Conformational analysis. Part 33.[1] An NMR, solvation and theoretical investigation of conformational isomerism in *N*,*N*-dimethylfluoroacetamide and *N*,*N*-dimethyl-α-fluoropropionamide

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The solvent and temperature dependence of the ^{1}H and ^{13}C NMR spectra of *N*,*N*-dimethylfluoroacetamide (DMFA) and *N*,*N*-dimethyl-α-fluoropropionamide (DMFP) are reported and the $^{5}J_{CF}$, $^{1}J_{CF}$ and $^{4}J_{CF}$ couplings analysed by solvation theory. Density function theory (DFT) at the B3LYP/6-311+G(d,p) level with ZPE (zero point energy) corrections was used to obtain the conformer geometries. In DMFA, the DFT method gave only two minima for the *cis* (F–C–C=O, 0°) and *gauche* (F–C–C=O, 140.6°) rotamers. The *trans* rotamer was not a minimum in the energy surface. Assuming only the *cis* and *gauche* forms, the observed couplings when analysed by solvation theory gave the energy difference ($E_{cis} - E_g$) of 2.5 kcal mol^{-1} in the vapour phase, (*cf*. the *ab initio* value of 2.3 kcal mol^{-1}) decreasing to 0.87 kcal mol^{-1} in CCl_4 and to −1.29 kcal mol^{-1} in DMSO. In DMFP the *ab initio* calculations gave three minima; the *cis* (F–C–C=O, 30.4°), *gauche*-1 (F–C–C=O, 144.7°) and *gauche*-2 (F–C–C=O, −124.1°) rotamers with ($E_{cis} - E_{g2}$) equal to 2.5 kcal mol^{-1} and ($E_{g1} - E_{g2}$) equal to 0.3 kcal mol^{-1}. The observed couplings were analysed by solvation theory assuming one "average" *gauche* conformer to give ($E_{cis} - E_{g(AV)}$) equal to 2.1 kcal mol^{-1} in the vapour phase, decreasing to 0.83 kcal mol^{-1} in CCl_4 and to −1.11 kcal mol^{-1} in DMSO.

Introduction

Fluorine substituents can have profound stereoelectronic and polar effects on the conformation of organic molecules.[2] The F–C–C=O group has been shown to have a predominantly two-fold potential in fluoroacetyl fluoride,[3] fluoroacetic acid,[4] fluoroacetyl chloride[5] and fluoroacetone,[6–8] in all of which the equilibrium was shown to be between *cis* and *trans* rotamers and not the expected *cis* and *gauche* forms. This is not the case for the difluoro compounds, where both *cis–trans* and *cis–gauche* equilibria have been reported.[1,8–13]

In the preceeding paper in this series[1] a combined NMR, solvation and theoretical investigation examined the conformational isomerism in 3-fluorobutan-2-one (FB) and 3,3-difluorobutan-2-one (DFB) using the solvent dependence of the $^{4}J_{HF}$, $^{1}J_{CF}$ and $^{2}J_{CF}$ couplings. For FB the NMR data was in complete agreement with *ab initio* calculations at the MP2/6-31G** level. The equilibrium was between the *cis* (F–C–C=O, 22.8°) and *trans* (F–C–C=O, 178°) conformers, with the energy difference ($E_{cis} - E_{trans}$) varying from 3.7 kcal mol^{-1} in the vapour state to 0.14 kcal mol^{-1} in DMSO solution. For DFB *ab initio* theory gave only one stable rotamer in the vapour phase at the MP2/6-311++G** level (*cis* C–C–C=O, 0°) and this was consistent with the NMR and IR data. The coupling constants did not change with solvent and the FTIR spectrum showed a single sharp band for the carbonyl absorption in all the solvents studied. The replacement of a hydrogen atom by a methyl group shifts the conformational equilibrium in these compounds significantly compared with those of fluoroacetone (FA) and difluoroacetone (DFA).[8] The increased steric repulsion destabilizes the *cis* rotamer in FB and precludes the existence of the *gauche* rotamer of DFB.[1]

Here we investigate the conformer equilibrium in *N*,*N*-dimethylfluoroacetamide (DMFA) and *N*,*N*-dimethyl-α-fluoropropionamide (DMFP) (Fig. 1), in which the NMe_2 group replaces the Et group in FA and DFA.

