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Conformational analysis. Part 35.[1] NMR, solvation and theoretical investigation of rotational isomerism in methyl fluoroacetate and methyl difluoroacetate

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

[a] *The Chemistry Department, University of Liverpool, PO Box 147, Liverpool, UK L69 3BX*
[b] *Instituto de Química, Universidade Estadual de Campinas, Caixa Postal 6154, 13083-970, Campinas, São Paulo, Brasil*

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The solvent and temperature dependence of the ^{13}C NMR spectra of methyl fluoroacetate (MFA) and methyl difluoroacetate (MDFA) are reported and the $^1J_{CF}$ coupling analysed in terms of the conformer couplings and energies. Density Functional Theory (DFT) calculations were used to obtain the conformer geometries and solvation theory gave the solvent dependence of the conformer energies. In MFA the DFT method at the B3LYP/6-311+G(d,p) level gave only two energy minima for the *cis* (F–C–C=O 0°) and *trans* (F–C–C=O 180°) conformers of *ca*. equal energy. The *gauche* conformer was not a minimum in the energy surface. The FTIR spectra of MFA support this result as two resolved carbonyl bands are observed whose relative intensity changes markedly with solvent polarity. Assuming only these forms, the observed coupling when analysed by solvation theory leads to the energy difference ($E_{cis} - E_{trans}$) between the *cis* and *trans* conformers of 0.90 kcal mol^{-1} in the vapour phase, decreasing to 0.41 kcal mol^{-1} in CCl_4 and -0.71 kcal mol^{-1} in DMSO. In MDFA the DFT calculations gave two minima for the *cis* (H–C–C=O 0°) and *gauche* (H–C–C=O 141.9°) conformers with an energy difference ($E_{cis} - E_{gauche}$) of 0.2 kcal mol^{-1}. The FTIR spectra of MDFA support this result as in the non-polar solvent (CCl_4) two resolved bands are observed but in solvents of medium and high polarity the carbonyl absorption appears as a single band. Assuming only the two forms, the observed coupling when analysed by solvation theory leads to the energy difference ($E_{cis} - E_{gauche}$) between the *cis* and *gauche* conformers of 0.0 kcal mol^{-1} in the vapour phase, increasing to 0.46 kcal mol^{-1} in CCl_4 and 1.12 kcal mol^{-1} in DMSO.

Introduction

Fluorinated compounds are widely used in biochemistry, medicinal chemistry and pharmacology.[2] The substitution of hydrogen by fluorine in pharmacologically active organic molecules can have profound effects on the activity.[3] The *gem*-difluoromethylene group is of particular importance in this regard as it serves to isosterically replace oxygen in phosphate analogues and to block the metabolic oxidation of methylene groups.[3]

Introduction of a fluorine atom at a sugar carbon in nucleosides alters their biological activities toward various cellular, pathogenic and tumor-specific enzymes in various ways. The replacement of a hydroxy group by a fluorine atom causes only a minor change in the steric effect of the functionality, but such a substitution has profound effects on the chemical properties as well as on the stereoelectronic properties, which results in specific overall conformational change of the fluorinated nucleosides.[2]

Fluorine substitution in the α-position to a carbonyl group, as in α-fluoroaldehydes,[4] α-fluoroketones,[5,6] α-fluoroesters[7] and α-fluoroamides,[8] gives only two conformers. The more stable form in the vapour phase and in non-polar solvents has the F–C–C=O moiety in a *trans* arrangement but the energy difference between the *cis* and *trans* conformations is not large (0.8–3.5 kcal mol^{-1}).

