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An NMR, IR and theoretical investigation of the methyl effect on conformational isomerism in 3-fluoro-3-methyl-2-butanone and 1-fluoro-3,3-dimethyl-2-butanone

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ABSTRACT: The solvent dependence of the ^{1}H and ^{13}C NMR spectra of 3-fluoro-3-methyl-2-butanone (FMB) and 1-fluoro-3,3-dimethyl-2-butanone (FDMB) was examined and the $^{4}J_{HF}$, $^{1}J_{CF}$ and $^{2}J_{CF}$ couplings are reported. Density functional theory (DFT) at the B3LYP/6–311 ++ G(2df,2p) level with ZPE (zero point energy) corrections was used to obtain the conformer geometries. In both FMB and FDMB, the DFT method gave only two minima for *cis* (F—C—C═O, 0°) and *trans* (F—C—C═O, 180°) rotamers. Assuming the *cis* and *trans* forms, the observed couplings in FMB when analysed by solvation theory gave the energy difference $E_{cis} - E_{trans}$ of 3.80 kcal mol^{-1} (1 kcal = 4.184 kJ) in the vapour phase (cf. the DFT value of 3.21 kcal mol^{-1}), decreasing to 2.6 kcal mol^{-1} in CCl_4 and to 0.27 kcal mol^{-1} in DMSO. In FDMB the observed couplings when analysed similarly by solvation theory gave $E_{cis} - E_{trans}$ = 1.80 kcal mol^{-1} in the vapour phase, decreasing to 0.47 kcal mol^{-1} in CCl_4 and to −1.25 kcal mol^{-1} in DMSO. The introduction of a methyl group geminal to the fluorine atom shifts the conformational equilibrium towards the *trans* rotamer, in contrast to no significant effect when the methyl group is introduced at the α-carbon further from the fluorine atom. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: conformational analysis; fluoroketones; NMR; solvation; theoretical calculations

INTRODUCTION

The last three decades have seen tremendous interest in fluorinated biological analogues and their pharmacological properties.[1] In determining the mode of action of fluoro compounds *in vivo*, the conformational changes induced by the fluorine substituent are of primary importance. These are primarily electronic as the steric effect of fluorine is very small. An example is the interaction between fluorine and the oxygen of a carbonyl group (i.e. F—C—C═O) which has been widely investigated. This group has been shown to have a predominantly twofold potential in fluoroacetic acid,[2] fluoroacetyl chloride[3] and fluoroacetone[4–6] in all of which the conformational isomerism was shown to be between the *cis* and *trans* forms. In these cases the *cis* form is more stable in solvents of medium and high polarity.

It has also been observed[7] that a small change in structure (the replacement of a hydrogen atom by a methyl group) shifts the conformational isomerism significantly. In fluoroacetone (FA),[4] the *trans* rotamer predominates over the *cis* rotamer only in solvents of low polarity (CCl_4, CS_2 and $CDCl_3$), whereas for 3-fluoro-2-butanone (FB)[7] the *trans* rotamer predominates over the *cis* rotamer in all solvents (CCl_4 to DMSO). This behaviour is presumably due to the increased steric repulsion between the two methyl groups in the *gauche* position which destabilizes the *cis* rotamer in 3-fluoro-2-butanone.

Here we investigated the conformational isomerism in the related compounds 3-fluoro-3-methyl-2-butanone (FMB), where the remaining hydrogen atom in C-3 of FB is replaced by a methyl group [Fig. 1(a)] and 1-fluoro-3,3-dimethyl-2-butanone (FDMB), where all the hydrogen atoms of C-3 in FA are replaced by methyl groups [Fig. 1(b)].

The ^{1}H and ^{13}C NMR spectra and the IR spectra of FMB and FDMB in different solvents were obtained. Both the $^{4}J_{HF}$, $^{1}J_{CF}$ and $^{2}J_{CF}$ couplings and the IR spectra are sensitive to the F—C—C═O orientation. The use of DFT calculations plus solvation theory[8] allows us both to define the interconverting rotamers in FMB and FDMB and to obtain the conformer energy differences in the vapour phase and in solution.

