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# Conformational analysis of fluoroacetoxime and of its *O*-methyl ether by $^{1}H$, $^{13}C$ and $^{15}N$ NMR and theoretical calculations

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ABSTRACT: The solvent dependence of the $^{1}H$, $^{13}C$ and $^{15}N$ NMR spectra of (*E*)-fluoroacetoxime [(*E*)-FAO] and of (*E*)-fluoroacetoxime *O*-methyl ether [(*E*)-FAOME], was examined and the HF, CF and NF couplings are reported. Density functional theory (DFT) at the B3LYP/6–311++g(2df,2p) level with ZPE (zero point energy) correction was used to obtain the rotamer geometries. In both (*E*)-FAO and (*E*)-FAOME the DFT method gave two energy minima corresponding to the *cis* (F—C—C═N, 0 °) and *gauche* (F—C—C═N, 124.1 °) rotamers. In contrast, in (*Z*)-FAO the DFT method gave only one energy minimum corrsponding to the *trans* rotamer. The $^{4}J_{HF}$ and $^{1}J_{CF}$ couplings in (*E*)-FAO were analyzed by solvation theory assuming the *cis* and *gauche* forms to give $E_{cis} - E_{gauche} = 3.3$ kcal mol$^{-1}$ in the vapor phase, decreasing to 1.54 kcal mol$^{-1}$ in $CCl_4$ and $-1.19$ kcal mol$^{-1}$ in DMSO (1 kcal = 4.184 kJ. In (*E*)-FAOME the observed couplings, when analysed similarly by solvation theory, gave $E_{cis} - E_{gauche} = 2.2$ kcal mol$^{-1}$ in the vapor phase, 0.91 kcal mol$^{-1}$ in $CCl_4$ and $-1.18$ kcal mol$^{-1}$ in DMSO. The $^{3}J_{NF}$ coupling was independent of the molecular conformation, as it did not change with the solvent polarity. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: $^{1}H$, $^{13}C$, $^{15}N$ NMR; conformations; fluoroacetoximes; solvation theory; theoretical calculation

## INTRODUCTION

Oximes constitute an important and very interesting class of organic compounds owing to their ambifunctional nucleophilic character and their biological properties. They are amongst the most useful and versatile synthetic intermediates in organic chemistry,[1,2] as nicely exemplified by the synthesis of several 5-substituted 2-acetylthiophenes.[3]

The introduction of a fluorine atom in oximes has led to compounds of tremendous interest in biological chemistry. The last three decades have seen increasing interest in fluorinated biological analogues in studies of metabolism and biosynthetic pathways and also in the pharmacological properties of fluoroximes.[4] Thus, selectively $\beta$-fluorinated $\alpha$-amino acids have been extensively explored as surrogate substrates for decarboxylases, racemases and transaminases, and other fluorinated amino acids which are assimilated biochemically into proteins.[5]

However, in contrast to fluoroacetone, its precursor, the conformational analysis of fluoroacetoxime (FAO) and of its *O*-methyl ether (FAOME) has been almost entirely neglected. Microwave,[6] IR, Raman and *ab initio* calculations[7] and a recent NMR, IR and theoretical investigation[8] have all shown that fluoroacetone has two stable rotamers, the *cis* (F—C—C═O, 0 °) and *trans* (F—C—C═O, 180 °). However, for the oxime (FAO) just qualitative (or semiquantitative) investigations have been reported[9,10] and none for the oxime *O*-methyl ether. An NMR and theoretical investigation[11] has shown that the conformational equilibrium of 2-methylcyclohexanone oxime and of its *O*-methyl ether is between the equatorial and axial conformers with $\Delta E_{eq-ax} = 0.88$ kcal mol$^{-1}$ for the oxime and 0.75 kcal mol$^{-1}$ (1 kcal = 4.184 kJ) for the methyl ether, in both polar (acetone) and non-polar ($C_2H_2Cl_4$) solvents.

We present here the conformational isomerism of fluoroacetoxime [Fig. 1(a)] and of its corresponding *O*-methyl ether [Fig. 1(b] by a combined theoretical, NMR and solvation technique, which has given good results for other systems.[8]

Oximes show strong intermolecular hydrogen bonding in non-polar solvents,[9,12] which affects the $^{1}H$ NMR chemical shifts.[13] The influence of this interaction on the conformational equilibrium, and on some selected coupling constants ($^{4}J_{HF}$, $^{1}J_{CF}$ and $^{2}J_{CF}$) was evaluated. The synthesis of FAO and FAOME gave the two geometric

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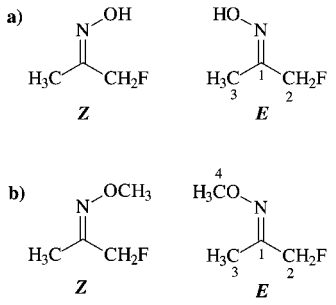


**Figure 1.** Geometric isomers for (a) FAO and (b) FAOME

isomers, *E* and *Z*, with more than 80% of the *E*-isomer. Sensitivity considerations meant that only the *E*-isomer could be studied by the solvation technique in which accurate values in the coupling constants are required.