The IR spectrum of DMFA showed an increase in the intensity ratio of the two overlapping carbonyl stretching bands upon changing the solvent from CCl_4 to $CHCl_3$ and this was associated with the occurrence of two overlapping carbonyl bands in the first overtone region at frequencies approximately twice those of the fundamentals.[14] This strongly indicated the occurrence of a *cis–gauche* rotational isomerism.

An X-ray and theoretical investigation[2] showed that the introduction of an α-fluorine substituent in the substituted amides MeCHFC(O)NHR (R = Me, Bz) stabilises the conformation with the fluorine atom *trans* to the carbonyl group.

The magnetically nonequivalent *N*-methyl groups[15] in *N*,*N*-dimethylamides were assigned from their unequal upfield ASIS (aromatic solvent induced shifts). A model for the amide–benzene collision complex was proposed, in which the *anti*-*N*-Me group was at the centre of the aromatic ring and the *syn*-*N*-Me group near the edge of the ring with less ring current shielding.[15]

Here we show that the $^{5}J_{HF}$, $^{1}J_{CF}$ and $^{4}J_{CF}$ couplings of DMFA and DMFP in different solvents 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 and also to obtain the conformer energy differences.

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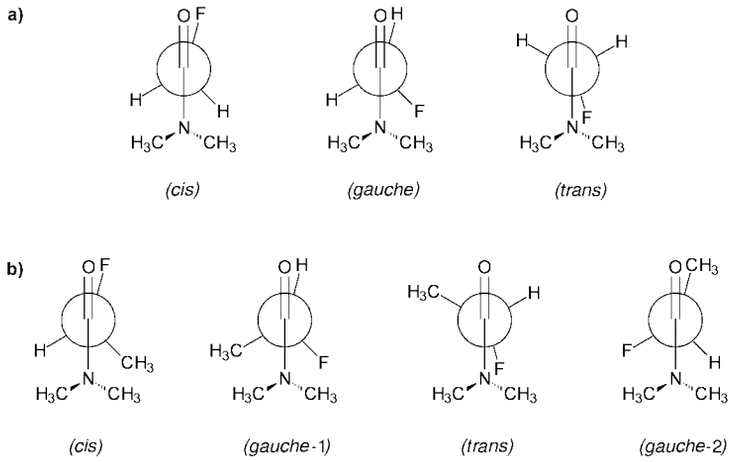

Fig. 1 Possible conformers for: a) DMFA and b) DMFP.

Theoretical calculations

The *ab initio* calculations with the DFT (B3LYP) method were performed using the *GAUSSIAN98* program[16] and the solvation calculations using the *MODELS* program.[17] In the latter, the solvation energy of a molecule is given by including both the dipole and quadrupole reaction fields and also a direct dipole–dipole term. The theory has been given in detail and shown to give an accurate account of the solvent dependence of a variety of conformational equilibria.[17–19]

For any molecule (A), the solvation energy is the difference between the energy in the vapour (E_A^V) and in any solvent (E_A^S) of relative permittivity ε and is given by eqn. (1),

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

$x = (\varepsilon - 1)/(2\varepsilon + 1)$; $l = 2(n_D^2 - 1)/(n_D^2 + 2)$; $b = 4.30(a^{3/2}/r^3)$-$(k_A + 0.5h_A)^{1/2}$ and $f = [(\varepsilon - 2)/(\varepsilon + 1)/\varepsilon]^{1/2}$ for $\varepsilon > 2$ and is zero otherwise. n_D is the refractive index, T the temperature (K), k_A and h_A are μ_A^2/a^3 and q_A^2/a^5, μ_A and q_A being the dipole and quadrupole moments of molecule A. a is the solute radius and r ($= a + 1.8$) the solute–solvent distance. The solute radius is obtained from the molar volume (V_M) of the solute and the solute refractive index (n_D) may be 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 ΔE^S ($E_A^S - E_B^S$), the energy difference in any solvent S of given relative permittivity, in terms of ΔE^V ($E_A^V - E_B^V$) and calculable parameters. The dipole and quadrupole moments are obtained from the partial atomic charges given by the CHARGE programme.[20]

The temperature dependence of the pure liquid (or solvent) relative permittivity can appreciably affect the value of the energy difference. 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).[17] The correction factor

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

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

$T(\mathrm{d}H/\mathrm{d}t)$ is as much as 0.5 kcal mol^{-1} for moderately polar solutes and solvents,[8,17] thus it cannot be ignored in any accurate determination of conformer energies.