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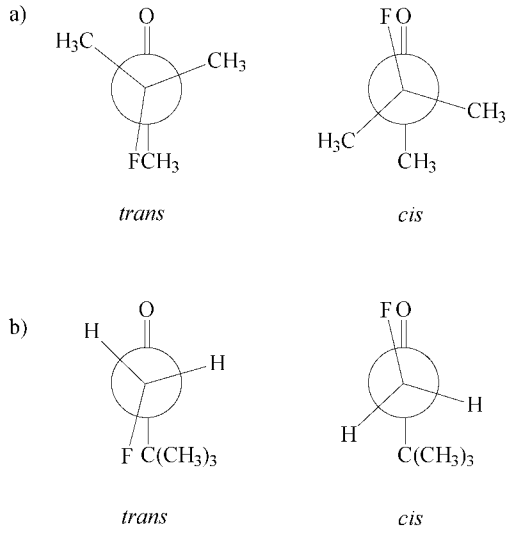

Figure 1. (a) Rotamers *trans* and *cis* for FMB; (b) rotamers *trans* and *cis* for FDMB

THEORY

Ab initio (DFT) calculations were performed using the Gaussian 98 program.[9] The potential energy surfaces were obtained at the recommended B3LYP/6–31G(d,p) level to find the most stable rotamers for the studied molecules. The optimized geometries, which would be used in solvation theory, were obtained at a higher level, the B3LYP/6–311 ++ G(2df,2p) level, and to determine more accurate energies zero point energy (ZPE) corrections[10] were performed. However, the ZPE calculations do not lead to changes in the geometry parameters. The solvation calculations were performed using the MODELS program, applying the geometries from Gaussian as input file. This theory (solvation theory) has been described fully elsewhere,[4,7,8,11,12] so only a brief description is given here. 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 vapour ($E_A{}^V$) and in any solvent ($E_A{}^S$) of relative permittivity ε, is given by the equation

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

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 and T is the temperature (K). The first term is due to the solute dipole ($k_A = \mu_A{}^2/a^3$, μ_A is the solute dipole) and the second term to the solute quadrupole ($h_A = q_A{}^2/a^5$, q_A is the solute quadrupole) and a is the solute radius. The third term is the dipole–dipole term for very polar media. The solute radius is obtained directly from the molar volume (V_M) of the solute ($V_M/N = 4\pi a^3/3$, where N is Avogadro's number). The molar volume can be obtained from the density of 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 relative permittivity, in terms of ΔE^V ($E_A{}^V - E_B{}^V$) and calculable or measurable parameters. The dipole and quadrupole moments of the molecules are calculated directly from the partial atomic charges in the molecule using the CHARGE routine.[13] This theory has been shown to give an accurate account of the solvent dependence of a variety of conformational equilibria.[4,7,11,12]

RESULTS AND DISCUSSION

To our knowledge, there have been no previous theoretical study of these molecules. The Gaussian calculations gave for both FMB and FDMB two stable rotamers, the *cis* and *trans* forms. The optimized geometries and energies of these rotamers are given in Table 1. The DFT-calculated dipole moments are for FMB 0.94 D (*trans*) and 4.41 D (*cis*) and for FDMB 1.29 D (*trans*) and 4.28 D (*cis*). Using the DFT geometries, the CHARGE routine[13] gave dipole moments for FMB of 1.05 D (*trans*) and 4.70 D (*cis*) and for FDMB dipole moments of 1.04 D (*trans*) and 4.42 D (*cis*). The DFT and CHARGE dipole moments are in good agreement, hence the partial atomic charges may be used with confidence in the solvation calculations. The values of the solvation

