Conformational analysis in *N*-methylfluoroamides. A theoretical, NMR and IR investigation

Cláudio F. Tormena,[a] Nader S. Amadeu,[a] Roberto Rittner *[a] and Raymond J. Abraham *[b]

[a] *Physical-Organic Chemistry Laboratory, Instituto de Química, UNICAMP CP 6154, 13083-970 - Campinas, S.P., Brazil*
[b] *The Chemistry Department, The University of Liverpool, PO Box 147, Liverpool, UK L69 3BX*

Received (in Cambridge, UK) 3rd December 2001, Accepted 21st February 2002
First published as an Advance Article on the web 12th March 2002

Theoretical calculations plus the solvent dependence of the ^{1}H, ^{13}C NMR and IR spectra were used to determine the conformational equilibrium in *N*-methyl-2-fluoroacetamide (NMFA) and *N*-methyl-2-fluoropropionamide (NMFP). *Ab initio* calculations were used to identify the stable rotamers and obtain their geometries and the application of solvation theory on the $^{1}J_{CF}$ coupling constant gave the conformer populations in the solvents studied. In NMFA *ab initio* calculations at the CBS-Q level yielded only two stable rotamers, the *cis* and *trans*, with ΔE(*cis–trans*) = 19.7 kJ mol^{-1}. The presence of two conformers was confirmed by the FTIR spectra. Assuming these forms, the observed couplings when analysed by solvation theory gave ΔE = 21.3 kJ mol^{-1} in the vapour phase, decreasing to 8.9 kJ mol^{-1} in $CDCl_3$ and to 0.8 kJ mol^{-1} in DMSO. For NMFP the B3LYP calculations at the 6-311++g(2df,2p) level gave only the *trans* rotamer as stable, while the *gauche* form was a plateau in the potential energy surface. However the FTIR spectra clearly showed the presence of two conformers. A minimum for the *gauche* rotamer was only found when the SCRF (self consistent reaction field) routine was included in the theoretical calculations. The equilibrium in NMFP was therefore analysed by solvation theory in terms of the *trans* and *gauche* rotamers to give ΔE(*gauche–trans*) = 15.9 kJ mol^{-1} in the vapour phase, decreasing to 10.8 kJ mol^{-1} in CCl_4 and to 0.5 kJ mol^{-1} in DMSO.

Introduction

Substitution of a hydrogen atom or a hydroxy group by fluorine in enzyme substrate analogues has been widely practised in various areas of bioorganic and medicinal chemistry. For example selectively β-fluorinated α-amino acids have been extensively explored as suicide substrates for decarboxylases, racemases and trans-aminases, and other fluorinated amino acids are assimilated biochemically into proteins.[1] For a single fluorine substituent at the α-position to a carbonyl group, as in α-fluoroaldehydes[2] and α-fluoroketones,[3–5] the preferred conformation of the F–C–C=O moiety is *trans* in the vapour phase and in non-polar solvents, while in some cases[3,4] the *cis* form becomes the most stable in polar solvents ($CDCl_3$ to DMSO). It is noteworthy that in methyl fluoroacetate[6] the *cis* form is more stable than the *trans* even in the vapour phase, but 3-fluorobutan-2-one and 3-fluoro-3-methylbutan-2-one exhibit the reverse behaviour, the *trans* form being the most stable form in the vapour phase and in solvents of varying polarity.[3,5]

Recent work in our laboratories on *N*,*N*-dimethyl-α-fluoroacetamide and -propionamide found that in the vapour phase and in solvents of low polarity the *gauche* rotamer predominates, while in polar solvents (CD_2Cl_2 to DMSO) the *cis* form becomes more stable than the *gauche*.[7]

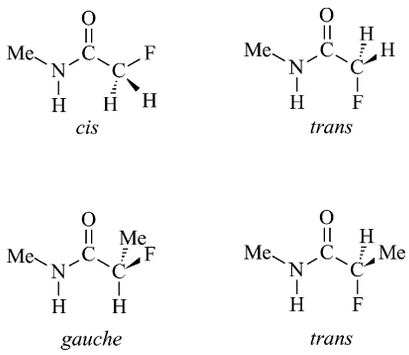
Banks *et al.*[8] synthesised (*S*)-*N*-fluoroacetylphenylalanine and *N*-phenyl-2-fluoropropionamide and reported *ab initio* and X-ray studies on these compounds. The X-ray structures of both compounds showed the C–F bond oriented nearly *cis* to the N–H and *trans* to the C=O bond. The rotational profile of the FCC=O bond in these compounds was investigated by a DFT analysis of *N*-methyl-2-fluoropropionamide at the B3LYP/6-31g(d) level. The calculated energy profile showed a single distinct minimum at τ(F–C–C=O torsion) = 180° (C–F and N–H bonds eclipsed), a maximum at τ = 300° and a plateau at about τ = 60°.[8] No solution studies were undertaken, thus no experimental conformer energies were obtained. In a further report[9] on the enzymatic resolution of an α-fluoroamide with an acylase, the same authors used their previous results[8] and found that the *trans* conformation (F–C–C=O 180°) is again the only conformer in the solid state for these amides. As the vapour phase calculations[8] had shown that the *trans* form was the only minimum in the rotational energy profile, the authors concluded that the fluorine atom and not the methyl group would dictate the conformation of these amides.[9] Therefore the methyl groups of the two α-fluoropropionamide enantiomers would necessarily have to be located in opposite spacial sites around the stereogenic centre. This is anticipated to impose significantly different diastereomeric interactions during the binding of such enantiomers to an enzyme.[9]