Ab initio calculations

To our knowledge there has been no previous theoretical study of these molecules. The potential energy surfaces were obtained at the HF/6-31G(d,p) level and the geometries optimized at the B3LYP/6-311+G(d,p) level with zero point correction (ZPE).[21] In DMFA two stable rotamers were found, the *cis* and *gauche* forms. The *trans* isomer was not a minimum on the potential energy surface. The potential energy surface for DMFP shows three stable rotamers, *gauche*-1, *gauche*-2 and *cis* (Fig. 2). The optimised geometries and energies of all the rotamers are given in Table 1.

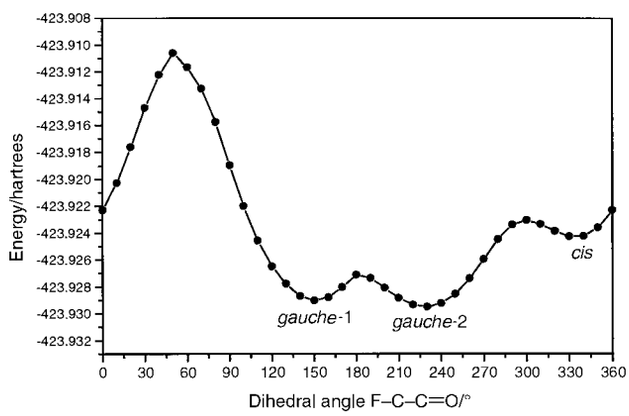

Fig. 2 Potential energy surface for DMFP at HF/6-31G(d,p) level.

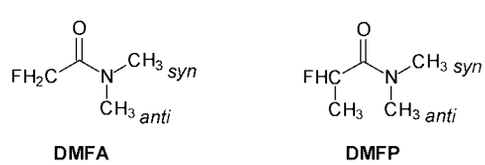

Fig. 3 *syn*- and *anti*-Methyl groups in DMFA and DMFP.

The calculated dipole moments at the DFT level are for DMFA, 3.05 (*gauche*) and 5.51 D (*cis*), and for DMFP, 2.95 (*gauche*-1), 3.05 (*gauche*-2) and 5.57 D (*cis*). Using the DFT geometries, the CHARGE routine[20] gave dipole moments for DMFA of 2.52 (*gauche*) and 5.07 D (*cis*) and for DMFP dipole moments of 2.40 (*gauche*-1), 2.44 (*gauche*-2) and 4.94 D (*cis*). The *ab initio* and CHARGE dipole moments are all reasonably consistent, and thus the partial atomic charges may be used with confidence in the solvation calculations. The values of the solvation parameters (eqn. (1)) are given in Table 1. The refractive index and molar volume were calculated by the program. As both the energy and the dipole moments of the two *gauche* conformers of DMFP are almost equal they will show no differential solvation dependence. They may be considered as one "averaged" conformer in the solvation analysis and this is shown in Table 1.

Table 1 Calculated geometries (bond lengths in Å, angles in degrees) and energies (kcal mol^{-1}) and reaction-field parameters for DMFA and DMFP