Table 1. Calculated geometries and energies for FMB and FDMB

	FMB		FDMB	
Parameter	*trans*	*cis*	*trans*	*cis*
r(C═O) (Å)	1.208	1.203	1.209	1.204
r(C—C) (Å)	1.522	1.526	1.531	1.529
r(C_F—C_{Me}) (Å)	1.542	1.541	1.543	1.541
r(C—F) (Å)	1.411	1.393	1.390	1.375
r(C—H) (Å)	1.092	1.091	1.091	1.090
∠(C—C=O)°	118.2	121.2	122.9	122.6
∠(F—C—C)°	109.0	107.4	116.2	111.0
∠(H—C—C)°	109.6	110.5	109.2	111.0
ϕ(F—C—C=O)	180.0	0.00	180.0	0.00
$E_{rel.}$ (kcal mol^{-1})	0.00	3.20	0.00	1.70
Dipole moment (D)	0.94	4.41	1.29	4.28

Table 2. Parameters for reaction-field calculations

		Dipole moment (D)	k (kcal mol^{-1})	h (kcal mol^{-1})	n_D	V_M	l
FMB	*cis*	4.70	7.3249	0.7371	1.3739	109.89	0.4566
	trans	1.05	0.3642	5.1805	1.3739	109.89	0.4566
FDMB	*cis*	4.42	5.5267	1.6604	1.3786	128.68	0.4618
	trans	1.04	0.3072	2.9080	1.3786	128.68	0.4618

Table 3. Chemical shifts (ppm) and coupling constants[a] (Hz) for FMB

Solvent	H-3	H-4	C-2	C-3	C-1	C-4	$^3J_{HF}$	$^4J_{HF}$	$^1J_{CF}$	$^2J_{CF}$[b]	$^2J_{CF}$[c]
CCl_4	2.20	1.40	207.7	97.8	23.7	23.7	21.17	5.20	179.4	29.9	24.0
$CDCl_3$	2.28	1.45	210.6	98.7	24.5	23.9	21.49	5.06	178.5	29.7	24.0
Pure liquid	2.82	2.02	209.4	98.9	24.0	23.8	21.38	5.05	178.4	29.2	24.2
CD_2Cl_2	2.24	1.43	210.4	99.1	24.6	24.0	25.54	4.95	178.2	29.2	24.2
Acetone-d_6	2.22	1.41	210.0	99.3	24.4	24.0	21.46	4.87	178.0	28.9	24.2
CD_3CN	2.21	1.42	210.4	99.3	24.4	23.3	21.67	4.78	177.4	28.5	24.3
DMSO-d_6	2.22	1.40	209.5	98.4	24.3	23.4	21.72	4.59	177.8	28.1	23.9

[a] HF couplings accurate to ±0.04 Hz and CF couplings accurate to ±0.1 Hz.
[b] F—C—C=O.
[c] F—C—CH_3.

Table 4. Chemical shifts (ppm) and coupling constants[a] (Hz) for FDMB

Solvent	H-2	H-4	C-2	C-1	C-3	C-4	$^2J_{HF}$	$^1J_{CF}$	$^2J_{CF}$
CCl_4	4.88	1.12	206.7	82.2	42.4	25.5	47.71	186.0	14.0
$CDCl_3$	5.12	1.16	209.4	82.2	42.7	25.8	47.11	183.6	12.6
CD_2Cl_2	5.13	1.16	209.3	82.6	42.8	26.0	47.11	181.7	12.5
Pure liquid	5.60	1.56	209.1	82.4	42.6	25.8	47.40	180.5	12.3
Acetone-d_6	5.28	1.16	209.3	83.0	42.9	26.0	47.41	179.3	12.3
CD_3CN	5.21	1.13	209.9	83.1	42.7	25.8	47.11	178.2	11.8
DMSO-d_6	5.36	1.09	209.4	82.4	41.7	25.4	46.50	176.7	11.5

[a] HF couplings accurate to ±0.04 Hz and CF couplings accurate to ±0.1 Hz.

parameters [Eqn. (1)] are given in Table 2. The refractive index and molar volume were also calculated by the program.

