COMMUNICATION

The preferred conformation of α-fluoroamides

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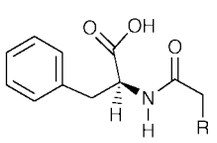
Received (in Cambridge, UK) 14th September 1999, Accepted 24th September 1999

X-Ray structures of two α-fluoroamide derivatives show the O=C–C–F moiety tending towards a *trans* planar conformation, for which *ab initio* calculations suggest a deep (up to 8 kcal mol^{-1}) potential minimum.

Fluorine substituents can have profound stereoelectronic and polar effects[1] on the conformation of organic molecules, *e.g.* the *gauche* effect in 1,2-difluoroethane[2] or the fluorine anomeric effect in α-fluoroethers.[3] With *one* fluorine substituent in the α-position to a carbonyl group, as in α-fluoroaldehydes,[4] α-fluoroketones[5] and α-fluoroesters,[6] the preferred conformation of the O=C–C–F moiety is *trans*-planar, but the energy difference between *cis* and *trans*-conformations is rather small (0.8–2.0 kcal mol^{-1}). For fluoroacetamide FCH_2CONH_2, MO calculations[7] suggest a much bigger difference, 7.5 kcal mol^{-1} in favour of the *trans*-disposition of the F and O atoms, which was actually found by X-ray[8] and neutron[7] diffraction studies (it is noteworthy that the parent acetamide adopts an entirely different conformation[9]). It could be expected therefore that introduction of an α-fluorine substituent into a substituted amide will stabilise the N–C(O)–C–F moiety in the conformation with the F atoms *trans* to the carbonyl and *cis* to the NH group. To verify this, we undertook the synthesis and X-ray structural and theoretical studies of mono-fluorinated compounds **1a** and **2**, and of non-fluorinated **1b** for comparison.†



1a R = F

1b R = Me

N-Fluoroacetyl-(*S*)-phenylalanine **1a**, the first *N*-fluoroacylated amino acid derivative, was prepared by coupling (*S*)-phenylalanine with the acid chloride of monofluoroacetic acid FCH_2COCl, and **1b** respectively with C_2H_5COCl. The X-ray structure of **1a** (Fig. 1) shows the C–F bond oriented nearly *cis* to the N–H and *trans* to the C=O bond, with the N(1)C(4)C(5)F torsion angle of −16.0(2)°. The entire HO_2C–C–NH–C(=O)–C–F moiety is roughly planar, with the torsion angles O(2)-C(1)C(2)N(1) −9.2(2)° and C(1)C(2)N(1)C(4) −162.2(1)°, compared to 151.6(2)° and −58.9(3)°, respectively, in **1b**. Thus, while in **1b** both the carboxy and the amide protons participate in *inter*molecular hydrogen bonds (Fig. 2), in **1a** only the former does, while H(1N) forms a bifurcated intramolecular hydrogen bond with F and O(2), at distances H···F 2.27(2) and H···O 2.29(2) Å.

α-Fluoropropionamide **2** was then studied, to establish whether the *trans* conformation is affected when a substituent is

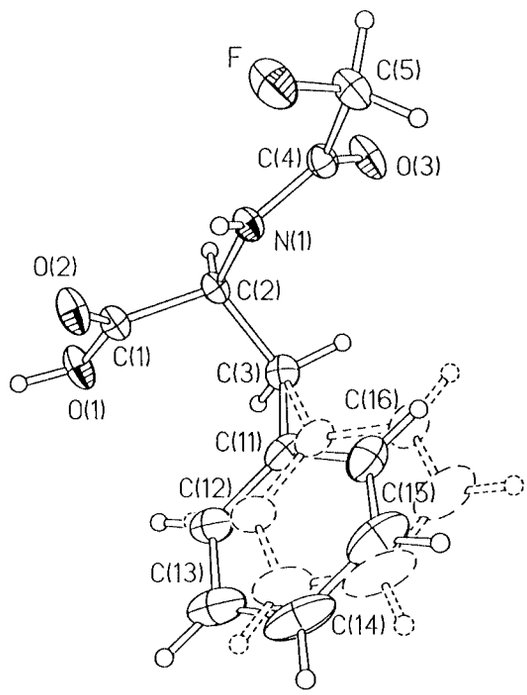


Fig. 1 Molecular structure of **1a** (50% thermal ellipsoids) showing disorder in the phenyl group.