Parameter	DMFA		DMFP		
	Gauche	*Cis*	*Gauche*-1	*Gauche*-2	*Cis*
r(C=O)[a]	1.225	1.216	1.226	1.223	1.218
r(C–N)	1.458	1.459	1.362	1.365	1.372
r(C–C)	1.531	1.535	1.537	1.543	1.542
r(N–C_{Me})	1.458	1.459	1.459	1.458	1.459
r(C–F)	1.402	1.378	1.414	1.417	1.394
∠C–C=O	118.2	121.1	115.8	119.6	119.5
∠N–C=O	123.4	123.8	122.8	122.9	122.9
∠Me_{anti}–N–C[b]	125.4	123.2	126.7	125.9	125.5
∠Me_{syn}–N–C[b]	118.8	119.4	118.2	118.8	118.5
∠F–C–C	113.5	110.0	113.2	108.6	107.5
θ (Me_{anti}–N–C=O)	168.2	180.0	170.6	179.3	175.0
θ (Me_{syn}–N–C=O)	5.5	0.00	2.9	4.6	3.7
θ (F–C–C=O)	134.7	0.00	144.7	−124.1	30.4
E_{rel}[c]	0.00	2.29	0.30	0.00	2.82
μ[d]	3.14	5.57	2.95	3.05	5.51
k[c]	2.279	9.175	1.742	1.742	7.348
h[c]	4.436	0.920	4.175	4.175	1.495
n_D	1.3884	1.3884	1.3912	1.3912	1.3912
V_M[e]	101.91	101.91	120.69	120.69	120.69

[a] r(N–Me) 1.458 ± 0.001, r(C–H) 1.092 ± 0.002. [b] *syn*- and *anti*-methyl groups are defined in Fig. 3. [c] kcal mol^{-1} (1 cal = 4.184 J). [d] Dipole moment/Debye. [e] In ml.

Table 2 Chemical shifts (ppm) and coupling constants (Hz) for *N*,*N*-dimethylfluoroacetamide (DMFA)[a]

Solvent	H^2	H^3 (*anti*)	H^3 (*syn*)	C^1	C^2	C^3 (*anti*)	C^3 (*syn*)	$^2J_{HF}$	$^5J_{HF}$	$^1J_{CF}$	$^2J_{CF}$	$^4J_{CF}$
CCl_4–C_6D_{12}	4.85	2.99 (d)	2.89 (s)	165.4	79.8	35.5 (d)	34.9 (s)	47.53	1.57	180.2	17.8	6.1
$CDCl_3$	4.98	2.98 (d)	2.99 (s)	166.7	79.6	35.7 (d)	35.4 (s)	47.13	1.45	178.4	18.3	4.5
CD_2Cl_2	4.95	2.90 (d)	2.92 (s)	166.7	79.9	35.7 (d)	35.4 (s)	47.04	1.13	175.8	18.6	3.4
Acetone-d_6	5.04	2.88 (d)	2.96 (s)	166.5	79.5	34.6 (d)	34.1 (s)	47.10	0.71	173.5	18.5	2.2
CD_3CN	4.98	2.84 (s)	2.87 (s)	167.9	80.5	35.7 (s)	35.4 (s)	46.92	—	171.8	18.9	—
Pure liquid	5.12	2.87 (s)	2.91 (s)	167.5	80.1	35.2 (d)	34.9 (s)	46.85	—	170.7	18.9	1.9
DMSO-d_6	5.08	2.84 (s)	2.84 (s)	166.6	79.2	34.8 (s)	34.6 (s)	46.74	—	170.3	18.8	—

[a] *syn*- and *anti*-Methyl groups are defined in Fig. 3. (d) Doublet. (s) Singlet.

Table 3 Chemical shifts (ppm) for *N*,*N*-dimethyl-α-fluoropropionamide (DMFP)[a]

Solvent	H^2	H^3 (*anti*)	H^3 (*syn*)	H^4	C^1	C^2	C^3 (*anti*)	C^3 (*syn*)	C^4
CCl_4–C_6D_{12}	5.10	3.09 (d)	2.91 (d)	1.48	167.2	86.5	36.2 (d)	35.5	17.4
$CDCl_3$	5.28	3.09 (d)	2.98 (d)	1.55	169.0	86.4	36.7 (d)	35.9	17.7
CD_2Cl_2	5.27	3.03 (d)	2.93 (d)	1.49	169.1	86.4	36.8 (d)	35.9	17.9
Acetone-d_6	5.41	3.08 (d)	2.89 (d)	1.43	169.0	86.4	36.6 (d)	35.5	17.8
Pure liquid	5.71	3.32 (d)	3.15 (d)	1.69	168.8	85.7	36.1 (d)	35.0	17.4
CD_3CN	5.36	2.99 (d)	2.88 (d)	1.43	169.4	86.1	36.6 (d)	35.4	17.7
DMSO-d_6	5.48	2.98 (s)	2.84 (s)	1.38	168.3	84.8	36.0 (d)	35.0	17.4

[a] *syn*- and *anti*-Methyl groups are defined in Fig. 3. (d) Doublet. (s) Singlet.