The ^{1}H and ^{13}C NMR data (chemical shifts and coupling constants) for FMB and FDMB are given in Tables 3 and 4. These data can now be used with the calculations given earlier to determine the conformational equilibria in these molecules. The couplings were first shown to be linearly related. For FMB the $^4J_{HF}$ vs $^2J_{CF}$ plot is linear (correlation coefficient 0.98) and for FDMB the $^1J_{CF}$ vs $^2J_{CF}$ plot is linear (correlation coefficient 0.98). Thus, as in previous investigations,[4,7,11] the change in coupling constants with solvent may be reasonably attributed to changes in the rotamer populations.

3-Fluoro-3-methyl-2-butanone

The Gaussian calculations show that there are two stable rotamers in the vapour phase, *cis* and *trans*. The NMR data in Table 3 can now be combined with the solvation calculations via the equation

$$J_{obs} = n_{cis}J_{cis} + n_{trans}J_{trans}$$
$$n_{cis} + n_{trans} = 1$$
$$n_{cis}/n_{trans} = e^{-\Delta E/RT}$$
$$\Delta E = E_{cis} - E_{trans} \quad (2)$$

where n_{cis} and n_{trans} are the mole fractions of the *cis* and *trans* rotamers. The value of the $^2J_{CF}$ in the pure liquid (29.2 Hz) gives with the data in Table 3, an interpolated value of 7.5 for the pure liquid relative permittivity.

The solvent data in Table 3 can now be used with Eqn. (2) to search for the best solution for both the rotamer energy difference and the values of J_{cis} and J_{trans}. This gives $\Delta E^V = 3.80$ kcal mol^{-1}, $^2J_{CF(cis)} = 25.3$ Hz and

Table 5. Conformer energy differences (kcal mol^{-1}) and observed and calculated couplings for FMB and FDMB

	FMB			FDMB		
		$^2J_{CF}$ (Hz)			$^2J_{CF}$ (Hz)	
Solvent	$E_{cis} - E_{trans}$	Calc.	Obs.	$E_{cis} - E_{trans}$	Calc.	Obs.
CCl_4	2.59	29.7	29.9	0.47	14.1	14.0
$CDCl_3$	1.77	29.6	29.7	−0.22	12.9	12.6
CD_2Cl_2	1.28	29.3	29.2	−0.62	12.3	12.5
Acetone-d_6	0.77	28.9	28.9	−1.00	12.0	12.3
CD_3CN	0.42	28.3	28.3	−1.19	11.8	11.8
DMSO-d_6	0.27	28.1	28.1	−1.25	11.7	11.5
Pure liquid	1.40	29.4	29.2	−0.91	12.0	12.3

$^2J_{CF(trans)} = 29.8$ Hz, and the energy differences in the solvents and couplings given in Table 5. The values of the remaining couplings for the two rotamers may be obtained from the linear relationships between the observed couplings (Table 3), to give for the $^4J_{HF}$ couplings, 5.19 Hz (*trans*) and 3.80 Hz (*cis*) and for $^1J_{CF}$ 179.0 Hz (*trans*) and 174.9 Hz (*cis*). The energy difference in the vapour phase compares well with that calculated by Gaussian 98 [3.21 kcal mol^{-1} (1 kcal = 4.184 kJ)].

The NMR data in Table 5 show that for FMB the *trans* rotamer is the most stable form in all solvents, a conclusion which is in agreement with the results from the FTIR spectra (Fig. 2). In non-polar and medium-polarity solvents [Fig. 2(a)–(d)] the carbonyl absortion is a single sharp band, whereas in a polar solvent (CH_3CN) [Fig. 2(e)] there is a shoulder at a higher frequency, which has been assigned to the *cis* form.[14] The predominance of the *trans* over the *cis* form is probably due to the steric repulsion between the methyl groups in the *cis* form.