The above results indicate that the introduction of an α-fluorine substituent into an *N*-methylamide should stabilize the N–C(O)–C–F moiety in the conformation with the fluorine atom *gauche* to the carbonyl, as in the *N*,*N*-dimethylamides, or *trans* to the NH as in the *N*-methylamides. The formation of hydrogen bonding C–F···H–N (or electrostatic attraction) should shift the equilibrium even further towards the *trans* rotamer.

We present here the conformational analysis of two of the simplest molecules with the F·C·CO·NH·C linkage, *N*-methyl-2-fluoroacetamide (NMFA) and *N*-methyl-2-fluoropropionamide (NMFP) (Scheme 1).

Ab initio and DFT calculations, ^{1}H and ^{13}C NMR spectra and FTIR spectra in different solvents for NMFA and NMFP are reported. The NMR data showed that the $^{1}J_{CF}$ coupling was sensitive to the F–C–C=O orientation. The use of *ab initio* and DFT calculations plus solvation theory[10] allowed us to define both of the interconverting rotamers of NMFA and NMFP and to obtain the rotamer energy differences in the vapour phase as well as in solution.

DOI: 10.1039/b111048a



Scheme 1 Conformers of NMFA and NMFP.

Theory

The *ab initio* calculations at the CBS-Q and DFT(B3LYP) levels were performed with the GAUSSIAN98 program[11] and the solvation calculations using the MODELS program. The solvation theory has been described fully elsewhere[10] thus only a brief description is given here. The solvation energy of any molecule in state A is the difference between the energy in the vapour (E_A^V) and in any solvent (E_A^S) of relative permittivity ε. This is given in terms of the dipolar (k_A) and quadrupolar (q_A) reaction field terms plus a direct dipole–dipole term to take account of the breakdown of the Onsager reaction-field theory in very polar media.[10] The required quantities are simply the dipole and quadrupole moments plus the solute radius which is obtained from the molar volume (V_M) and refractive index n_D, all of which are calculated in the program. In state B a similar equation is obtained differing only in the values of the dipole and quadrupole terms. Subtraction of the two equations gives ΔE^S ($E_A^S - E_B^S$), the energy difference in any solvent of given relative permittivity in terms of ΔE^V and calculable parameters. The theory has been given in detail previously and shown to give an accurate account of the solvent dependence of a variety of conformational equilibria.[3–7]

The calculations were performed with the MODELS program, using as input the geometries from GAUSSIAN. The dipole and quadrupole moments of the molecules are calculated directly from the partial atomic charges in the molecule obtained from the CHARGE routine.[12]

Theoretical calculations

The *N*-methyl group in NMFA and NMFP can be *syn* or *anti* to the C=O bond, but preliminary theoretical calculations showed that the energy difference between these two forms is around 100 kJ mol^{-1} for both compounds in favour of the *syn* conformer. Thus, the *N*-methyl group has to be *syn* to the C=O bond and this was assumed in the subsequent theoretical calculations.

The potential energy surface (PES) for NMFA at the B3LYP/6-31g(d,p) level showed two stable rotamers, *cis* and *trans*. Their geometries and energies were optimised at the CBS-Q level with recomended basis sets and are given in Table 1. The CBS-Q level was shown to be the best procedure in GAUSSIAN98.[13] The *ab initio* dipole moments are 2.40 D (*trans*) and 5.73 D (*cis*). Using the *ab initio* geometries, the CHARGE routine[10] gave dipole moments for NMFA of 1.70 (*trans*) and 4.98 D (*cis*). The *ab initio* and CHARGE dipole moments are reasonably consistent, and thus the partial atomic charges calculated in CHARGE may be used with confidence in the solvation calculations. The values of the solvation parameters [eqn. (1)] are given in Table 2. The refractive index and molar volume were calculated by the program.