Thus, the $^{1}H$ and $^{13}C$ NMR spectra, in different solvents, were obtained. Both the $^{4}J_{HF}$ and $^{1}J_{CF}$, couplings are sensitive to the F—C—C═N orientation. However, there are no reports regarding the use of the $^{3}J_{NF}$ coupling constant in conformation analysis, or if this coupling is sensitive or not to the F—C—C═N orientation. The use of density functional theory (DFT) calculations plus solvation theory[14] allowed us to define the interconverting rotamers in (*E*)-FAO and (*E*)-FAOME and hence to use the observed coupling constants to obtain the conformer energy differences in the vapor phase and in solution.

## THEORY

The *ab initio* study (DFT/B3LYP level) was performed through the Gaussian 98 program.[15] The solvation theory has been fully described elsewhere,[14,16] hence only a brief description is given here. The solvation energy of any molecule in state A is the difference between the energy in the vapor ($E_A^V$) and in any solvent ($E_A^S$) of relative permittivity $\varepsilon$. 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 into account the breakdown of the Onsager reaction-field theory in very polar media.[14] The input for the program is simply the dipole and quadrupole moments plus the solute radius and refractive index, both calculated by 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 $\Delta E^S$ ($E_A^S - E_B^S$), the energy difference in any solvent of given relative permittivity in terms of $\Delta E^V$ and calculable parameters. An accurate account of the solvent dependence of a variety of conformational equilibria is obtained.[8,16–20]

It should be noted that the calculated energies correspond to potential energy differences whereas the experimental results refer to free energies ($\Delta G$). However, the entropy value for the present system is negligible, hence $\Delta G = \Delta E$.

The calculations were performed with the MODELS program,[14] using as input the geometries from Gaussian. The dipole and quadrupole moments of the molecules were calculated directly from the partial atomic charges in the molecule, obtained from the CHARGE routine.[21]

## RESULTS

### Theoretical calculations

The potential energy surface (PES) for the *E*-isomer of fluoroacetoxime [(*E*)-FAO] (Fig. 2), at the B3LYP/6–31g(d,p) level showed two stable rotamers, *cis* and *gauche* (Fig. 3). The PES for the *E*-isomer of fluoroacetoxime *O*-methyl ether [(*E*)-FAOME] presents the same shape and the same stable rotamers. Their geometries and energies were optimized at the B3LYP/6–311++g(2df,2p) level with ZPE (zero point energy) correction and are given in Table 1. In contrast, similar calculations for the *Z*-isomer of FAO [(*Z*)-FAO] gave only one minimum at the *trans* form (F—C—C═N,

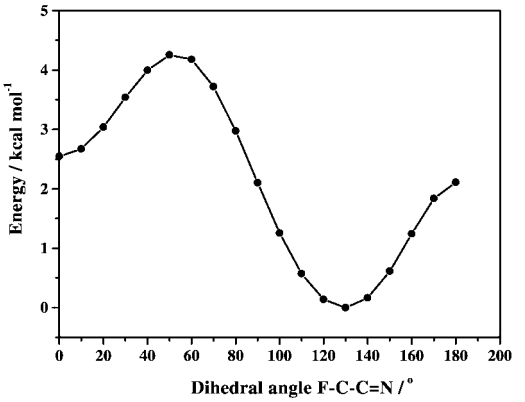


**Figure 2.** Potential energy surface for (*E*)-FAO

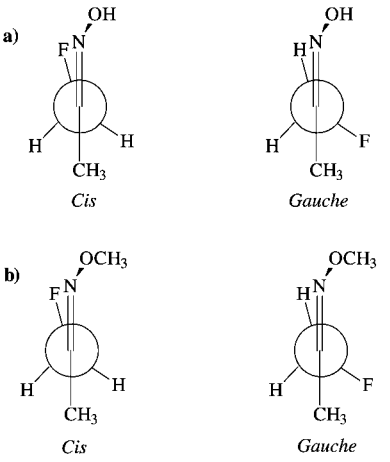


**Figure 3.** The *cis* and *gauche* rotamers for (a) (*E*)-FAO and (b) (*E*)-FAOME

**Table 1.** Calculated geometries [bond lengths (Å) and angles (degrees)], energies and dipole moments for (*E*)-FAO and (*E*)-FAOME at the B3LYP/6–311++g(2df,2p) level

