PERKIN 2
COMMUNICATION

The preferred conformation of *N*-β-fluoroethylamides. Observation of the fluorine amide *gauche* effect

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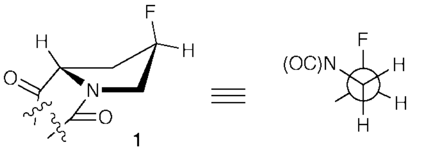
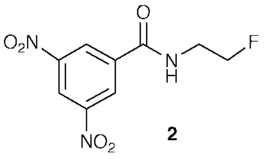
Experimental and theoretical data indicate a preferred conformation for *N*-β-fluoroethylamides in which the C–F and C–N(CO) bonds are *gauche* rather than *anti* to each other. Theoretical calculations on a model system predict the *gauche* conformation to be 1.8 kcal mol^{-1} lower in energy than the *anti* conformation. This compares with a value of 0.7 kcal mol^{-1} for the *gauche* effect in 1,2-difluoroethane.

The steric influence of a fluorine atom over a hydrogen atom in an organic compound is very small with the van der Waals radius of fluorine (1.47 Å) falling in between that of hydrogen (1.2 Å) and oxygen (1.57 Å).[1,2] Of course the replacement of C–H by C–F can change dramatically the electronic profile of a given compound. For example, we have recently demonstrated a strong conformational dependence for α-fluoroamides[3] where the C–F bond orientates *anti* to and planar with the C=O bond. In this Communication the conformational preference of *N*-β-fluoroethylamides is explored.



1

This study was stimulated by recent reports[4,5] which propose a *gauche* effect influencing the conformation of the pyrrolidine ring in synthetic peptide analogues of collagen containing the 4-fluoro-L-proline residue **1**. It was suggested[4] that the well known *gauche* effect,[6–8] where the C–F bonds of 1,2-difluoroethane prefer to be *gauche* rather than *anti* to each other, may be operating to hold the pyrrolidine ring in a C^{γ}*exo* puckered conformation. Thus, the electron deficient C–N bond replaces the second C–F bond of 1,2-difluoroethane, and the *gauche* effect is maintained. To explore this phenomenon further, an assessment of the preferred conformation of *N*-β-fluoroethylamides appeared appropriate as this system could exhibit the fluorine amide *gauche* effect, but importantly it is devoid of a ring template. Clearly there are inherent features of the five-membered ring in addition to the C–F bond, which may contribute stabilisation to an apparent *gauche* effect in **1**, and it was important to delineate these issues. The *N*-β-fluoroethylamides **2** and **3** were synthesised as model systems for X-ray structure analysis.



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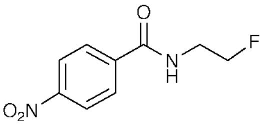

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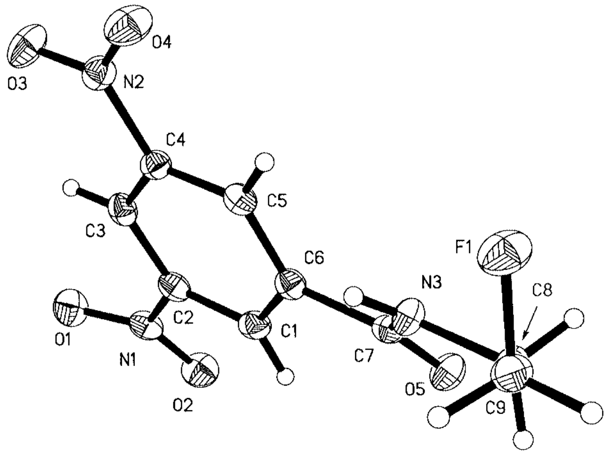

Fig. 1 Structure of **2**, viewed down the (F)–C–C bond, showing the *gauche* relationship between the C–F and C–N(CO) bonds.