1-Fluoro-3,3-dimethyl-2-butanone

The Gaussian 98 calculations show two stable rotamers in the vapour phase, *cis* and *trans*. The value of the $^2J_{CF}$ in the pure liquid (12.3 Hz) gives, with the data in Table 4, an interpolated value of 16.3 for the pure liquid relative permittivity. The NMR data in Table 4 can be combined with Eqn. (2) to search for the best solution for both the rotamer energy difference and the values of J_{cis} and J_{trans}. This gives $\Delta E^V = 1.80$ kcal mol^{-1}, $^2J_{CF(cis)} = 11.3$ Hz and $^2J_{CF(trans)} = 15.3$ Hz, and the energy differences and couplings given in Table 5. The values of the $^1J_{CF}$ coupling in the two rotamers may be obtained from the linear relationship between the observed couplings, to give $^1J_{CF(cis)} = 176.2$ Hz and $^1J_{CF(trans)} = 193.4$ Hz. The energy difference in vapour phase again compares very well with that calculated by Gaussian 98 (1.70 kcal mol^{-1}).

The NMR data in Table 5 show that for FDMB the *trans* rotamer is more stable than the *cis* rotamer in CCl_4 only ($\Delta E = 0.47$ kcal mol^{-1}), whereas in the other solvents the *cis* form is the most stable. These results are in agreement with the data from the FTIR spectra (Fig. 3) in solvents of varying polarity. In CCl_4 [Fig. 3(a)], two partially resolved carbonyl absorption bands, bearing almost the same intensity, are observed. Moreover, the higher frequency band (which has been assigned to the *cis* form)[14] has the greater intensity in the remaining solvents [Fig. 3(b)–(d)], indicating the predominance of the *cis* over the *trans* rotamer in these solvents. It has been shown[15] that the molar absorptivity is different for each rotamer, so the IR data cannot be used as a quantitative measure of the conformational equilibrium, but it does support the above analysis.

The results obtained for FDMB and FA[4] (Fig. 4) are very similar, with a population inversion from the *trans* to the *cis* rotamer in more polar solvents. FMB also shows a similar behaviour to FB[7] (Fig. 4), the *trans* rotamer predominating in all solvents. Hence both pairs of compounds show that the introduction of methyl groups at the α-carbon, further from the fluorine atom, does not lead to any significant effect in the rotational equilibrium. However, the introduction of a methyl group geminal to the fluorine atom (FB in comparison with FA and FMB in comparison with FDMB) shifts the equilibrium towards the *trans* rotamer even in more polar solvents.

These observations indicate that there are steric interactions in the *cis* rotamers between the acetyl methyl group and one α-methyl group in FB and two methyl groups in FMB. Moreover, there is steric repulsion between the methyl group geminal to the fluorine atom and the fluorine lone pairs, which now interact with the carbonyl group orbitals destabilizing the *cis* rotamer, shifting the equilibrium towards the *trans* rotamer. This destabilizing effect is clearly shown by the relative energies ($E_{cis} - E_{trans}$), in the vapour phase, which are 2.20 and 3.70 kcal mol^{-1} for FA[4] and FB[7] and 1.80 and 3.80 kcal mol^{-1} for FDMB and FMB.