| | (*E*)-FAO | | (*E*)-FAOME | |
|---|---|---|---|---|
| Parameter | *gauche* | *cis* | *gauche* | *cis* |
| *r*(C═N) | 1.274 | 1.269 | 1.276 | 1.271 |
| *r*(N—O) | 1.401 | 1.406 | 1.391 | 1.397 |
| *r*(C—C) | 1.498 | 1.501 | 1.498 | 1.501 |
| *r*(C—F) | 1.400 | 1.377 | 1.402 | 1.377 |
| *r*(O—H) | 0.962 | 0.961 | | |
| *r*(O—C) | | | 1.424 | 1.423 |
| *r*(C—H) | 1.091 | 1.092 | 1.090 | 1.091 |
| ∠(C—C═N) | 114.8 | 117.5 | 114.9 | 117.5 |
| ∠(C═N—O) | 111.9 | 112.9 | 112.2 | 113.1 |
| ∠ (N—O—H) | 102.8 | 102.2 | | |
| ∠(N—O—C) | | | 109.5 | 108.9 |
| ∠(F—C—C) | 109.8 | 113.5 | 109.8 | 113.5 |
| ∠(H—C—C) | 110.5 | 110.4 | 110.8 | 111.3 |
| θ(F—C—C═N) | 124.1 | 0.00 | 124.1 | 0.00 |
| θ(C═N—O—H) | 178.9 | 180.0 | | |
| θ(C═N—O—C) | | | 178.9 | 180.0 |
| $E_{rel}$ (kcal mol$^{-1}$) | 0.00 | 3.4 | 0.00 | 3.2 |
| μ (D) | 1.63 | 2.41 | 1.84 | 2.45 |

180 °) (Fig. 4). The *cis* form is at an energy maximum and is 8.2 kcal mol$^{-1}$ higher in energy. There is no other minimum, even when solvation effects are included in the calculations.

The DFT calculated dipole moments are 1.63 D (*gauche*) and 2.41 D (*cis*) for (*E*)-FAO and 1.84 D (*gauche*) and 2.45 D (*cis*) for (*E*)-FAOME. Using the DFT geometries, the CHARGE routine[21] gave as dipole moments 1.40 D (*gauche*) and 2.56 D (*cis*) for (*E*)-FAO and 1.42 D (*gauche*) and 2.76 D (*cis*) for (*E*)-FAOME. The DFT and CHARGE dipole moments are reasonably consistent, hence the partial atomic charges calculated through CHARGE may be used with confidence in the solvation calculations. The values of the solvation parameters are given in Table 2. The refractive index and molar volume were calculated by the program.

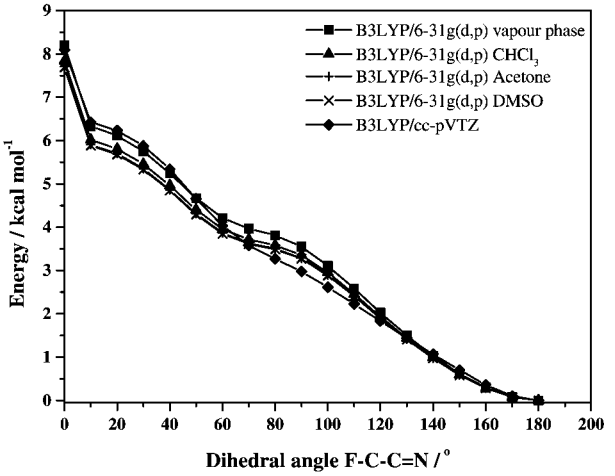


**Figure 4.** Potential energy surface for (*Z*)-FAO

## NMR data

The results from theoretical calculation can now be combined with NMR data and solvation theory to determine the rotamer populations in solution. The $^{1}$H, $^{13}$C and $^{15}$N NMR data (chemical shifts and coupling constants) for (*E*)-FAO and (*E*)-FAOME are given in Tables 3 and 4; the data for the corresponding *Z*-isomers are not included, owing to their low intensity. Although the use of $^{3}J_{HH}$ coupling (Karplus equation) in conformational analysis is well established,[22] this is not the case for the $^{4}J_{HF}$, $^{1}J_{CF}$ and $^{2}J_{CF}$ couplings measured here. Hence it is necessary to determine how much the observed changes in the coupling values are due to changes in conformer populations and how much to an intrinsic solvent dependence.

**Table 2.** Parameters for reaction-field calculations for (*E*)-FAO and (*E*)-FAOME

| Isomer | Rotamer | Dipole moment (D) | k (kcal mol$^{-1}$) | h (kcal mol$^{-1}$) | $n_D$ | $V_M$ | *l* |
|---|---|---|---|---|---|---|---|
| (*E*)-FAO | *gauche* | 1.40 | 0.9001 | 4.2003 | 1.3916 | 79.314 | 0.4758 |
| | *cis* | 2.56 | 3.0028 | 11.4761 | 1.3916 | 79.314 | 0.4758 |
| (*E*)-FAOME | *gauche* | 1.42 | 0.7430 | 2.6114 | 1.3945 | 98.100 | 0.4789 |
| | *cis* | 2.76 | 2.8352 | 6.8643 | 1.3945 | 98.100 | 0.4789 |