Experimental

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

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX 400 spectrometer operating at 400.14 MHz (^{1}H) and 100.63 MHz (^{13}C) and on a Varian Gemini 300 operating at 300.06 MHz (^{1}H) and 75.45 MHz (^{13}C), all referenced to Me_4Si. Spectra were of *ca*. 20 mg cm^{-3} solutions with a probe temperature of *ca*. 25 °C. [$^2H_{12}$]Cyclohexane was used as the deuterium lock signal for the CCl_4 solution and pure liquid. Typical conditions were: proton spectra 48 transients, spectral width 3000 Hz with 32K data points and zero filled to 128K to give a digital resolution of 0.04 Hz. Proton-decoupled carbon spectra were obtained with typical conditions 1028 transients, 3 s pulse delay, spectral width 18000 Hz with 64K data points and zero filled to 256K for a 0.1 Hz digital resolution.

The ASIS were obtained from five experiments for both DMFA and DMFP. To 10 mg DMFA in 0.6 ml $CDCl_3$ was added aliquots of benzene-d_6, ranging from 0.00 to 0.40 ml. The ASIS of the *N*-methyl groups in DMFA were 0.51 and 0.27 ppm for the high-field and low-field methyl groups, which clearly assigns the high-field group as the *anti* methyl. In DMFP the ASIS for the NMe groups were 0.15 and 0.09 ppm and again the larger ASIS was assigned to the *anti* methyl group, though the difference is much smaller in this case. These results are given in detail in ref. 22.

The spectra were all first-order and the coupling constants and chemical shifts taken directly from the spectra. These data are given in Tables 2–6.

In DMFA only one methyl group from the NMe_2 group couples with the fluorine atom ($^5J_{HF}$ and $^4J_{CF}$). In DMFP both protons and one carbon from this group couple with the fluorine atom ($^5J_{HF}$ and $^4J_{CF}$). The HETCOR sequence was used for the assignments of the *N*-methyl groupings.

Table 4 Coupling constants (Hz) for *N*,*N*-dimethyl-α-fluoropropionamide (DMFP)

Solvent	$^3J_{HH}$	$^2J_{HF}$	$^3J_{HF}$	$^5J_{HF}$	$^5J_{HF}$	$^1J_{CF}$	$^1J_{CF}$ [a]	$^2J_{CF}$ [b]	$^4J_{CF}$
CCl_4–C_6D_{12}	6.56	48.40	24.41	—	2.39	178.4	19.0	22.6	8.5
$CDCl_3$	6.60	48.36	24.52	1.27	1.91	176.7	19.7	22.8	6.3
CD_2Cl_2	6.56	48.29	24.66	1.23	1.60	174.8	20.1	23.1	5.1
Acetone-d_6	6.40	47.99	24.61	1.23	1.34	172.3	20.0	23.1	4.3
Pure liquid	6.46	47.98	24.74	1.10	1.31	171.9	20.0	23.1	4.0
CD_3CN	6.51	48.13	24.81	1.11	1.20	171.0	20.0	23.2	3.7
DMSO-d_6	6.47	47.87	24.87	—	—	170.1	20.2	23.0	3.2

[a] F–C–CH_3. [b] F–C–C=O.

Table 5 Chemical shifts (ppm) and coupling constants (Hz) for *N*,*N*-dimethyl-α,α,α-trifluoroacetamide (DMTFA)[a]

Solvent	H^1	H^2	C^1	C^2	C^3	C^4	$^5J_{HF}$	$^1J_{CF}$	$^2J_{CF}$	$^4J_{CF}$
CCl_4–C_6D_{12}	3.13 (q)	3.01 (s)	159.0	116.4	36.2 (s)	36.1 (q)	1.47	287.9	35.8	4.0
$CDCl_3$	3.15 (q)	3.06 (q)	157.0	116.6	36.7 (s)	36.3 (m)	1.48; 0.61	287.7	35.5	
Acetone-d_6	3.17 (q)	3.03 (q)	156.9	117.7	36.7 (s)	36.8 (q)	1.63; 0.77	287.7	36.0	4.01
DMSO-d_6	3.10 (q)	2.98 (q)	156.1	116.9	36.7 (s)	36.7(m)	1.68; 0.72	288.5	34.6	
Pure liquid	3.15 (q)	3.03 (q)	157.8	118.3	36.9 (s)	37.0 (q)	1.59; 0.76	287.5	35.2	3.9

[a] (q) Quartet. (s) Singlet. (m) Multiplet.