It has been demonstrated[9,10] that, for a wide variety of carbonyl compounds, the presence of an asymmetrical group adjacent to the carbonyl group causes a splitting of the carbonyl infrared absorption band. This splitting is generally ascribed to rotational isomerism involving rotation about the carbon–carbon bond joining the methylene and the carbonyl carbons.[9]

Studies on methyl fluoroacetate (MFA) and on methyl difluoroacetate (MDFA) using Raman and infrared spectroscopy and also *ab initio* calculations at the 4-21G and 6-31G level have been performed by van der Veken *et al.*[7] The authors concluded that for MFA the equilibrium in the vapour and the pure liquid was between the *trans* (F–C–C–OCH_3 180°) and *gauche* (F–C–C–OCH_3 30.3°) rotamers. For MDFA their calculations predicted the existence of the *trans* (H–C–C–OCH_3 180°) and *gauche* (H–C–C–OCH_3 49.9°) rotamers in the vapour and the pure liquid. However, it is known that larger basis sets and correction for electron correlation are often important in determining the calculated properties of molecules,[11] and this will be clearly shown in this paper.

We present here the ^1H and ^{13}C NMR spectra of MFA and MDFA in solvents of varying polarity and show that the $^1J_{CF}$ coupling is sensitive to the F–C–C=O orientation. The use of the DFT method (which includes electron correlation) plus solvation calculations allows us to define both the interconverting conformers in MFA and MDFA and also to obtain the conformer energy differences in the vapour phase as well as in solution.

Theoretical

The theoretical calculations with the DFT B3LYP method were performed using the GAUSSIAN 98 program[12] and the solvation calculations using the MODELS program.[13] In the latter the solvation energy of a molecule is given by including

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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. This theory has been given in detail and shown to give an accurate account of the solvent dependence of a variety of conformational equilibria.[13–15]

On this basis the solvation energy of any molecule in state A, *i.e.* the difference between the energy in vapour (E_A^V) and in any solvent (E_A^S) of electric permittivity 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 $x = (\varepsilon - 1)/(2\varepsilon + 1)$; $l = 2(n_D^2 - 1)/(n_D^2 + 2)$; $b = 4.30(a^{3/2}/r^3)(k_A + 0.5h_A)^{1/2}$ and $f = [(\varepsilon - 2)(\varepsilon + 1)/\varepsilon]^{1/2}$ for $\varepsilon > 2$ and is zero otherwise; n_D is the refractive index; T is 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 and a is 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. The dipole and quadrupole moments of the molecule (μ and q) are calculated directly from the partial atomic charges in the molecule, given by the CHARGE routine.[16]

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 eqn. (2) where H for any given rotamers A and

$$\Delta E^S(E_A^S - E_B^S) = \Delta E^V - H \quad (2)$$

B is only a function of the solvent relative permittivity and temperature.

In the application of this theory we note that the energy of interaction of the molecular charge distribution with the environment, *i.e.* the solvation energy of the molecule, is the Helmholtz free energy and is given by the reversible work involved in charging the distribution in the presence of a dielectric.[17] Thus the calculations are in terms of potential energy whereas the experimental data are in terms of enthalpy. Since we are interested only in *differences* between solvents the zero-point energy, the contribution of higher vibrational states and pdV terms are expected to cancel out (for a full discussion see ref. 18). Indeed this may be extended to assume that the entropy differences between the rotational isomers are negligible, apart from the statistical weight. This assumption is justified by the fact that despite numerous investigations over four decades there is still no measurement of any significant entropy difference between non-sterically hindered acyclic rotational isomers.[19]

An important factor in the determination of the conformational equilibrium between two conformers of very different dipole moments is that the temperature dependence of pure liquid (or solvent) relative permittivity can appreciably affect the value of the energy difference obtained. It has been shown[13] that the true value of the free energy difference at any temperature [$\Delta E(t)$] is related to that obtained using the van't Hoff equation, eqn. (3), by eqn. (4).

$$\mathrm{d}\ln K/\mathrm{d}(1/t) = -\,\Delta E^\circ/R \quad (3)$$

$$\Delta E(t) = \Delta E^\circ + T(\mathrm{d}H/\mathrm{d}t) \quad (4)$$

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,[5,13] thus it cannot be ignored in any accurate determination of conformer energy differences.