**Table 3.** Chemical shifts (ppm) and couplings constants (Hz) for (*E*)-FAO

| Solvent | δH | $\delta H_2$ | $\delta H_3$ | $\delta C_1$ | $\delta C_2$ | $\delta C_3$ | δN | $^{2}J_{HF}$ | $^{4}J_{HF}$ | $^{1}J_{CF}$ | $^{2}J_{CF}$ | $^{3}J_{CF}$ | $^{3}J_{NF}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CCl_4$ | 9.44 | 4.78 | 1.97 | 153.8 | 82.6 | 10.8 | −27.3 | 47.16 | 0.86 | 169.5 | 20.4 | 1.1 | 7.8 |
| $CDCl_3$ | 9.00 | 4.84 | 1.99 | 154.6 | 83.8 | 11.1 | | 46.90 | 0.90 | 168.2 | 19.4 | 1.3 | |
| $CD_2Cl_2$ | 9.00 | 4.84 | 1.97 | 154.8 | 83.8 | 11.0 | | 46.90 | 0.95 | 167.2 | 18.8 | 1.4 | |
| Pure liquid | 10.95 | 5.20 | 2.32 | 155.2 | 83.3 | 10.6 | −23.5 | 47.91 | 0.76 | 166.2 | 18.7 | 1.4 | 7.9 |
| Acetone-$d_6$ | 10.24 | 4.83 | 1.91 | 153.4 | 85.1 | 10.9 | −23.5 | 47.34 | 1.58 | 163.2 | 19.0 | 0.9 | 8.0 |
| $CD_3CN$ | 8.96 | 4.82 | 1.89 | 154.4 | 85.2 | 11.2 | | 47.16 | 1.46 | 163.0 | 18.7 | 1.1 | |
| DMSO-$d_6$ | 10.76 | 4.84 | 1.83 | 151.7 | 84.2 | 11.0 | −16.6 | 47.25 | 1.70 | 161.9 | 18.5 | 0.7 | 8.1 |

**Table 4.** Chemical shifts (ppm) and coupling constants (Hz) for (*E*)-FAOME

| Solvent | $\delta H_2$ | $\delta H_4$ | $\delta H_3$ | $\delta C_1$ | $\delta C_2$ | $\delta C_3$ | $\delta C_4$ | $\delta N$ | $^2J_{HF}$ | $^4J_{HF}$ | $^6J_{HF}$ | $^1J_{CF}$ | $^2J_{CF}$ | $^3J_{CF}$ | $^3J_{NF}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CCl_4$ | 4.72 | 3.83 | 1.88 | 151.6 | 82.7 | 61.9 | 11.1 | 0.9 | 47.34 | 1.10 | 0.73 | 168.2 | 20.6 | 1.1 | 7.7 |
| $CDCl_3$ | 4.81 | 3.89 | 1.93 | 152.7 | 83.5 | 61.8 | 11.5 | −1.6 | 47.07 | 1.15 | 0.60 | 166.8 | 19.6 | | 7.8 |
| $CD_2Cl_2$ | 4.79 | 3.86 | 1.90 | 152.9 | 84.0 | 61.9 | 11.5 | | 47.17 | 1.25 | | 165.7 | 19.2 | 0.9 | |
| Pure liquid | 4.89 | 3.91 | 2.02 | 152.9 | 83.9 | 61.5 | 10.9 | | 47.11 | 1.23 | 0.60 | 165.4 | 19.8 | 0.9 | |
| Acetone-$d_6$ | 4.83 | 3.83 | 1.88 | 153.3 | 84.4 | 61.9 | 11.5 | 1.2 | 47.17 | 1.40 | 0.66 | 164.0 | 19.0 | 1.1 | 7.8 |
| $CD_3CN$ | 4.81 | 3.84 | 1.88 | 153.5 | 84.4 | 61.9 | 11.4 | 0.2 | 47.05 | 1.38 | 0.70 | 163.6 | 18.7 | | 8.0 |
| DMSO-$d_6$ | 4.86 | 3.82 | 1.85 | 152.6 | 83.3 | 61.4 | 11.5 | −0.2 | 46.92 | 1.31 | 0.68 | 163.2 | 18.4 | | 8.0 |

**Table 5.** Chemical shifts (ppm) and coupling constants for (*E*)-TFAO

| Solvent | $\delta H_1$ | $\delta H_2$ | $\delta C_1$ | $\delta C_2$ | $\delta C_3$ | $^1J_{CF}$ | $^2J_{CF}$ |
|---|---|---|---|---|---|---|---|
| Acetone-$d_6$ | 11.62 | 2.01 | 145.7 | 122.0 | 8.8 | 271.1 | 32.1 |
| $CD_3CN$ | 10.01 | 1.97 | 147.1 | 120.5 | 8.9 | 271.1 | 32.2 |
| DMSO-$d_6$ | 12.39 | 1.95 | 144.0 | 121.0 | 8.8 | 271.3 | 31.5 |