Table 6 Temperature dependence of CF coupling (Hz) for DMFA in $CDCl_3$, acetone-d_6 and $CDCl_2$–$CDCl_2$

$CDCl_3$				Acetone-d_6				$CDCl_2$–$CDCl_2$				
T/K	$^1J_{CF}$	$^2J_{CF}$	$^4J_{CF}$	*T*/K	$^1J_{CF}$	$^2J_{CF}$	$^4J_{CF}$	*T*/K	$^1J_{CF}$	$^2J_{CF}$	$^4J_{CF}$	$^5J_{HF}$
293	178.2	18.8	3.8	293	172.8	18.7		293	176.4	18.7		0.31
273	177.8	18.7	3.3	273	171.8	18.9	2.46	313	177.0	18.5		
253	176.6	19.1	2.9	253	171.0	19.1	2.03	333	177.8	18.2		
				233	170.3	19.3	1.61	353	178.4	17.9		1.16
				213	169.7	19.5		373	179.0	18.4	2.69	1.11
				193	169.1	19.6						

Methyl fluoroacetate

To a 250 ml three-neck flask, equipped with magnetic stirrer, a distillation head and condenser, were added dry acetamide (16 g), methyl chloroacetate (37.2 g, 0.344 mol) and potassium fluoride (30.0 g, 0.516 mol, dried at 120 °C overnight). The reaction mixture was heated with stirring, and its colour gradually darkened. Soon after it started to reflux, a small amount of methanol was distilled off. The temperature at the distilling head then rose to 100 °C and remained at 100–110 °C while the reaction was in progress, about 3 hours. During this time, methyl fluoroacetate distilled from the reaction flask and was collected. After two redistillations, pure methyl fluoroacetate (bp 102 °C (lit.[23] 104–105 °C), 9.2 g (30% yield)), was obtained.

Methyl α-fluoropropionate

The reaction was carried out as described above, but with methyl 2-chloropropionate (40.0 ml, 0.352 mol), potassium fluoride (26.5 g, 0.458 mol, dried at 120 °C overnight) and dry acetamide (12 g). The product was distilled at 100–115 °C over 3 hours. After redistillations, pure methyl α-fluoropropionate (bp 105 °C (lit.[24] 106.5–108.5 °C), 12 g (32% yield)), was obtained.

N,*N*-Dimethylfluoroacetamide (DMFA)

To a 50 ml two-neck flask, equipped with magnetic stirrer, reflux condenser and dry ice–ethanol bath, was added methyl fluoroacetate (15 g, 0.141 mol). The flask was cooled down to −10 °C, *N*,*N*-dimethylamine (9 g, 0.2 mol) was added and the reaction mixture was stirred overnight. The desired product was vacuum distilled through a Vigreux column to give pure *N*,*N*-dimethylfluoroacetamide (bp 88 °C/25 mmHg, 5.6 g (32.7% yield)).[25]

N,*N*-Dimethyl-α-fluoropropionamide (DMFP)

The reaction was carried out as described above, but with methyl α-fluoropropionate (12 g, 0.113 mol), and *N*,*N*-dimethylamine (9 g, 0.2 mol) to give pure *N*,*N*-dimethyl-α-fluoropropioamide (bp 78 °C/25 mmHg, 6.0 g (44.6% yield)).[25]

N,*N*-Dimethyl-α,α,α-trifluoroacetamide (DMTFA)

The reaction was carried out as described above for DMFA, but with methyl α,α,α-trifluoroacetate (13 g, 0.091 mol) and *N*,*N*-dimethylamine (5 g, 0.109 mol) to give pure *N*,*N*-dimethyl-α,α,α-trifluoroacetamide (bp 132 °C (lit.[26] 134–136 °C), 6.1 g (47.2% yield)).