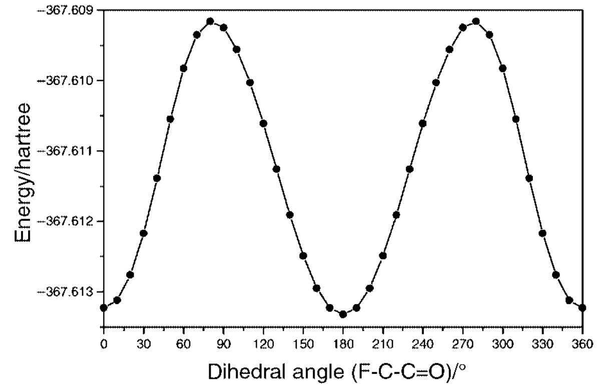

Fig. 1 Potential energy for MFA at the B3LYP/6-31G(d,p) level.

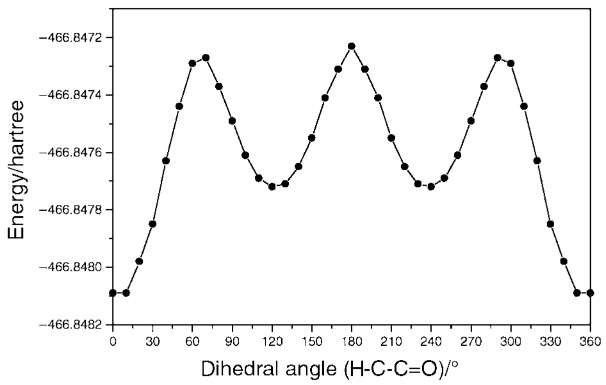

Fig. 2 Potential energy surface for MDFA at the B3LYP/6-31G(d,p) level.

Theoretical calculations

DFT analyses of MFA and MDFA were carried out at the B3LYP/6-31G(d,p) level, in order to quantify the conformational dependence on the torsional angle and the geometry of the stable conformers optimized at the B3LYP/6-311+g(d,p) level with zero-point energy correction (ZPE).[20] In MFA the potential energy surface (Fig. 1) shows two distinct stable conformers with F–C–C=O torsion angles (ϕ) = 0° for the *cis* form and 180° for the *trans* form. Their geometries and relative energies are given in Table 1. The *trans* conformer (F–C–C=O 180°) had not been considered a stable form by van der Veken *et al.*,[7] who used another dihedral angle (F–C–C–O) to identify the observed conformers.

A similar analysis of MDFA was performed in terms of the dependence on the H–C–C=O torsion angle (ϕ). The potential energy surface (Fig. 2) shows two distinct stable conformers the *cis* $\phi = 0°$ and *gauche* $\phi = 141.5°$. Their geometries and relative energies are given in the Table 1.

The B3LYP dipole moments for MFA are 3.71 (*cis*) and 0.99 (*trans*) and for MDFA are 1.84 (*cis*) and 3.74 D (*gauche*) which compare well with those from the CHARGE routine[16] (using the same geometries) of, for MFA 3.99 (*cis*) and 0.59 D (*trans*) and for MDFA 0.96 (*cis*) and 3.68 D (*gauche*). *Ab initio* dipole moments are very basis set dependent and the CHARGE partial atomic charges have been shown to be very reliable when used in the MODELS solvation calculations,[13–15] thus they are used here. 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 by the program.

Table 1 Calculated geometries for MFA and MDFA at the B3LYP/6-311+G(d,p) level

	MFA		MDFA	
Parameter	*cis*	*trans*	*cis*	*gauche*
r(C=O)[a]	1.198	1.206	1.203	1.198
r(C–O)	1.349	1.333	1.329	1.337
r(O–C_{Me})	1.443	1.444	1.446	1.445
r(C–C)	1.520	1.520	1.537	1.540
r(C–F)	1.378	1.384	1.363	1.352; 1.370
r(C–H)	1.093	1.092	1.090	1.091
∠ O–C=O	125.9	126.2	127.2	126.1
∠ C–O–C	118.1	117.9	118.3	116.1
∠ F–C–C	110.6	114.0	110.1	109.8
∠ H–C–O[b]	110.3	110.5	110.5	110.0
ϕ F–C–C=O	0.00	180.0	—	—
ϕ H–C–C=O	—	—	0.00	141.9
Energy[c]	−367.64935	−367.64923	−466.92657	−466.92686
Relative energy[d]	0.0	0.1	0.2	0.0
Dipole moment[e]	3.71	0.99	1.84	3.74

[a] Å. [b] Averaged values. [c] hartree. [d] kcal mol^{-1} (1 cal = 4.184 J). [e] D.