This can be answered by comparing the observed changes with the solvent in (*E*)-FAO and (*E*)-FAOME (Tables 3 and 4) with those of 1,1,1-trifluoroacetoxime (TFAO) presented in Table 5, for which there is only one conformer, as can be concluded from its calculated PES and from the invariance of its coupling constants with the solvent. Moreover, the TFAO was obtained as a single configurational isomer (*E*-isomer). The $^1J_{CF}$ coupling in (*E*)-TFAO is essentially independent of the solvent, thus the large changes in these couplings for (*E*)-FAO (169.5 $\rightarrow$ 161.9 Hz) are appreciable but smaller changes for (*E*)-FAOME (168.2 $\rightarrow$ 163.2 Hz) may be attributed to changes in rotamer populations. An alternative method of testing whether the changes in the couplings are due to population changes only is simply to plot one variable against another. If the changes are due solely to population changes, the plots are linear.[8] This procedure showed that, for both (*E*)-FAO and (*E*)-FAOME, the $^1J_{CF}$ vs $^4J_{HF}$ plots are accurately linear (correlation coefficients 0.97), but this is not the case for $^2J_{CF}$. Therefore, we will consider only the $^1J_{CF}$ and $^4J_{HF}$ couplings.

The results in Tables 3 and 4 show that any intermolecular hydrogen bonding does not affect the coupling constants, because the values of $^1J_{CF}$ for (*E*)-FAO are very similar to those for (*E*)-FAOME, which cannot form a hydrogen bond. To test this result further, $^1H$ and $^{13}C$ NMR spectra in $CCl_4$ and DMSO were recorded for (*E*)-FAO, at different concentrations, and the results are shown in Table 6. The coupling constants do not change with concentration, hence no appreciable effect from a possible intermolecular hydrogen bond is observed in the (*E*)-FAO coupling constants.

It is also noted that the $^3J_{NF}$ couplings in (*E*)-FAO and (*E*)-FAOME (Tables 3 and 4) are almost constant in all solvents, indicating that this coupling is independent of the molecular conformation.

## (*E*)-Fluoroacetoxime

The theoretical calculations have shown that (*E*)-FAO occurs as two stable rotamers in the vapor phase, *cis* and *gauche*. The NMR data from Table 3 can now be combined with the solvation calculations via Eqn. (1), where $n_{cis}$ and $n_{gauche}$ are the mole fractions of the *cis* and *gauche* rotamers:

$$\begin{aligned} J_{obs} &= n_{cis}J_{cis} + n_{gauche}J_{gauche} \\ n_{cis} + n_{gauche} &= 1 \\ n_{cis}/n_{gauche} &= 1/2e^{(-\Delta E/RT)} \\ \Delta E &= E_{cis} - E_{gauche} \end{aligned} \quad (1)$$

In Eqn. (1), the statistical weight of two for the *gauche* rotamer is due to the occurrence of two mirror image

**Table 6.** Coupling constants (Hz) for (*E*)-FAO, in $CCl_4$ and DMSO-$d_6$, at different concentrations

| $CCl_4$ | | | | | | DMSO | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Concentration (mol $l^{-1}$) | $^2J_{HF}$ | $^4J_{HF}$ | $^1J_{CF}$ | $^2J_{CF}$ | $^3J_{CF}$ | Concentration (mol $l^{-1}$) | $^2J_{HF}$ | $^4J_{HF}$ | $^1J_{CF}$ | $^2J_{CF}$ | $^3J_{CF}$ |
| 0.079 | 47.1 | 0.84 | 169.6 | 20.4 | 1.26 | 0.099 | 47.2 | 1.72 | 161.7 | 18.4 | 0.9 |
| 0.190 | 47.1 | 0.84 | 169.6 | 20.2 | 1.26 | 0.187 | 47.2 | 1.72 | 161.7 | 18.5 | 0.9 |
| 0.306 | 47.1 | 0.80 | 169.6 | 20.2 | 1.26 | 0.286 | 47.2 | 1.71 | 161.7 | 18.5 | 0.8 |
| 0.382 | 47.0 | 0.84 | 169.6 | 20.1 | 1.26 | 0.359 | 47.2 | 1.71 | 161.7 | 18.5 | 0.8 |
| 0.469 | 47.0 | 0.84 | 169.5 | 20.1 | 1.26 | 0.460 | 47.2 | 1.72 | 161.6 | 18.4 | 0.9 |
| 0.577 | 47.0 | 0.84 | 169.5 | 20.1 | 1.27 | 0.571 | 47.2 | 1.72 | 161.7 | 18.4 | 0.8 |
| 0.788 | 47.0 | 0.84 | 169.4 | 20.1 | 1.26 | 0.756 | 47.2 | 1.72 | 161.7 | 18.4 | 0.8 |
| 0.950 | 47.0 | 0.84 | 169.3 | 20.1 | 1.26 | 0.963 | 47.2 | 1.72 | 161.7 | 18.4 | 0.8 |