Results

The data in Tables 2–6 can now be used with the calculations given earlier to determine the conformational equilibria in these molecules. 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 answered by comparing the observed changes in DMFA and DMFP (Tables 2 and 4) with those of DMTFA (Table 5), in which there is only one possible conformer. The $^1J_{CF}$ coupling in DMTFA is essentially independent of solvent, thus the large change in this coupling in DMFA (180.2→170.3 Hz) and DMFP (178.4→170.1 Hz) may be reasonably attributed to changes in conformer populations. Similar behaviour is observed for $^5J_{HF}$ and $^4J_{CF}$. The HETCOR spectra together with the ASIS experiment, assign the methyl group *anti* to the carbonyl group to the high field methyl and this methyl couples with the fluorine atom in DMFA and

Table 7 Conformer energy differences (kcal mol^{-1}) and observed and calculated couplings for DMFA and DMFP

	DMFA			DMFP		
		$^1J_{CF}$/Hz			$^1J_{CF}$/Hz	
Solvent	[a] $E_{cis} - E_g$	Obs.	Calc.	[b] $E_{cis} - E_{g(AV)}$	Obs.	Calc.
CCl_4–C_6D_{12}	0.87	180.2	180.3	0.83	178.4	178.6
$CDCl_3$	0.14	178.4	178.1	0.17	176.7	176.5
CD_2Cl_2	−0.24	175.8	175.5	−0.24	174.8	174.5
Acetone-d_6	−0.76	173.5	172.5	−0.68	172.3	172.2
CD_3CN	−1.13	171.8	170.6	−0.99	171.0	170.8
DMSO-d_6	−1.29	170.3	170.0	−1.11	170.1	170.3
Pure liquid	−1.17	170.7	170.5	−0.72	171.9	172.0

[a] ΔE^V = 2.5 kcal mol^{-1}. [b] ΔE^v = 2.1 kcal mol^{-1}.

DMFP. The $^5J_{HF}$ and $^4J_{CF}$ couplings in DMTFA are essentially independent of solvent, thus the large change in $^4J_{CF}$ in DMFA (6.1→1.9 Hz) and DMFP (8.5→3.2 Hz) and the appreciable but smaller change in $^5J_{HF}$ in DMFA (1.57→0.71 Hz) and DMFP (2.39→1.20 Hz) may be attributed to changes in the rotamer populations. In DMFP the $^5J_{HF}$ coupling between the *syn* methyl protons and the fluorine atom does not change with solvent, suggesting that this coupling is not sensitive to the conformation.

N,*N*-Dimethylfluoroacetamide (DMFA)

The *GAUSSIAN* calculations show that there are two stable conformers in the vapour phase, the *cis* and *gauche*. The NMR data in Table 2 can now be combined with the solvation calculations *via* eqn. (4), where n_{cis} and n_g are the mole fractions of the *cis* and *gauche* conformers. Note the statistical weight of two for the *gauche* conformer, with two mirror image forms.

$$J_{obs} = n_{cis}J_{cis} + n_gJ_g$$

$$n_{cis} + n_g = 1$$

$$n_g/n_{cis} = 2\exp(-\Delta E/RT)$$

$$\Delta E = E_{cis} - E_g \qquad (4)$$

The value of the $^1J_{CF}$ in the pure liquid (170.7 Hz) gives with the data in Table 2, an interpolated value of 39.3 for the pure liquid relative permittivity.

The data in Table 6 show that the $^1J_{CF}$ coupling increases with increasing temperature in all the solvents used. This indicates that one rotamer predominates in all solvents from $CDCl_3$ to DMSO-d_6. This experiment was not possible in $CFCl_3$, as DMFA is insoluble in this solvent at low temperature.

The solvent data in Table 2 may now be used with eqn. (4) to search for the best solution for both the conformer energy difference and the values of J_{cis} and J_g. This gives ΔE^V 2.5 kcal mol^{-1}, J_{cis} 167.9 and J_g 182.1 Hz, and the energy differences and couplings given in Table 7. The values of the remaining couplings in the two rotamers may be obtained from the linear relationships between the observed couplings, together with these values, to give, for the $^5J_{HF}$ couplings, 2.37 (*gauche*) and 0.13 (*cis*), and for $^4J_{CF}$ 8.1 (*gauche*) and 0.4 Hz (*cis*).