Table 2 Parameters for reaction-field calculations for MFA and MDFA

	Conformer	Dipole moment[a]	k[b]	h[b]	n_D	V_M	l
MFA	*cis*	3.99	7.3899	0.9356	1.3627	78.63	0.4443
	trans	0.59	0.1630	10.8041			
MDFA	*cis*	0.93	0.3759	8.5632	1.3305	84.47	0.4086
	gauche	3.68	5.8290	1.5363			

[a] D. [b] kcal mol^{-1}.

Table 3 Chemical shifts (ppm) and coupling constants (Hz) for MFA (F$H^1_2C^1$–C^2O_2–$C^3H^3_3$)

Solvent	H^1	H^3	C^1	C^2	C^3	$^2J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	4.76	3.77	77.1	167.4	51.5	47.22	185.3	21.8
$CDCl_3$	4.86	3.82	78.2	169.3	52.7	47.01	182.9	21.8
CD_2Cl_2	4.85	3.78	78.5	169.2	52.6	46.96	181.2	21.9
Acetone-d_6	4.95	3.75	78.7	169.6	52.3	46.84	178.6	21.9
Pure liquid	4.91	3.78	79.2	170.5	52.8	46.71	178.3	21.8
CD_3CN	4.88	3.74	79.2	170.1	52.8	46.69	177.7	21.8
DMSO-d_6	5.03	3.72	78.0	168.9	51.9	46.43	176.6	21.8

Experimental

Methyl difluoroacetate was obtained from Fluorochem Ltd. Methyl fluoroacetate and methyl trifluoroacetate (MTFA) were prepared by literature procedures.[21,22] 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, and on a Varian Gemini 300 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 ^1H and ^{13}C spectra were all referenced to Me_4Si (TMS). Typical conditions were: proton spectra 48 transients, spectral width 3000 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.04 Hz. Proton-decoupled carbon spectra were obtained with typical conditions 528 transients, 3 s pulse delay, spectral width 22000 Hz with 64 K data points and zero filled to 256 K for a 0.1 Hz digital resolution. The spectra were all first-order and the coupling constants and chemical shifts taken directly from the spectra are given in Tables 3–5. The temperature dependence of the proton spectrum of MFA was recorded in $CFCl_3$ and the data are given in Table 6.

The carbonyl stretching bands both in fundamental (1850–1600 cm^{-1}) and in the first overtone regions (3650–3300 cm^{-1}) (Fig. 3 and 4) were obtained from the infrared spectra, recorded in a Bomem FT-IR MB-100 spectrometer, of 0.02 M solutions for MFA and MDFA in solvents of varying polarity, using 0.5 mm sodium chloride matched and 1.00 cm quartz matched cells, respectively.

Results

The NMR data of Tables 3–5, IR spectra (Fig. 3 and 4) and theoretical calculations can now be used to determine the conformational equilibrium in these molecules.

Although the use of $^3J_{HH}$, $^4J_{HF}$ and $^2J_{CF}$ couplings in conformational investigations is well established,[5,6,15] this is not the case for the $^1J_{CF}$ coupling. Thus it is first necessary to determine how much of the observed variation of the coupling is due to changes in the conformer populations and how much to an intrinsic solvent dependence.

This question can be answered by comparing the observed changes in MFA (Table 3) with those of MTFA (Table 5), in which there is only one conformer. The $^1J_{CF}$ coupling in MTFA is essentially independent of solvent, thus the large change in this coupling in MFA (185.3→176.6 Hz) may be reasonably attributed to changes in conformer populations.