When the PES was scanned for NMFP at the B3LYP/6-31g(d,p) level only one minimum was found, corresponding to the *trans* form, and a plateau was observed at the F–C–C=O dihedral angle at *ca.* 60°, suggesting a *gauche* form (Fig. 1). However, this *gauche* form is not defined as a stable minimum, and the question is: does this conformer exist in solution? The IR spectrum (Fig. 2) provides an unequivocal answer as there are clearly two carbonyl absorption bands in the spectrum in the polar DMSO solvent, but what happens in the non-polar solvents?.

To find the answer to this question, a solvation routine[13] was included in the GAUSSIAN calculations at the B3LYP/6-31g(d,p) level. We used the simplest SCRF (self-consistent reaction field) model, the Onsager reaction field model. In this method, the solute occupies a fixed spherical cavity of radius a_0 within the solvent field. The solute dipole polarises the medium, and the reaction field thus formed in the solvent in turn interacts with the molecular dipole, leading to net stabilisation.

The energy profiles for chloroform, acetone and DMSO are shown in Fig. 1. The plateau for the more polar *gauche* form becomes a minimum with increasing solvent relative permittivity. Moreover, in all cases, the *cis* form is still a maximum in the PES, which can be attributed to steric interactions between the CH_3 and NH groups. Therefore, we may confidently conclude from these results that the conformational equilibrium in NMFP is between the *gauche* and *trans* conformers, and the *trans* is the most stable one both in the vapour phase and in solution (Fig. 1).

Table 1 Calculated geometries [bond lengths (Å) and angles (degrees)], energies and dipole moments for NMFA at MP2/6-311+g(d,p) and CBS-Q levels,[a] and for NMFP at the B3LYP/6-311++g(2df,2p) level[b]

	NMFA		NMFP	
Parameter	*trans*	*cis*	*trans*	*gauche*
r(C=O)	1.224 (1.225)	1.217 (1.219)	1.224	1.221
r(C–N)	1.345 (1.353)	1.357 (1.365)	1.351	1.356
r(C–C)	1.521 (1.525)	1.531 (1.533)	1.532	1.537
r(N–C_{Me})	1.453 (1.452)	1.454 (1.454)	1.454	1.457
r(C–F)	1.390 (1.393)	1.367 (1.371)	1.415	1.406
r(N–H)	1.004 (1.008)	1.004 (1.008)	1.009	1.008
r(C–H)	1.091 (1.097)	1.092 (1.100)	1.092	1.092
∠(C–C=O)	119.6 (120.3)	123.5 (123.1)	119.0	121.5
∠(N–C=O)	124.4 (124.8)	123.2 (123.2)	125.3	123.8
∠(Me–N–C)	120.5 (120.2)	120.3 (119.8)	123.1	122.4
∠(H–N–C)	118.5 (118.5)	120.0 (120.6)	117.2	119.1
∠(F–C–C)	112.2 (112.1)	110.5 (110.0)	110.3	107.7
θ(C–N–C=O)	0.00 (0.00)	0.00 (0.00)	0.00	0.00
θ(F–C–C=O)	180.0 (180.0)	0.00 (0.00)	176.3	51.4
$E_{rel.}$/kJ mol^{-1}	0.00 (0.00)	21.7 (19.7)	0.00	12.1
μ/D	2.38 (2.40)	5.90 (5.73)	2.36	5.94

[a] Data at the CBS-Q level in parentheses. [b] Including the solvation routine (ε = 46.7).

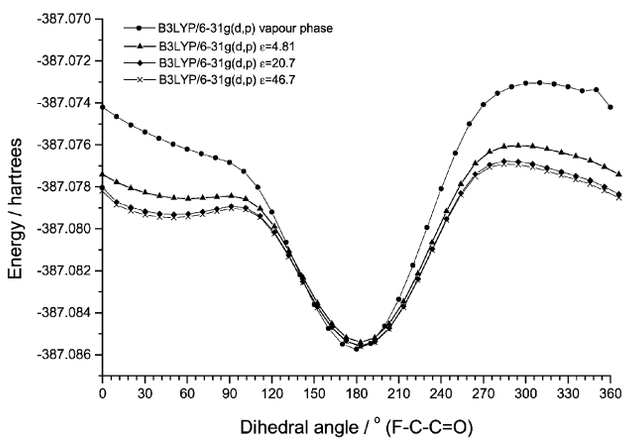


Fig. 1 Potential energy surface for *N*-methylfluoropropionamide at the B3LYP/6-31g(d,p) level at different values of medium relative permittivity.