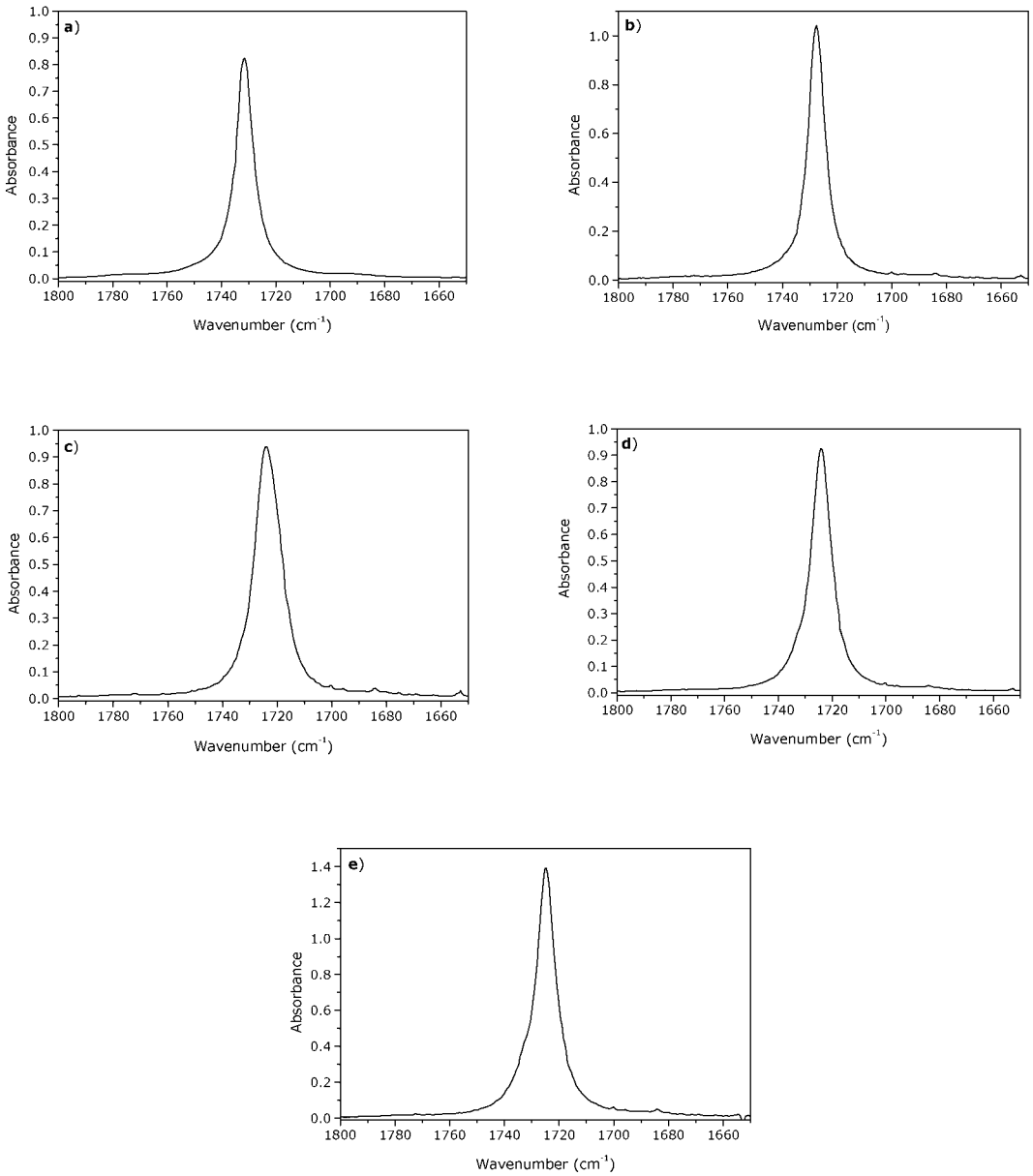

Figure 2. The carbonyl absorption band in the IR spectrum of FMB in (a) hexane, (b) CCl_4, (c) $CHCl_3$, (d) CH_2Cl_2 and (e) CH_3CN

The results of this work demonstrate that a geminal methyl group has a significant effect on the conformational equilibria of these α-fluoroketones.

CONCLUSION

NMR data, combined with solvation theory, provide a consistent analysis of conformational isomerism in FMB and FDMB in solvents of varying polarity. In FMB the *trans* rotamer predominates over the *cis* rotamer in all solvents, but in the FDMB the *trans* form prevails over the *cis* form only in CCl_4, whereas in more polar solvents the *cis* form is more stable than the *trans* form.

The predominance of the *trans* rotamer in FMB can be attributed to the steric effects between the two methyl groups, which tend to be as far apart as possible, while there are no significant steric effects in FDMB. Moreover, the conformational equilibrium displayed by FMB, which has a methyl group geminal to a fluorine atom, shows a marked resemblance to that of 3,3-difluorobutanone.[7] The latter exhibits just one stable conformer, the one with the methyl group *cis* to the carbonyl group, leaving the two methyl groups (C-1 and C-4) in a *trans* (or *anti*) arrangement.