Table 4 Chemical shifts (ppm) and coupling constants (Hz) for MDFA ($F_2H^1C^1–C^2O_2–C^3H^3{}_3$)

Solvent	H^1	H^3	C^1	C^2	C^3	$^2J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	5.84	3.88	106.3	162.0	52.4	53.28	249.7	28.9
$CDCl_3$	5.92	3.91	106.5	162.9	53.2	53.24	249.1	28.8
CD_2Cl_2	5.95	3.88	107.6	163.8	53.8	53.29	249.1	28.6
Acetone-d$_6$	6.27	3.88	108.5	164.3	53.7	53.03	246.8	28.6
CD_3CN	6.08	3.84	108.1	163.9	53.9	52.97	245.9	28.4
DMSO-d$_6$	6.44	3.84	107.4	163.7	53.3	52.65	246.2	28.4
Pure liquid	6.02	3.89	108.6	164.8	54.1	53.19	246.4	28.6

Table 5 Chemical shifts (ppm) and coupling constants (Hz) for MTFA ($F_3C^1–C^2O_2–C^3H^1{}_3$)

Solvent	H^1	C^1	C^2	C^3	$^1J_{CF}$	$^2J_{CF}$
CCl_4	3.96	115.1	158.0	54.3	284.9	42.6
$CDCl_3$	3.98	114.5	158.0	54.3	285.1	42.4
Acetone-d$_6$	4.03	115.6	158.4	55.2	284.5	41.8
CD_3CN	3.95	115.4	158.3	55.3	284.5	41.7

Table 6 The temperature dependence of the CF couplings (Hz) for MFA in $CDCl_3$

Temp./K	$^1J_{CF}$	$^2J_{CF}$
290	184.2	21.8
273	183.7	21.9
253	183.2	22.0
233	182.4	22.2
213	181.6	22.3

Methyl fluoroacetate

The DFT calculations show that there are two stable conformers in the vapour phase, the *cis* and *trans* of comparable energy and that the *cis* conformer is more polar than the *trans* form (Table 1). The IR data (Fig. 3) support this and show very clearly the presence of two C=O bands whose relative intensities vary considerably with solvent. These may safely be assigned to the two conformers and on the basis that the more polar *cis* form will be more stabilised in polar sovents, the absorption band at 1768 cm^{-1} is assigned to the *cis* conformer and that at 1750 cm^{-1} to the *trans*. The C=O band for the carbonyl group in CCl_4 (Fig. 3a) showed the presence of two resolved bands and one "shoulder" which may be assigned to a third stable conformer. However when the spectrum was recorded at the first overtone stretching region only two resolved bands were observed (Fig. 3b), confirming that the "shoulder" in the fundamental stretching region was due to Fermi resonance and that there were only two conformers.

If the extinction coefficients of the two carbonyl bands are equal the relative intensity of the two bands in acetonitrile solution (Fig. 3e) of *ca.* 3 : 1 would give ($E_{cis} - E_{trans}$) equals *ca.* −0.6 kcal mol^{-1} in this solvent. The molar absorption coefficients may well not be equal, but this provides a useful reference for the NMR calculations.

The above conclusions are supported by the NMR data. In other compounds investigated in this series (fluoroketones and amides)[5,6,23] the $^1J_{CF}$ coupling for the *cis* forms are smaller than those for the *trans* or *gauche* forms. *e.g.* In fluoroacetone $^1J_{CF}$ *cis* is 179.6 Hz, *cf.* the *trans* coupling of 188.0 Hz.[5] The variable temperature NMR data (Table 6) show that the $^1J_{CF}$ coupling decreases with decreasing temperature in $CFCl_3$ indicating that the *cis* conformer is more stable in this solvent.