Table 2 Parameters for reaction-field calculations for NMFA and NMFP

		Dipole mom./D	k/kcal mol^{-1} [a]	h/kcal mol^{-1} [a]	n_D [a]	V_M/ml [a]
NMFA	*trans*	1.70	1.2059	7.4600	1.3843	83.127
	cis	4.98	10.8535	1.1535	1.3843	83.127
NMFP	*trans*	1.67	1.0007	6.6528	1.3884	101.913
	gauche	4.61	7.5961	2.4649	1.3884	101.913

[a] See text.

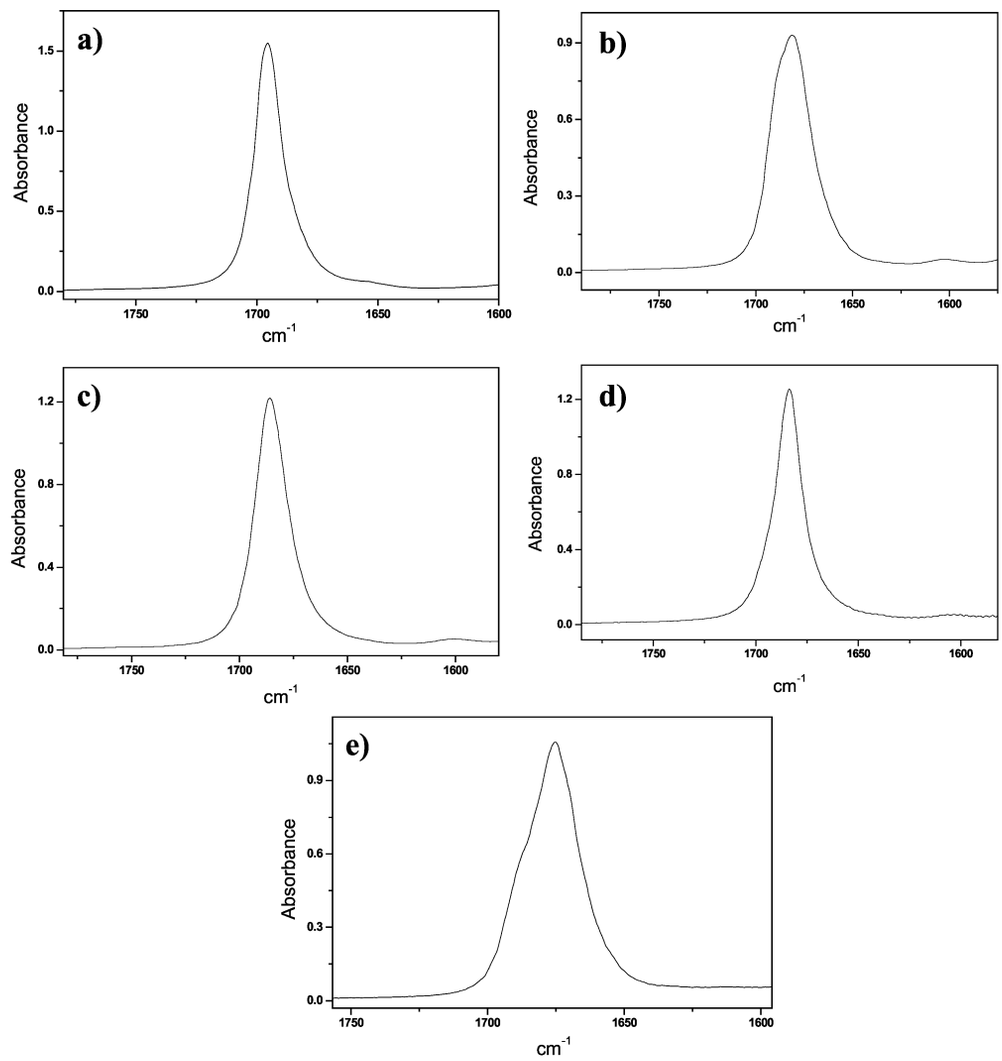


Fig. 2 The carbonyl absorption band in the IR spectrum of NMFP in: a) CCl_4, b) $CHCl_3$, c) CH_2Cl_2, d) CH_3CN and e) DMSO.

The energies and geometries for the NMFP *gauche* and *trans* forms were then calculated at the B3LYP/6-311++g(2df,2p) level with the inclusion of the solvation routine for DMSO as solvent and are given in Table 1.