N,*N*-Dimethyl-α-fluoropropionamide (DMFP)

The *GAUSSIAN* calculations show clearly the presence of three stable conformers in the vapour phase, the *cis*, *gauche*-1 and *gauche*-2. As both the energy of the *gauche* forms in the vapour phase and their dipole moments are almost equal, one would expect there to be no differential solvation of these conformers in solution. We therefore use the "average" of these conformers in the solvation calculations. In this case, as these conformers have the same contributions in the equilibrium, the *gauche* average has a statistical weight of two in DMFP, similar to that in DMFA.

The solvation analysis of the NMR data (Table 4) for this compound proceeds in the same manner as for DMFA. The value of the $^1J_{CF}$ in the pure liquid (171.9 Hz) gives with the data in Table 4, an interpolated value of 22.5 for the pure liquid relative permittivity.

The solvent dependence of the $^1J_{CF}$ couplings in DMFA and DMFP is almost identical (Tables 2 and 4), thus the analysis is very similar. The best solution for both the conformer energy difference and the values of J_{cis} and $J_{g(AV)}$ gave values of ΔE^V of 2.1 kcal mol^{-1}, J_{cis} 167.3 and $J_{g(AV)}$ 180.0 Hz and the solution energy differences and couplings of Table 7. The values of the remaining couplings in the two rotamers were obtained from the linear relationships between the couplings in Table 4 ($^5J_{HF}$ *vs.* $^1J_{CF}$, correlation coefficient 0.98; and $^4J_{CF}$ *vs.* $^1J_{CF}$, correlation coefficient 0.97). These gave, for the $^5J_{HF}$ coupling, 2.54 (*gauche*(AV)) and 0.54 Hz (*cis*), and for the $^4J_{CF}$ coupling, 8.9 (*gauche*(AV)) and 1.1 Hz (*cis*).

Discussion

The NMR data, combined with the solvation theory, provide a consistent analysis of the conformational isomerism in DMFA and DMFP in solvents of varying polarity. In DMFA the equilibrium is between the *cis* and *gauche* rotamers. The energy difference is 2.5 kcal mol^{-1} in the vapour phase, which compares very well with that calculated (2.3 kcal mol^{-1}) by DFT at B3LYP/6-311+G(d,p) level.

In DMFP the equilibrium is similar to that of DMFA (*cis* and *gauche*) except that in the *cis* isomer of DMFA the fluorine atom is eclipsed by the carbonyl group (F–C–C=O, 0°), while in DMFP (*cis*) the dihedral angle is distorted (F–C–C=O, 30.4°) due to the steric repulsion between the propionyl methyl and the *anti*-*N*-methyl groups (Fig. 1). The energy difference ($E_{cis} - E_{g(AV)}$) is 2.1 kcal mol^{-1} in the vapour phase, which compares very well with that calculated (2.5, 2.8 kcal mol^{-1}) at the B3LYP/6-311+G(d,p) level.

The *trans* rotamers in these molecules are not a minimum in the potential energy surface, which is very probably due to the steric repulsion between the fluorine atom and the near methyl group of the NMe_2 fragment.

It is noteworthy that in the ketone series (fluoroacetones [8] and fluorobutanones [1]) a large change in the conformer energy was observed when a hydrogen atom was replaced by a methyl group, which was attributed to a steric repulsion between the two methyl groups. In DMFA and DMFP the conformer energy ($E_{cis} - E_g$) does not change when a similar replacement is made (Table 7) but there is a small distortion in the dihedral angle for the *cis* rotamer in DMFP (Table 1).

Note also that the $^2J_{CF}$ couplings in DMFA and DMFP are independent of the molecular conformation (Tables 3, 5)

again unlike the corresponding ketones, while the $^{5}J_{HF}$ and $^{4}J_{CF}$ couplings are very dependent on the conformation.

It is well known that it has been difficult to prepare amino-acids or peptides containing fluorine in the α-position,[27] but clearly, if synthetic methods are developed, the $^{1}J_{CF}$ coupling could be a valuable tool with which to analyse peptide conformation.

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