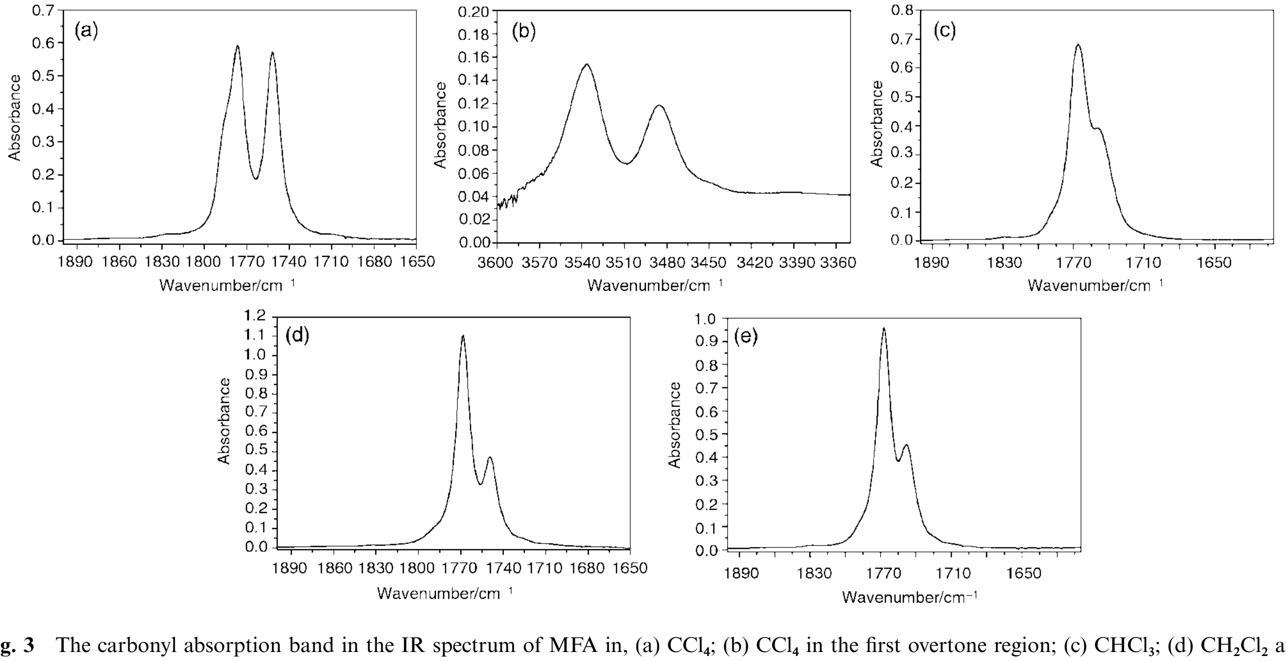

Fig. 3 The carbonyl absorption band in the IR spectrum of MFA in, (a) CCl_4; (b) CCl_4 in the first overtone region; (c) $CHCl_3$; (d) CH_2Cl_2 and (e) CH_3CN.

Table 7 Conformer energy difference (kcal mol^{-1}) and observed and calculated couplings for MFA and MDFA

	MFA			MDFA		
		$^1J_{CF}$/Hz			$^1J_{CF}$/Hz	
Solvent	$E_{cis} - E_{trans}$	Calc.	Obs.	$E_{cis} - E_{gauche}$	Calc.	Obs.
CCl_4–C_6D_{12}	0.41	185.7	185.3	0.46	251.1	249.7
$CDCl_3$	0.05	182.7	182.9	0.70	248.8	249.1
CD_2Cl_2	−0.19	180.7	181.2	0.86	247.6	249.1
Acetone-d_6	−0.46	178.7	178.6	1.01	246.7	246.8
Pure liquid	−0.48	178.4	178.3	1.05	246.3	246.4
CD_3CN	−0.65	177.4	177.7	1.09	246.3	245.9
DMSO-d_6	−0.71	176.9	176.6	1.12	246.1	246.2