Using these geometries, the CHARGE routine [12] gave dipole moments for NMFP of 1.67 D (*trans*) and 4.61 D (*gauche*). The *ab initio* dipole moments had been obtained using the solvation routine, so they cannot be compared to those obtained through CHARGE program, although the differences between both sets are not large. The values for the solvation parameters [eqn. (1)] are given in Table 2. The refractive index and molar volume were calculated by the program.

Experimental

N-Methyl-2-fluoroacetamide (NMFA), *N*-methyl-2-fluoropropionamide (NMFP) and *N*-methyl-2,2,2-trifluoroacetamide (MTFA) were prepared by a literature procedure.[14] 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 Varian Gemini spectrometer operating at 300.06 MHz for proton and 75.45 MHz for carbon. 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. The ^{1}H and ^{13}C spectra were all referenced to Me_4Si. Typical conditions were: proton spectra 48 transients, spectral width 2500 Hz with 32k data points zero filled to 128k to give a digital resolution of 0.04 Hz. Proton-decoupled carbon-13 spectra were obtained with typical conditions 1024 transients, 3 s pulse delay, spectral width 18000 Hz with 64k data points zero filled to 256k for 0.1 Hz digital resolution.

The spectra were all first-order and the coupling constants and chemical shifts taken directly from the spectra. The NMR data are presented in Tables 3 to 5.

Table 3 Chemical shifts (δ ppm) and coupling constants (Hz) for NMFA

Solvent	H_4	H_2	H_3	C_1	C_2	C_3	$^3J_{HH}$	$^2J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
$CDCl_3$	6.38	4.80	2.91	168.2	80.4	25.5	5.00	47.22	185.4	17.3
CD_2Cl_2	6.43	4.77	2.84	168.3	81.0	25.6	4.96	47.06	183.9	17.2
Acetone-d_6	7.48	4.77	2.78	168.4	81.1	25.4		47.42	183.1	18.3
CD_3CN	6.84	4.73	2.74	168.6	81.0	25.2	4.85	47.06	181.6	17.2
DMSO-d_6	8.26	4.92	2.78	167.5	80.1	25.2	4.69	47.00	180.2	18.1

Table 4 Chemical shifts (δ ppm) and coupling constants (Hz) for NMFP

Solvent	H_5	H_2	H_3	H_4	C_1	C_2	C_3	C_4	$^3J_{HH}$	$^3J_{HH}$ [a]	$^2J_{HF}$	$^3J_{HF}$	$^1J_{CF}$	$^2J_{CF}$	$^2J_{CF}$ [b]
CCl_4	6.58	4.86	2.81	1.52	169.8	88.4	25.3	18.3	6.75	4.84	49.67	24.32	182.9	21.3	18.5
$CDCl_3$	6.45	4.99	2.88	1.57	171.4	89.0	25.7	18.4	6.72	4.81	49.38	24.65	181.8	21.5	19.7
CD_2Cl_2	6.44	4.96	2.81	1.53	171.4	89.5	25.8	18.7	6.75	4.98	49.37	24.83	181.7	22.1	18.8
Acetone-d_6	7.36	4.95	2.76	1.46	171.5	89.4	25.7	18.8	6.71	4.81	49.36	24.80	180.7	22.1	19.8
CD_3CN	6.83	4.94	2.72	1.46	171.4	89.4	25.4	18.4	6.79	4.83	49.17	24.63	180.4	22.8	18.2
DMSO-d_6	8.06	4.97	2.62	1.41	170.1	88.0	25.2	18.40	6.72	4.60	48.82	24.41	179.2	22.0	20.5

[a] $CH_3.NH$. [b] F.C.CO.

Table 5 Chemical shifts (δ ppm) and coupling constants (Hz) for *N*-methyltrifluoroacetamide

Solvent	H_3	H_4	C_1	C_2	C_3	$^3J_{HH}$	$^5J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
$CDCl_3$	2.96	6.73	158.1	115.9	26.4	4.97	0.65	286.1	36.9
CD_2Cl_2	2.91	6.74	158.1	116.4	26.6	4.93	0.65	286.2	35.5
Acetone-d_6	2.87	8.39	157.8	117.0	26.3	4.76	0.65	285.6	35.9
DMSO-d_6	2.92	9.34	156.4	115.8	25.8	4.65	0.65	285.9	36.0

The IR spectra were recorded with a Bomem model MB 100 FTIR spectrometer, using a sodium chloride cell with a 0.5 mm spacer for dilute (*ca.* 0.03 M) solutions, with the solvent as background when recording the solute spectrum.

Results

The results from theoretical calculations may now be combined with the NMR data and solvation theory to determine the rotamer populations in solution.