It is noteworthy that FDMB presents a conformational behaviour similar to that of α-fluoroacetone,[4] for which there is no possibility of methyl group steric interactions from both sides of the carbonyl group.

It is also remarkable that no steric effect from a methyl

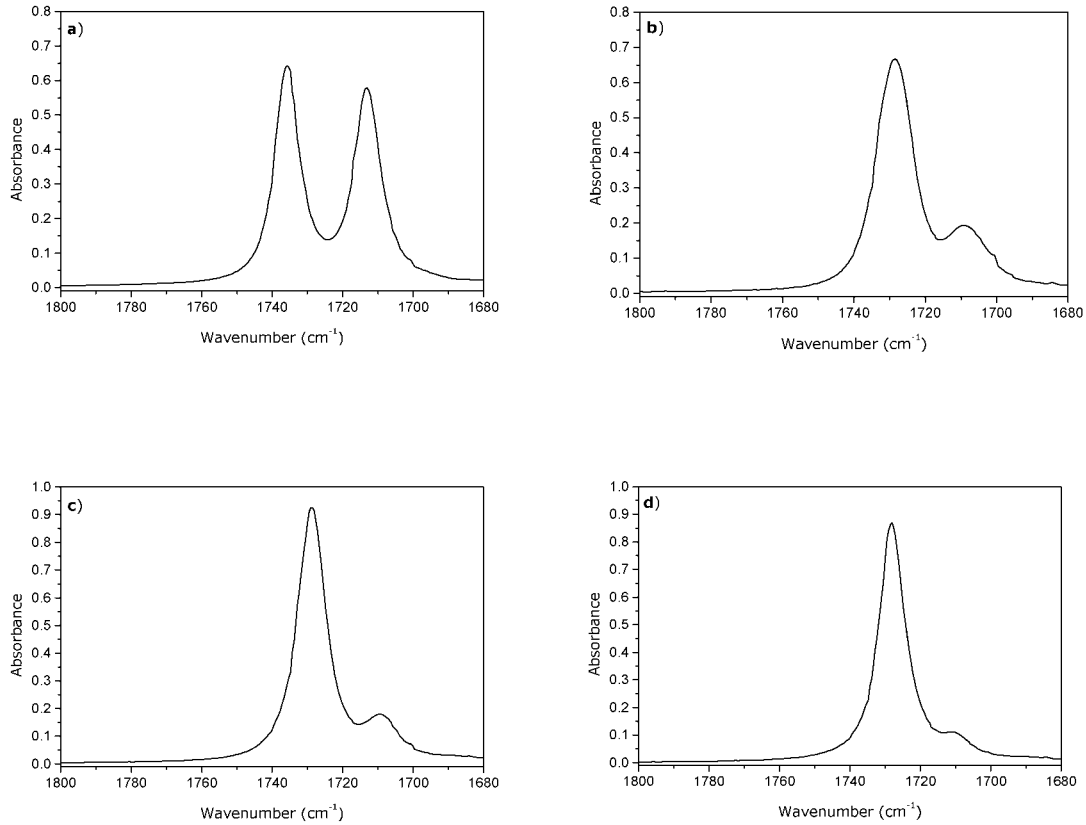

Figure 3. The carbonyl absorption band in the IR spectrum of FDMB in (a) CCl_4, (b) $CHCl_3$, (c) CH_2Cl_2 and (d) CH_3CN

group was observed in fluoroesters[12] and fluoroamides,[11] where the replacement of hydrogen by a methyl group did not lead to significant changes in their conformational equilibria.

EXPERIMENTAL

The solvents were obtained commercially, stored over molecular sieves and used without further purification. ^1H 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 ^1H and ^{13}C spectra were all referenced to internal Me_4Si. Typical conditions were proton spectra 48 transients, spectral width 2500 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 1024 transients, 3 μs pulse delay, spectral width 18 000 Hz with 64K data points and zero filled to 256K for 0.1 Hz digital resolution.