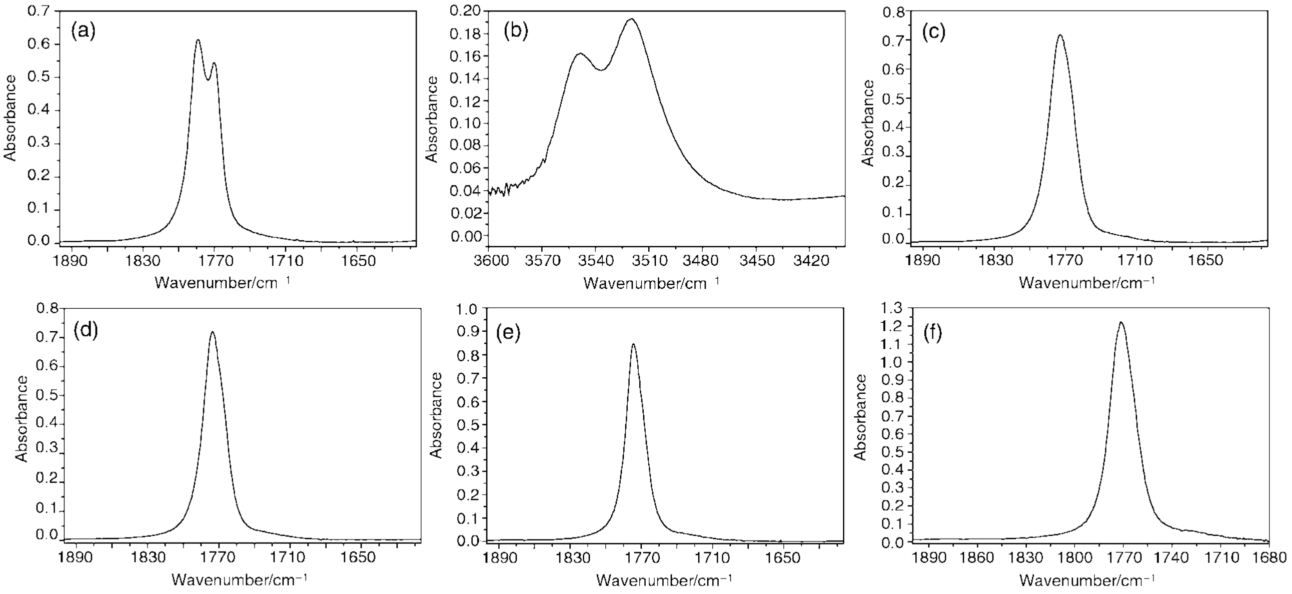

Fig. 4 The carbonyl absorption band in the IR spectrum of MDFA in, (a) CCl_4; (b) CCl_4 in the first overtone region; (c) $CHCl_3$; (d) CH_2Cl_2; (e) CH_3CN and (f) DMSO.

The NMR data in Table 3 may now be combined with the solvation calculations to provide a detailed account of the conformational equilibrium in this compound *via* eqn. (5).

$$J_{obs} = n_{cis}J_{cis} + n_{trans}J_{trans}$$
$$n_{cis} + n_{trans} = 1$$
$$n_{cis}/n_{trans} = \exp(-\Delta E/RT)$$
$$\Delta E = E_{cis} - E_{trans} \qquad (5)$$

The value of $^1J_{CF}$ in the pure liquid (178.3 Hz) gives with the data of Table 3 an interpolated value of 22.8 for the pure liquid relative permittivity.

With the above considerations in mind the solvent data in Table 3 may be used with the solvation theory to search for the most appropriate solution for both the conformer energy difference and values of $^1J_{CF(cis)}$ and $^1J_{CF(trans)}$. The best agreement was for $\Delta E^V = 0.9$ kcal mol^{-1}, $^1J_{CF(cis)} = 172.3$ and $^1J_{CF(trans)} = 192.4$ Hz with an rms error of 0.32 Hz. The energy differences and the observed and calculated couplings are given in Table 7.