Although the use of $^3J_{HH}$ coupling (Karplus equation) in conformational investigations is well established,[15] this is not the case for the $^1J_{CF}$ 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 answered by comparing the observed changes in NMFA and NMFP (Tables 3 and 4) with those of MTFA (Table 5), in which there is only one possible conformer. The $^1J_{CF}$ coupling in MTFA is essentially independent of solvent, thus the large change for this coupling in NMFA (185.4 to 180.2 Hz) and the appreciable but smaller change in NMFP (182.9 to 179.2 Hz) may be reasonably attributed to changes in the conformer populations.

N-Methyl-2-fluoroacetamide

The theoretical calculations have shown that there are two stable rotamers in the vapour phase, the *cis* and the *trans*. The IR spectra of NMFA in solvents of varying polarity (Fig. 3) present a single sharp band for the CO stretch in solvents of low and medium polarity (Fig. 3a, b and c), while in solvents of high polarity there is a definite shoulder (Fig. 3d and 3e), supporting the NMR data and confirming that for NMFA there are two stable forms in solution as in the vapour phase. Convolution analysis of the IR band in DMSO solution gives the ratio of the two bands as 1 : 2.16. This cannot be used to determine the conformer populations due to possible differences in the intrinsic absorption coefficients of the bands.

The NMR data in Table 3 can now be combined with the solvation calculations, *via* eqn. (1), to search for the best solution for both the rotamer energy differences and the values of J_{cis} and J_{trans}, where n_{cis} and n_{trans} are the mole fractions of the *cis* and *trans* rotamers.

$$J_{obs} = n_{cis}J_{cis} + n_{trans}J_{trans}$$
$$n_{cis} + n_{trans} = 1$$
$$n_{cis}/n_{trans} = e^{(-\Delta E/RT)}$$

$$\Delta E = E_{cis} - E_{trans} \quad (1)$$

This was achieved using the programme BESTFIT.[10] This calculates the couplings in all the solvents from eqn. (1) for any given value of ΔE^V using the solvation energy calculated by MODELS and then compares the observed and calculated couplings. The best agreement was obtained with $\Delta E^V = 21.3$ kJ mol^{-1}, $J_{cis} = 173.4$ Hz and $J_{trans} = 185.3$ Hz. with an rms error (observed − calculated couplings) of 0.32 Hz. The energy differences in solution (ΔE^S) and couplings are given in Table 6. The error in ΔE^V is estimated at ≈0.5 kJ mol^{-1} and for the couplings ≈0.5 Hz.

N-Methyl-2-fluoropropionamide

The NMR data in Table 4 show that the $^1J_{CF}$ coupling changes with solvent, which can also be attributed to changes in the conformational equilibrium, as discussed above. The inclusion of the solvation routine[13] in the theoretical calculations (Fig. 1) led to a minimum for the *gauche* rotamer, in agreement with the changes observed in the NMR spectra. The IR spectra in solvents of varying polarity (Fig. 2) confirm the NMR and theoretical data. The IR spectra in solvents of low and medium polarity (Fig. 2a, b, c and d) show the carbonyl absorption as a single sharp band, but in a solvent of the highest polarity, DMSO (Fig. 2e), the carbonyl band exhibits a clear shoulder, which confirmed the presence of the second rotamer in this solvent. Convolution analysis gave the proportions of the two forms as 1 : 12.60.

The results from the theoretical/SCRF calculations, which indicated the presence of the stable *trans* and *gauche* rotamers,