The spectra were all first order and the coupling constants and chemical shifts were taken directly from the spectra. The NMR data is presented in Tables 3 and 4.

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

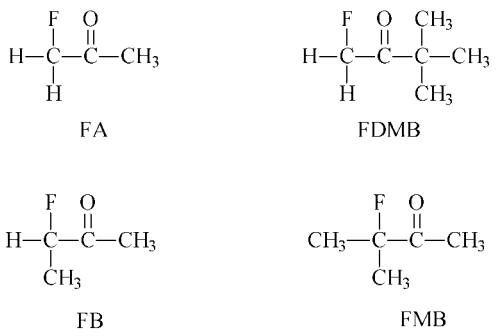

Figure 4. Structural formulae of fluoroketones

3-Bromo-3-methyl-2-butanone[16,17]. 3-Methyl-2-butanone (40.2 g, 0.467 mol) in diethyl ether (100 ml) was placed in a 250 ml three-necked flask equipped with a condenser, addition funnel and magnetic stirrer. Bromine (74.7 g, 0.467 mol) was added dropwise over a period of 60 min. The reaction mixture was washed with water (4 × 100 ml) and dried over $MgSO_4$. The solvent was

removed and the desired product was vacuum distilled through a Vigreux column to give pure 3-bromo-3-methyl-2-butanone (b.p. 64 °C/50 mmHg), yield 49.4 g (64.5%). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 2.4$ (s, 3H, CH_3), 1.8 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 203.5$, 63.7, 29.5, 24.1.

3-Fluoro-3-methyl-2-butanone[17,18]. The synthesis was carried out in a 250 ml three-neck flask, equipped with addition funnel, magnetic stirrer and a distillation column and condenser to remove the FMB immediately after its formation. 3-Bromo-3-methyl-2-butanone (74.0 g, 0.461 mol) was reacted with potassium bifluoride (52.8 g, 0.676 mol) in dry diethylene glicol (150 ml) at 170 °C. The low-boiling product immediately distilled over. The NMR spectrum of the distillate showed the correct pattern for FMB and indicated the presence of some impurity. Redistilation gave pure FMB, b.p. 88 °C, yield 11 g (23%). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 2.3$ [d, ^4J(H,F) = 5.0 Hz, 3H, CH_3], 1.4 [d, ^3J(H,F) = 21.5 Hz, 6H, $2CH_3$]. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 210.6$, 98.7, 24.5, 23.9.

1-Bromo-3,3-dimethyl-2-butanone[16]. Pinacolone (16.0 g, 0.16 mol) in diethyl ether (60 ml) was placed in a 150 ml three-neck flask equipped with a condenser, addition funnel and magnetic stirrer. Bromine (25.0 g, 0.16 mol) was added dropwise over a period of 60 min. The reaction mixture was washed with water (4 × 50 ml) and dried over $MgSO_4$. The solvent was removed and the desired product was vacuum distilled through a Vigreux column to give pure 1-bromo-3,3-dimethyl-2-butanone (b.p. 78 °C/4 mmHg), yield 18.5 g (65.0%). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 4.2$ (s, 2H, CH_2), 1.2 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 206.0$, 44.2, 31.7, 26.7.

1-Fluoro-3,3-dimethyl-2-butanone[18,19]. In a 250 ml three-neck flask, equipped with an addition funnel, magnetic stirrer and a distillation column and condenser to remove the FDMB immediately after its formation, potassium bifluoride (15.0 g, 0.252 mol) in dry diethylene glycol (150 ml) was heated at 200 °C and 1-bromo-3,3-dimethyl-2-butanone (30.0 g, 0.168 mol) was added dropwise. The low-boiling product immediately distilled over. The NMR spectrum of the distillate showed the correct pattern for FDMB and indicated the presence of some impurity. Redistilation gave pure FDMB, b.p. 125 °C, yield 8 g (40%). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 4.9$ [d, ^2J(H,F) = 47.7 Hz, 2H, CH_2], 1.1 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C, TMS): $\delta = 209.4$, 82.2, 42.7, 23.9.

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