**Table 7.** Conformer energy differences (kcal mol$^{-1}$) and observed and calculated couplings for (*E*)-FAO and (*E*)-FAOME

| | (*E*)-FAO | | | (*E*)-FAOME | | |
|---|---|---|---|---|---|---|
| | | $^1J_{CF}$ (Hz) | | | $^1J_{CF}$ (Hz) | |
| Solvent | $E_{cis}-E_{gauche}$ | Calc. | Obs. | $E_{cis}-E_{gauche}$ | Calc. | Obs. |
| $CCl_4$ | 1.54 | 169.6 | 169.5 | 0.91 | 168.2 | 168.2 |
| $CDCl_3$ | 0.58 | 168.4 | 168.2 | 0.15 | 166.8 | 166.8 |
| $CD_2Cl_2$ | 0.02 | 166.6 | 167.2 | 0.08 | 166.7 | 166.8 |
| Pure liquid | −0.11 | 166.1 | 166.2 | −0.28 | 165.6 | 165.7 |
| Acetone-$d_6$ | −0.58 | 164.1 | 163.2 | −0.73 | 164.3 | 164.0 |
| $CD_3CN$ | −1.01 | 162.4 | 163.0 | −1.05 | 163.4 | 163.6 |
| DMSO-$d_6$ | −1.19 | 161.8 | 161.9 | −1.18 | 163.1 | 163.2 |

forms. The value of the $^1J_{CF}$ in the pure liquid (166.2 Hz) gives, with the data from Table 3, an interpolated value of 11.8 for pure liquid relative permittivity.

The search for the best solution, for both the rotamer energy differences and the values of $^1J_{CF_{cis}}$ and $^1J_{CF_{gauche}}$, was performed through the program BESTFIT,[14] which calculates the couplings in all solvents through Eqn. (1), for any given value of $\Delta E^V$, using the solvation energy obtained from MODELS, and then compares the observed and calculated couplings. The best agreement was obtained with $\Delta E^V = 3.3$ kcal mol$^{-1}$, $^1J_{CF_{cis}} = 159.7$ Hz and $^1J_{CF_{gauche}} = 170.0$ Hz, with an r.m.s. error (observed—calculated couplings) of 0.5 Hz. The energy differences for each solution ($\Delta E^S$) and the couplings are given in Table 7. The value of the $^4J_{HF}$ coupling in the two rotamers may be obtained directly from the linear relationships noted earlier between the couplings in Table 3. This gives values of $^4J_{HF}$ of 1.94 Hz (*cis*) and 0.70 Hz (*trans*).

### (*E*)-Fluoroacetoxime *O*-methyl ether

The conformational analysis for this compound followed the same procedure. The $^1J_{CF}$ coupling again changes appreciably with solvent, owing to changes in the percentage of the *cis* and *gauche* rotamers. The best solution from BESTFIT for the rotamer energy difference and values of the conformer couplings was $\Delta E^V = 2.20$ kcal mol$^{-1}$, $^1J_{CF_{cis}} = 161.6$ Hz and $^1J_{CF_{gauche}} = 168.9$ Hz and using the linear relationships between the couplings gives $^4J_{HF}$ values of 1.50 Hz (*cis*) and 1.02 Hz (*gauche*). The error for the best solution is smaller than in the oxime, with an r.m.s. error (observed—calculated couplings) of 0.1 Hz. The energy differences in solution ($\Delta E^S$) and couplings are given in Table 7.

## DISCUSSION

The NMR data, combined with theoretical calculation and solvation theory, provide a consistent analysis of the conformational isomerism in (*E*)-FAO and (*E*)-FAOME in solvents of different polarity.

In (*E*)-FAO the isomerism is between the *cis* and *gauche* forms. The energy difference is 3.30 kcal mol$^{-1}$ in the vapor phase, which compares very well with that calculated (3.4 kcal mol$^{-1}$) by DFT at the B3LYP/6–311++g(2df,2p) level. In (*E*)-FAOME the isomerism is similar to that of (*E*)-FAO, and the observed energy difference of 2.2 kcal mol$^{-1}$ is also in fair agreement with that calculated (3.2 kcal mol$^{-1}$).

We noted earlier that hydrogen bonding usually affects proton chemical shifts,[13] and this is observed in the spectra of pure liquid (*E*)-FAO, in comparison with the data in solution (Table 3). However, it is noteworthy that similar changes do not occur for the coupling constants (Table 3), since no change was detected when the concentration was changed in non-polar and polar solvents (Table 6), and when the OH was replaced by $OCH_3$ to prevent the formation of hydrogen bonds (Tables 3 and 4).