Methyl difluoroacetate

The analysis of the NMR (Table 4) and IR data (Fig. 4) for MDFA proceeds in the same manner as for MFA, though in this case the *gauche* isomer has a statistical weight of two in the analysis *cf.* eqn. (6).

$$J_{obs} = n_{cis}J_{cis} + n_{gauche}J_{gauche}$$
$$n_{cis} + n_{gauche} = 1$$
$$n_{gauche}/n_{cis} = 2\exp(-\Delta E/RT)$$
$$\Delta E = E_{cis} - E_{gauche} \qquad (6)$$

The values of $^1J_{CF}$ in pure liquid (246.4 Hz) give with the data of Table 4 an interpolated value of 27.0 for the pure liquid relative permittivity.

The DFT calculations show clearly the presence of two stable conformers in the vapour phase (Fig. 1), and when the ZPE correction term was included in the calculations (Table 1) the more polar *gauche* conformer became more stable (0.2 kcal mol^{-1}) than the *cis*. Thus in solvents of medium and high polarity the *gauche* form should be the major or the predominant form in these solvents.

Table 4 shows that the $^1J_{CF}$ coupling changes very little in non-polar solvents, as well as in polar solvents, but there is an appreciable change (~3 Hz) between these classes of solvents. In solvents of medium and high polarity the $^1J_{CF}$ coupling is almost equal to that of the *gauche* conformer in 1,1-difluoroacetone[5] (247.9 Hz), confirming that in MDFA the *gauche* form is preponderant in these solvents.

The solvent data in Table 4 may be used with the solvation theory to search for the best solution for both the conformer energy difference and values of J_{cis} and J_{gauche}. This gave $\Delta E^{V} = 0.0$ kcal mol^{-1}, $J_{cis} = 286.6$ and $J_{gauche} = 243.0$ Hz, and the energy differences and couplings of Table 7.

These results are supported by the FTIR spectrum in solvents of varying polarity. In CCl_4 (Fig. 4a and 4b) a partially resolved doublet is observed both in the fundamental and in the first overtone stretching, but in all other solvents the carbonyl stretching is a single sharp band (Fig. 4c, d, e and f), confirming that in these solvents the *gauche* form is much more stable than the *cis*.

Discussion

The NMR and IR experimental data combined with the solvation calculations provide a consistent analysis of the conformational isomerism in the molecules studied here. In MFA the equilibrium is between the *cis* and *trans* conformers. The energy difference ($E_{cis} - E_{trans}$) is 0.9 kcal mol^{-1} in the vapour phase which is slightly higher than the calculated value (-0.1 kcal mol^{-1}) by DFT at the B3LYP/6-311+G(d,p) level.

In MDFA the DFT calculations showed the presence of two stable conformers in the vapour phase, while in solution the *gauche* form is more stable (more than 80%) in all solvents. This result is corroborated by both the NMR and IR data.

Note that the $^{2}J_{CF}$ couplings in MFA and MDFA are independent of the molecular conformation (Tables 3 and 4) unlike the corresponding ketones,[5,6] but similar to the amides,[20] possibly due to the resonance in the C(O)O fragment.

In MFA the more stable conformer has the fluorine atom *trans* (*anti*) with respect to the carbonyl oxygen atom. This agrees with the behaviour of the other series (ketones[5,6] and amides[23]) studied, where the fluorine atoms prefer to be *trans* to the carbonyl oxygen atom.

It is well known that natural products containing fluorine are rare, and practically nothing is known about their origins or the enzymatic process for generating C–F bonds. Some of these organofluorine (*e.g.* fluoroacetate) compounds are elaborated by plants, microorganisms and parasites. It is known that the caterpillar *Sindris albimaculatus* accumulates fluoroacetate, which is highly toxic to predators.[24] This property is due to the lethal synthesis pathway for the inhibition of Krebs' cycle, but clearly it would be of some interest to investigate the enzymatic process for generating C–F bonds. In this investigation, the $^{1}J_{CF}$ coupling could be a valuable tool for the analysis of the conformation of the C–F bond.

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