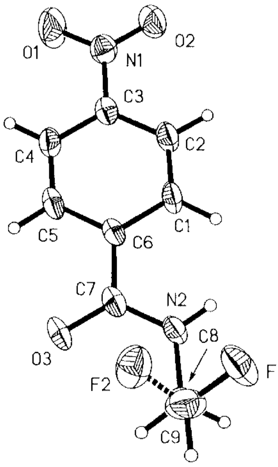

Fig. 2 The structure of **3**. The fluorine atom is disordered over two sites (F1, F2). The two fluorine atoms were refined anisotropically. The disordered hydrogen sites were positioned along the C–F bond vectors (C9–Hx 0.96 Å) and not refined.

Compounds **2** and **3** were prepared[9] by reaction of the corresponding acid chlorides with β-fluoroethylamine·HCl in an aqueous solution of potassium carbonate.† On purification both amides afforded crystals suitable for X-ray structure analysis. In the resultant structure of **2** (Fig. 1) the C–F and C–N bonds clearly adopt a *gauche* conformation with a dihedral angle of −63°. In the structure of **3** (Fig. 2) the fluorine and hydrogen atoms are disordered across two positions such that their bonds are superimposed; the two sites were modelled successfully with equal occupation. In both

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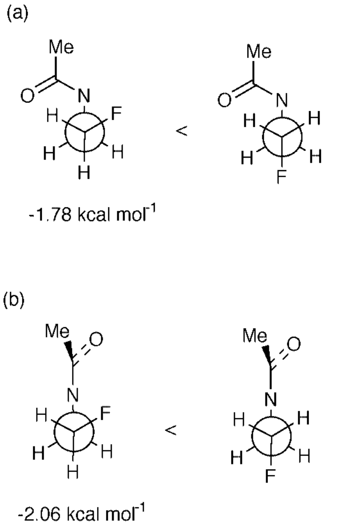
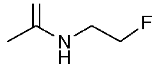


Fig. 3 Representations and relative energy differences of *gauche* and *anti* conformations of **4**. The structures in (a) were obtained from unconstrained geometry optimisations; those in (b) have the C=O bond constrained to be *anti* planar to the C–C(F) bond.



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orientations of the C–F bond the *gauche* relationship is maintained between the C–F and C–N bonds. Thus the X-ray structural data reveal a fluorine amide *gauche* effect in these amides in the solid state.

To quantify the magnitude of the *gauche* conformational preference, a theoretical study on the model *N*-acetyl-β-fluoroethylamine **4** was performed using Kohn–Sham density functional theory (DFT).[10] All calculations were performed with the CADPAC program,[11] using the B3LYP exchange-correlation energy functional[12] and the 6-31+G(d,p) basis set.[13] The calculated energy differences include zero-point vibrational corrections. To assess the quality of this level of theory, preliminary calculations were performed on the 1,2-difluoroethane molecule. Unconstrained geometry optimisations were performed to determine *gauche* and *anti* minimum energy conformations; the *gauche* conformation was predicted to be 0.74 kcal mol^{-1} lower in energy, in good agreement with the experimental value of 0.8 kcal mol^{-1}.[14] An unconstrained geometry optimisation was then performed to determine a *gauche* minimum conformation for the model system **4**. Based on this structure, a further unconstrained optimisation was performed to determine the analogous *anti* minimum conformation. These two conformations are represented in Fig. 3(a). The *gauche* conformation was found to be 1.78 kcal mol^{-1} lower in energy. Analysis of the calculated Mulliken charges highlights the electron withdrawing effect of the N(CO) group. The F and N atoms in the *gauche* conformation in Fig. 3(a) have charges of −0.34 and −0.37 electrons respectively. This compares with the F charges in 1,2-difluoroethane of −0.32 electrons. The comparison of *gauche* and *anti* conformations in **4** is more complicated than in 1,2-difluoroethane due to the additional flexibility arising from the NH(CO)–Me moiety. To assess the influence of the C=O orientation we performed additional calculations with the C–C–N–H, C–N–C–O, and C–C–N–C dihedral angles constrained at 0, 0, and 180° respectively as represented in Fig. 3(b). The *gauche* optimised conformation was again lower in energy, this time by 2.06 kcal mol^{-1}. Note, however, that in this case the conformations do not correspond to minima on the potential energy surface due to the dihedral constraints.