In $\alpha$-fluoro ketones[8,16,19] and methyl fluoroacetate,[18] the stable rotamers are the *cis* and *trans* forms but for (*E*)-FAO and (*E*)-FAOME the stable rotamers are *cis* and *gauche*, which is analogous to the case of allyl fluoride.[23] Thus the rotational profile about the C—C bond of the F—C—C=O fragment differs markedly from that in the F—C—C=N and F—C—C=C fragments. A possible explanation is that it is due to a stereoelectronic $\pi$ interaction of the form $F^+—C—C—O^-$ moiety, which would be maximized in the planar *cis* and *trans* isomers. This interaction is much less effective in the nitrogen and carbon analogues as these atoms are less electronegative than oxygen. However, it is clear from the theoretical results for (*Z*)-FAO, in which the *trans* rotamer, but not the *cis*, is the stable form, that the rotational profile around the F—C—C=N bond is very finely balanced and depends crucially on both the orientation and the substituents on the nitrogen atom. It is of interest also that there is no evidence for intramolecular hydrogen bonding in (*Z*)-FAO as the *cis* form is at an energy maximum.

The $^1J_{CF}$ and $^4J_{HF}$ couplings for (*E*)-FAO are 159.7 and 1.94 Hz (*cis*) and 170.0 and 0.70 Hz (*gauche*) and for

(*E*)-FAOME 161.6 and 1.50 Hz (*cis*) and 168.9 and 1.02 Hz (*gauche*). In fluoroacetone, its precursor, $^1J_{CF}$ and $^4J_{HF}$ are 179.6 and 3.4 Hz (*cis*) and 188.0 and 5.0 Hz (*trans*). For the compounds studied here, the C═N group leads to smaller couplings than C═O (fluoroacetone), probably owing to a reduced interaction between the coupled nuclei in (*E*)-FAO and (*E*)-FAOME.

Theoretical data for (*Z*)-FAO and (*Z*)-FAOME gave only one minimum (Fig. 4) for the *trans* form (F—C—C═N, 180 °). The $^1$H and $^{13}$C NMR spectra in $CDCl_3$ for (*Z*)-FAO and (*Z*)-FAOME with several scans gave us the couplings for the *Z*-isomer. According to the theoretical calculation, we have only one stable rotamer in the vapor phase and in solution. Hence the observed couplings in the *Z*-isomer for (*Z*)-FAO ($^1J_{CF} = 169.7$ Hz) and for (*Z*)-FAOME ($^1J_{CF} = 169.2$ Hz) are due to the *trans* rotamer. The $^4J_{HF}$ couplings were not measured owing to the superimposition in the spectra with signals for the *E*-isomer.

We note that for (*E*)-FAO and (*E*)-FAOME $^4J_{HF}$ and $^1J_{CF}$ are dependent on the molecular conformation, but this is not the case with $^3J_{NF}$, which is independent of the conformation. It is well known that the internuclear couplings are electron coupled interactions[24] for which there are three possible mechanisms: (1) the nuclear moments interact with the electronic currents produced by the orbiting electrons; (2) there is a dipolar interaction between the nuclear and electronic magnetic moments; (3) there is an interaction between the nuclear moments and the electronic spins in s-orbitals, the so-called Fermi contact term.[24]

For all couplings involving hydrogen, the Fermi contact term is dominant, and the other terms may be neglected. Hence this term is dependent on the molecular conformation. Recent studies[25–28] using *ab initio* and DFT techniques to calculate the various contributions, such as Fermi contact (FC), paramagnetic spin–orbit (PSO), diamagnetic spin–orbit (DSO) and spin–dipolar (SD) for $J_{CH}$, $J_{CF}$ and $J_{HF}$ confirmed the predominance of the Fermi contact contributions and agreed with experiment[8,16–20,29] that these couplings are dependent on the molecular conformation. It is probable that for the $^3J_{NF}$ coupling the other contributions (PSO, DSO and SD) predominate and in this case the coupling is independent of the molecular conformation.

It is noteworthy that there is an apparent contradiction between our results and trends reported in the literature[30] for $^1J_{CF}$ couplings corresponding to a C—F bond placed $\alpha$ to a $\pi$-electronic system. Two competitive effects may operate on $^1J_{CF}$ couplings in FAO and FAOME: (a) the hyperconjugative interaction between the C—F bond and the $\pi$-electronic system and (b) the proximity of the N and F atoms.[30]

The absolute value of $^1J_{CF}$ is reduced when the interaction (a) is increased, wherear an increase of effect (b) may lead to an increase or decrease of the $^1J_{CF}$ absolute value, depending on the charge at the proximate atom (in this case for the *cis* conformer it should correspond to a decrease in the $^1J_{CF}$ absolute value). Apparently, for the reported oximes effect (b) predominates and, therefore, for the *gauche* conformer the absolute value of $^1J_{CF}$ coupling is larger than for the *cis* conformer, where effect (b) is relieved.

