.

22 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, 1992.

23 J. B. Foreman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods: A Guide to Using Gaussian*, Gaussian Inc., Pittsburgh, PA, 1993.

24 R. J. Abraham and E. Bretschneider, in *Internal Rotation in Molecules*, ed. W. J. Orville-Thomas, Academic Press, London, 1974, ch. 13.

25 R. J. Abraham and L. Griffiths, *Tetrahedron*, 1981, **37**, 575.

26 R. J. Abraham, G. H. Grant, I. S. Haworth and P. E. Smith, *J. Comp. Aided Mol. Design*, 1991, **5**, 21.

27 H. Lumbroso, Ch. Liégeois and P. R. Olivato, *J. Mol. Struct.*, 1987, **162**, 131.

28 S. C. Choi and R. J. Boyd, *Can. J. Chem*, 1985, **63**, 836.

29 *Handbook of Chemistry and Physics*, ed. R. C. Weast, CRC Press, Boca Raton, Florida, 64th edn.

30 B. J. V. Veken, S. Truyen, W. A. Herrebout and G. Watkins, *J. Mol. Struct.*, 1993, **293**, 55.

31 R. J. Abraham, S. Angiolini, M. Edgar and F. Sancassan, *J. Chem. Soc.*, *Perkin Trans. 2*, 1995, 1973.

32 C. R. Kaisen, Ph.D. Thesis, Universidade Estadual de Campines, Campinas, 1982.

Paper 5/06366C
Received 27*th September* 1995
Accepted 16*th November* 1995