In summary it is shown that *N*-β-fluoroethylamides adopt a preferred conformation where the C–F and C–N(CO) bonds are *gauche* in the solid state. Calculations on a model system predict the *gauche* conformation to be 1.8 kcal mol^{-1} lower in energy than the *anti*. A knowledge of the stereoelectronic influence of the C–F bond in controlling peptide conformation could emerge as a valuable design tool in medicinal chemistry.

Acknowledgements

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Notes and references

† Selected analytical and spectroscopic data for **2** and **3**.

For **2**; mp 139–149 °C; δ_H(CDCl$_3$) 3.76 (2H, dq, $^3J_{H-F} = 27.9$ Hz, $^3J_{H-H} = 5.1$ Hz, NCH$_2$), 4.60 (2H, dt, $^2J_{H-F} = 47.3$ Hz, $^3J_{H-H} = 4.7$ Hz, CH$_2$F), 8.37 (1H, s, NH), 9.05 (2H, d, $^4J_{H-H} = 2.0$ Hz, H2), 9.12 (1H, t, $^4J_{H-H} = 2.0$ Hz, H4); δ_C(CDCl$_3$) 40.9 (1C, d, $^2J_{C-F} = 19.8$ Hz, NCH$_2$), 82.1 (1C, d, $^1J_{C-F} = 167.9$ Hz, CH$_2$F), 121.0 (1C, s, C4), 127.6 (2C, s, C2), 137.5 (1C, s, C1), 148.5 (2C, s, C3), 163.3 (1C, s, CO); δ_F (CDCl$_3$) −224.0 (1F, tt, $^2J_{H-F} = 47.2$ Hz, $^2J_{H-F} = 27.8$ Hz, CH$_2$CH$_2$F); *m*/*z* (EI): 257 ([M]$^+$ 18.5%), 237 ([M − HF]$^+$ 11.8%), 224 ([M − CH$_2$F]$^+$ 30.7%), 220 ([M − HF − OH]$^+$ 10.7%), 207 ([M − NO − HF]$^+$ 29.8%), 195 ([M − HNCH$_2$CH$_2$F]$^+$ 100%), 149 ([M − HNCH$_2$CH$_2$F − NO$_2$]$^+$ 39.0%), 103 ([M − HNCH$_2$CH$_2$F − 2(NO$_2$)]$^+$ 11.3%), 75 ([C$_6$H$_3$]$^+$ 44.7%) (Found C, 42.0; H, 3.1; N, 16.0. $C_9H_8N_3O_5$ requires C, 42.0; H, 3.1; N, 16.3%).