## EXPERIMENTAL

The solvents were obtained commercially, stored over molecular sieves and used without further purification. $^1$H, $^{13}$C and $^{15}$N NMR spectra were obtained on a Varian Gemini spectrometer operating at 300.06 MHz for proton, 75.45 MHz for carbon and 30.41 MHz for nitrogen. Proton and carbon spectra were of ca 20 mg ml$^{-1}$ solutions with a probe temperature of ca 25 °C. Benzene-$d_6$ was used for the deuterium lock signal for the $CCl_4$ solution and pure liquid. The $^1$H and $^{13}$C spectra were all referenced to internal TMS. Typical conditions for proton spectra were 48 transients, spectral width 4000 Hz, with 32K data points and zero filled to 128K to give a digital resolution of 0.06 Hz, and for proton-decoupled carbon spectra 1024 transients, pulse 45 °, relaxation delay 2.0 s, spectral width 25 000 Hz with 64K data points and zero filled to 256K for 0.1 Hz digital resolution.

The proton-decoupled nitrogen-15 spectra were obtained by applying a DEPT pulse sequence.[31] All spectra were acquired with a 10 mm tube, at natural abundance, with ca 300 mg of sample. Nitromethane was used as an external reference, in a capillary coaxial tube. Typical conditions were 4000 transients, spectral width 12 000 Hz with 64K data points and zero filled to 256K to give a digital resolution of 0.1 Hz. The spectra were all first order and the coupling constants and chemical shifts were taken directly from the spectra. The NMR data are presented in Tables 3–6.

*Fluoroacetoxime (FAO).* The synthesis was carried out in a 125 ml three-necked flask equipped with a magnetic stirrer and condenser. 1-Fluoroacetone (8.7 g, 0.114 mol), hydroxylamine hydrochloride (7.9 g, 0.114 mol) and sodium carbonate (6.04 g, 0.057 mol) were dissolved in methanol (20 ml) and water (40 ml) was added to the flask. Acetic acid was then added to the mixture with stirring to adjust the pH to 4.5 and the mixture was heated in a water-bath at reflux temperature for 2 h. After cooling, water (40 ml) and $CHCl_3$ (80 ml) were added to the solution. The organic phase was separated, washed with water (2 × 50 ml) and dried with magnesium sulfate. The solvent was evaporated and the residue was vacuum distilled through a Vigreux column to give pure 1-fluoroacetoxime (b.p. 68 °C/25 mmHg), yield 5.8 g (56%).[3] $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): *E*-isomer *E*, $\delta$9.0 (s, 1H, OH), 4.84 (d, 2H, $^2J_{HF} = 46.9$, $CH_2$), 1.99 (d, 3H, $^4J_{HF} = 0.90$, $CH_3$); *Z*-isomer, $\delta$ 9.0 (s, 1H, OH), 5.28 (d, 2H, $^2J_{HF} = 48.9$, $CH_2$).$^{13}$C NMR

(75 MHz, $CDCl_3$, 25 °C, TMS): *E*-isomer, $\delta$154.6 (d, $^2J_{CF} = 19.4$, C═N), 83.8 (d, $^1J_{CF} = 168.2$, $CH_2$), 11.1 (d, $^3J_{CF} = 1.3$, $CH_3$); *Z*-isomer, $\delta$157.3 (d, $^2J_{CF} = 23.2$, C═N), 78.8 (d, $^1J_{CF} = 169.7$, $CH_2$), 15.3 (d, $^3J_{CF} = 5.1$, $CH_3$).

*Fluoroacetoxime O-methyl ether (FAOME).* This compound was synthesized according to the procedure described above, replacing hydroxylamine hydrochloride by *O*-methoxylamine hydrochloride. The residue was vacuum distilled through Vigreux column to give pure fluoroacetoxime *O*-methyl ether [b.p. 84 °C; yield 4.4 g (56%)].[3] $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): *E*-isomer, $\delta$ 4.81 (d, 2H, $^2J_{HF} = 47.0$, $CH_2$), 3.89 (d, 3H, $^6J_{HF} = 0.6$, $OCH_3$), 1.93 (d, 3H, $^4J_{HF} = 1.15$, $CH_3$); *Z*-isomer, $\delta$ 5.18 (d, 2H, $^2J_{HF} = 48.2$, $CH_2$), 3.8 (s, 3H, $OCH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): *E*-isomer, $\delta$ 152.7 (d, $^2J_{CF} = 23.0$, C═N), 83.5 (d, $^1J_{CF} = 168.0$, $CH_2$), 61.8 ($OCH_3$), 11.5 (d, $^3J_{CF} = 5.5$, $CH_3$); *Z*-isomer, $\delta$ 155.6 (d, $^2J_{CF} = 23.0$, C═N), 78.8 (d, $^1J_{CF} = 169.2$, $CH_2$), 61.7 (s, $OCH_3$), 15.3 (d, $^3J_{CF} = 5.53$, $CH_3$).

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