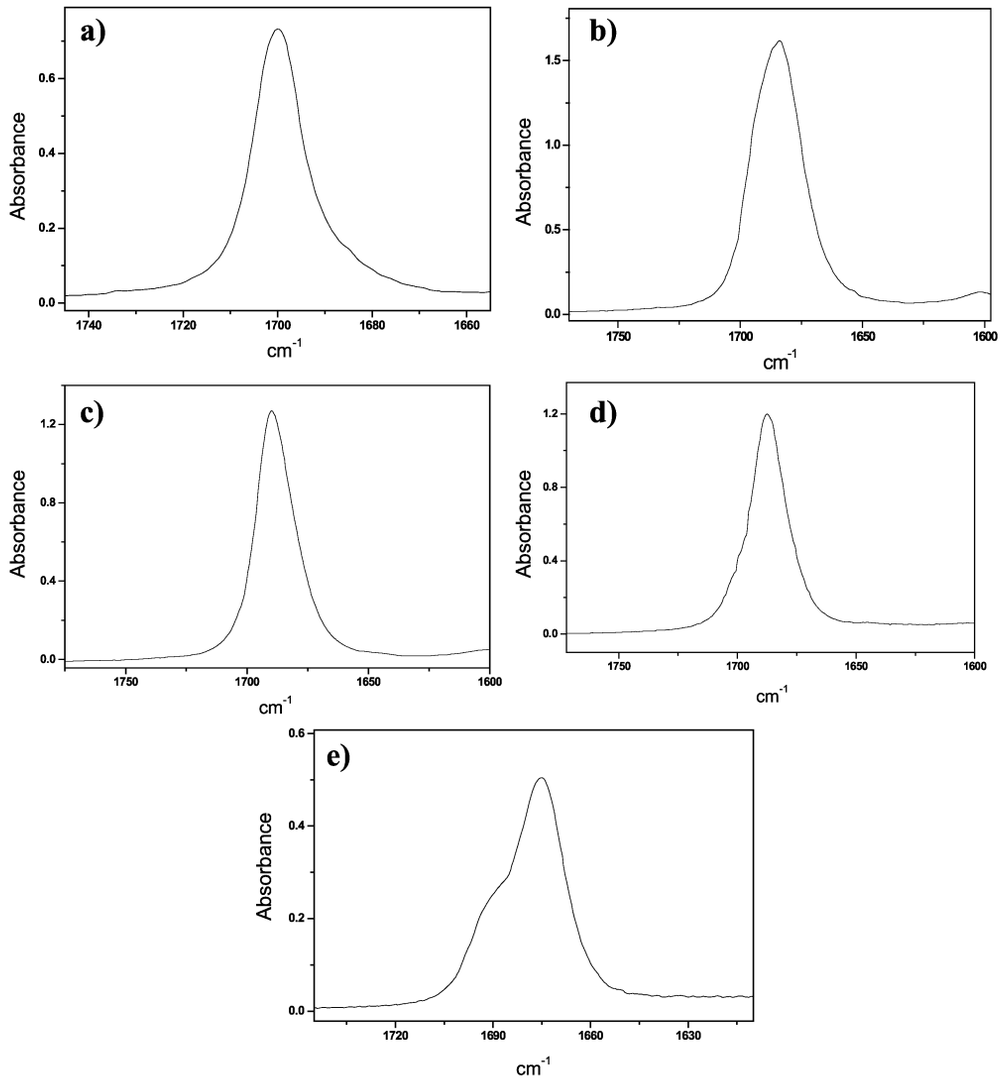


Fig. 3 The carbonyl absorption band in the IR spectrum of NMFA in: a) CCl_4, b) $CHCl_3$, c) CH_2Cl_2, d) CH_3CN and e) DMSO.

Table 6 Conformer energy differences (kJ mol^{-1}) and observed and calculated couplings for NMFA and NMFP

	NMFA			NMFP		
		$^1J_{CF}$/Hz			$^1J_{CF}$/Hz	
Solvent	$E_{cis} - E_{trans}$	Calc.	Obs.	$E_{gauche} - E_{trans}$	Calc.	Obs.
CCl_4				10.87	182.6	182.9
$CDCl_3$	9.00	185.0	185.4	7.20	182.3	181.8
CD_2Cl_2	6.40	184.5	183.9	4.93	181.8	181.7
Acetone-d_6	3.59	183.1	183.1	2.72	180.8	180.7
CD_3CN	1.59	181.2	181.6	1.21	179.8	180.4
DSMO-d_6	0.75	180.3	180.2	0.55	179.3	179.2

can be combined with the NMR data in Table 4 and the solvation calculations, *via* eqn. (4), to search for the best solution for both the rotamer energy difference and the values of J_{trans} and J_{gauche}. Eqn. (4) was adapted for this equilibrium by replacing *cis* by *gauche* in the four expressions.

The best solution from BESTFIT for both the rotamer energy difference and the values of J_{trans} and J_{gauche} gave ΔE^V = 15.9 kJ mol^{-1}, J_{trans} = 182.6 Hz and J_{gauche} = 175.1 Hz. In this very biased equilibrium the errors in the analysis are larger than for NMFA. $\Delta E^V \approx 1.0$ kJ mol^{-1} and $J_{gauche} \approx 1.0$ Hz but the value of J_{trans} is essentially the observed coupling in CCl_4 solution. The energy differences in solution (ΔE^S) and couplings are given in Table 6.

Discussion

The NMR, IR and theoretical/SCRF calculations provide a consistent analysis of the conformational isomerism for NMFA and NMFP in solvents of varying polarity. In NMFA the isomerism is between the *cis* and *trans* rotamers and the energy difference is 21.3 kJ mol^{-1} in the vapour phase, which compares very well with that calculated (19.7 kJ mol^{-1}) at the CBS-Q level, while for NMFP it is between the *trans* and *gauche* and the corresponding energy difference is 15.9 kJ mol^{-1} in the vapour phase, according to the solvation theory. The latter result is only supported by the *ab initio* calculations when the SCRF routine was included in the calculations.