For **3**; mp 123–124 °C; δ_H (CDCl$_3$) 3.82 (2H, dq, $^3J_{H-F} = 28.4$ Hz, $^3J_{H-H} = 5.1$ Hz, NCH$_2$), 4.63 (2H, dt, $^2J_{H-F} = 47.3$ Hz, $^3J_{H-H} = 4.7$ Hz, CH$_2$F), 6.59 (1H, s, NH), 7.94–7.98 (2H, m, H2), 8.28–8.33 (2H, m, H3); δ_C (CDCl$_3$) 40.7 (1C, d, $^2J_{C-F} = 19.4$ Hz, NCH$_2$), 82.5 (1C, d, $^1J_{C-F} = 167.1$ Hz, CH$_2$F), 123.9 (2C, s, C3), 128.2 (2C, s, C2), 139.6 (1C, s, C1), 149.7 (1C, s, C4), 165.6 (1C, s, CO); δ_F (CDCl$_3$) −224.7 (1F, tt, $^2J_{H-F} = 47.2$ Hz, $^2J_{H-F} = 28.2$ Hz, CH$_2$CH$_2$F); *m*/*z* (EI): 212 ([M]$^+$ 12.7%), 193 ([M − F]$^+$ 5.8%), 192 ([M − HF]$^+$ 42.3%), 179 ([M − CH$_2$F]$^+$ 9.2%), 163 ([M − NO − F]$^+$ 8.6%), 162 ([M − NO − HF]$^+$ 60.4%), 151 ([M − NCH$_2$CH$_2$F]$^+$ 6.6%), 150 ([M − HNCH$_2$CH$_2$F]$^+$ 60.9%), 120 ([M − HNCH$_2$CH$_2$F − NO]$^+$ 5.5%), 104 ([M − HNCH$_2$CH$_2$F − NO$_2$]$^+$ 23.9%), 76 ([C$_6$H$_4$]$^+$ 32.2%), 46 ([NO$_2$]$^+$ 43.9%), 30 ([NO]$^+$ 100%) (Found: C, 50.7; H, 4.3; N, 12.8. $C_9H_9N_2O_3$ requires C, 51.0; H, 4.3; N, 13.2%).

Crystal data. ‡

2: $C_9H_8FN_3O_5$, $M = 257.18$, monoclinic, space group $P2_1/n$, $a = 10.114(2)$, $b = 4.824(1)$, $c = 20.996(4)$ Å, $\beta = 93.60(3)°$, $U = 1022.3(4)$ Å^3, $F(000) = 528$, $Z = 4$, $D_c = 1.671$ mg m^{-3}, $\mu = 0.149$ mm^{-1} (Mo-Kα, $\lambda = 0.71073$ Å), $T = 150.0(1)$ K. 6836 reflections were collected on a Bruker SMART CCD 1K diffractometer (ω-scan, 0.3° per frame) yielding 2331 unique data ($R_{int} = 0.0283$). The structure was solved by direct method and refined by full-matrix least squares against F^2. All non-hydrogen atoms were refined with ADP, H atoms were located from a difference Fourier map and refined isotropically. Final $wR_2(F^2) = 0.0969$ for all data (195 refined parameters) and $R_1 = 0.0387$ for 1875 reflections with $I \geq 2\sigma(I)$, GOF = 1.062, max. peak on the residual map is 0.3 e Å^{-3}.

3: $C_9H_9FN_2O_3$, $M = 212.18$, orthorhombic, space group $Pna2_1$, $a = 9.9569(3)$, $b = 20.4211(8)$, $c = 4.6421(2)$ Å, $U = 942.88(6)$ Å^3, $F(000) = 440$, $Z = 4$, $D_c = 1.493$ mg m^{-3}, $\mu = 0.126$ mm^{-1} (Mo-Kα, $\lambda = 0.71073$ Å), $T = 150.0(1)$ K. 11 457 reflections were collected on a Bruker SMART CCD 1K diffractometer (ω-scan, 0.3° per frame) yielding 2644 unique data ($R_{int} = 0.0465$). The structure was solved by direct methods and refined by full-matrix least squares against F^2. All non-hydrogen atoms were refined with ADP, H atoms were located from a difference Fourier map and refined isotropically. The fluorine atom is disordered over two sites (F(1) and F(2)) along with a hydrogen atom (H(98) and H(99)). The two fluorine atoms were refined anisotropically as half-occupied sites. The disordered H atoms were positioned along C–F bond vectors at 0.96 Å from the C(9) and not refined. Final $wR_2(F^2) = 0.1374$ for all data (185 refined parameters) and $R_1 = 0.0480$ for 1906 reflections with $I \geq 2\sigma(I)$, GOF = 0.909, max. peak on the residual map is 0.24 e Å^{-3}.

‡ CCDC reference number 188/223. See http://www.rsc.org/suppdata/p2/b0/b000205o/ for crystallographic files in .cif format.

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