A comparison of the geometry of the NMFA *cis* rotamer, where the fluorine atom is eclipsed with the carbonyl group (F–C–C=O, 0°), with the corresponding rotamer (*gauche*) of NMFP, which has a dihedral angle (F–C–C=O) of 51.4°, strongly suggests that in NMFP steric repulsion between the CH_3 and N–H group leads to this distorted geometry.

The values for individual (*cis* and *trans*) $^1J_{CF}$ couplings in NMFA and NMFP compare very well with those of *N*,*N*-dimethylfluoroacetamide (DNMFA) and *N*,*N*-dimethyl-2-fluoropropionamide (DNMFP).[7] In DNMFA $^1J_{gauche}$ = 185.3 Hz and in NMFA $^1J_{trans}$ = 185.3 Hz. In DNMFP $^1J_{gauche}$ = 180.0 Hz and in NMFP $^1J_{trans}$ = 182.6 Hz, thus the above results agree very well with the results for DNMFA and DNMFP.

For both *N*-methylamides the *trans* rotamer is more stable in the vapour phase as well as in solution. This may be due to hydrogen bonding between the fluorine and the N–H atom, as the distance between the N–H hydrogen and the fluorine is just 2.18 Å.

These results confirm that the plateau, which had been observed by Banks and coworkers[8] for NMFP is a minimum in the potential energy surface, and thus, we can conclude that for NMFP there is a conformational equilibrium between the *gauche* and *trans* forms. The advantages of the above method of analysis is that accurate conformer energies can be obtained for the α-fluoroamides in solution. These can be applied to biological systems as was recently described by Banks and O'Hagan.[9] They found that lipase can hydrolyze the *S* isomer of a mono-fluorinated ester giving the pure *R* isomer with 99% ee, but it could not be definitively concluded which conformer was interacting with the enzyme. The old fashioned lock-and-key model cannot be used to describe such interactions, for in this dynamic process the enzyme gradually induces changes in the substrate conformation as they approach each other.[16] It is clear that studies in solution by ^{13}C NMR spectroscopy are complimentary to those of X-ray crystallography and may lead to more realistic analysis of the biological systems.

Acknowledgements

The authors thank FAPESP for financial support and for a scholarship (to N. S. A.) and a fellowship (to C. F. T.), and CNPq for a fellowship (to R. R.). Computer facilities (GAUSSIAN 98) from CENAPAD-SP are also gratefully acknowledged.

References

1 D. O'Hagan and H. S. Rzepa, *Chem. Commun.*, 1997, 645.
2 H. V. Phan and J. R. Durig, *J. Mol. Struct. (THEOCHEM)*, 1990, **209**, 333.
3 R. J. Abraham, C. F. Tormena and R. Rittner, *J. Phys. Org. Chem.*, 2002, **15**, 211.
4 R. J. Abraham, A. D. Jones, M. A. Warne, R. Rittner and C. F Tormena, *J. Chem. Soc., Perkin Trans. 2*, 1996, 533.
5 R. J. Abraham, C. F. Tormena and R. Rittner, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1663.
6 R. J. Abraham, C. F. Tormena and R. Rittner, *J. Chem. Soc., Perkin Trans. 2*, 2001, 815.
7 C. F. Tormena, R. Rittner, R. J. Abraham, E. A. Basso and R. M. Pontes, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2054.
8 J. W. Banks, A. S. Batsanov, J. A. K. Howard, D. O'Hagan, H. S. Rzepa and S. Martin-Santamaria, *J. Chem. Soc., Perkin Trans. 2*, 1999, 2409.
9 J. W. Banks and D. O'Hagan, *J. Fluorine Chem.*, 2000, **102**, 235.
10 R. J. Abraham and E. Bretschneider, in *Internal Rotation in Molecules*, Academic Press, London, 1974, ch. 13.
11 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomeli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, GAUSSIAN98, Revision A. 9, Gaussian Inc., Pittsburgh, 1998.
12 R. J. Abraham, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1999, **35**, 85.
13 J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, Gaussian, Pittsburgh, 1996, p. 155.
14 K. H. Abramson, P. T. Inglefield, E. Krakower and L. W. Reeves, *Can. J. Chem.*, 1966, **44**, 1685.
15 R. J. Abraham, P. Leonard, T. A. D. Smith and W. A. Thomas, *Magn. Reson. Chem.*, 1996, **34**, 71.
16 D. Voet and J. G. Voet, *Biochemistry*, 2nd edn., Wiley, New York, 1995, ch. 9.