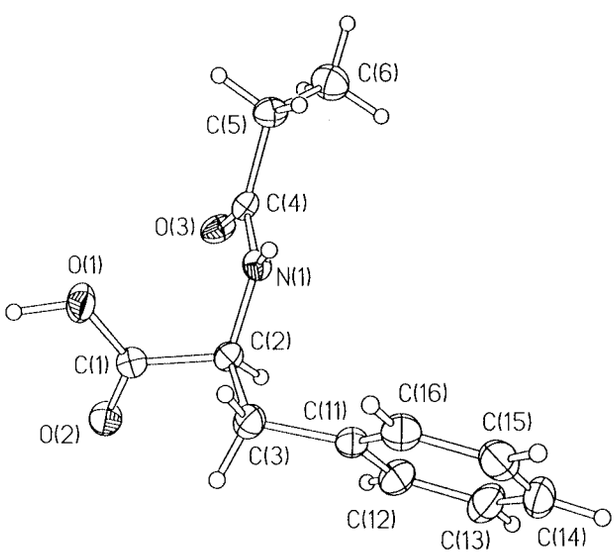


Fig. 2 Molecular structure of **1b**.

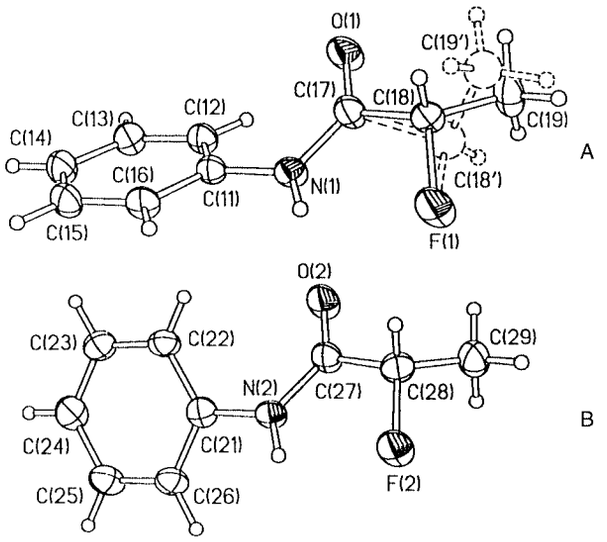
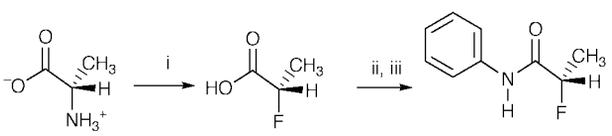


Fig. 3 An asymmetric unit in the structure of **2**, containing *S* (solid) and *R* (dashed) isomers.

attached to the fluoromethyl group. This amide **2** was prepared from (*S*)-alanine by a diazotisation reaction in the presence of hydrogen fluoride–pyridine[10,11] (see Scheme 1), whereby the

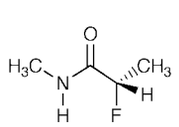


Scheme 1 i, $NaNO_2$, HF·pyridine (83%); ii, $SOCl_2$ (61%); iii, aniline (17%).

amino group is substituted by fluorine with predominant retention of the absolute configuration. The resultant α-fluoropropionic acid **3** comprised 90% of the (*S*) and 10% of the (*R*) enantiomer, as was assessed according to a previously described technique,[12] by ^{19}F NMR of its complex with a chiral base. By treating **3** with thionyl chloride, it was converted to its acid chloride, which was then coupled to aniline to generate **2**, which was characterised by its X-ray crystal structure.

The asymmetric unit of **2** (Fig. 3) contains two molecular sites, one of which (A) is occupied by 79(1)% of (*S*)-**2** and 21(1)% of (*R*)-**2** and the other (B) by the (*S*)-isomer only. Thus the overall (*S*/*R*) enantiomeric composition is *ca.* 9:1, in accordance with the NMR data. Molecule B retains the *anti* planar orientation of the C–F and C=O bonds, with the N–C(O)–C–F torsion angle of 9.9(4)°. At site A, this angle is increased to 24.5(5)° for the major (*S*) component and −35(1)° for the minor (*R*) one. This conformational distortion may be due to the peculiar crystal packing, required to accommodate both enantiomers at the same crystal site. Each molecule is linked with its own translational (along the *x* direction) equivalents by N–H···O hydrogen bonds of equal strength.

An *ab initio* analysis of *N*-methyl-2-(*S*)-fluoropropionamide **4** was carried out at the B3LYP/6-31G*(d) level using the



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GAUSSIAN98 program,[13] in order to quantify the dependence of the conformation on the F–C–C=O torsion angle (τ). The calculated energy profile (Fig. 4) shows a single distinct minimum at $\tau = 180°$ (C–F and N–H bonds eclipsed), the maximum at $\tau = 300°$ and a plateau at about $\tau = 60°$. The maximum is due

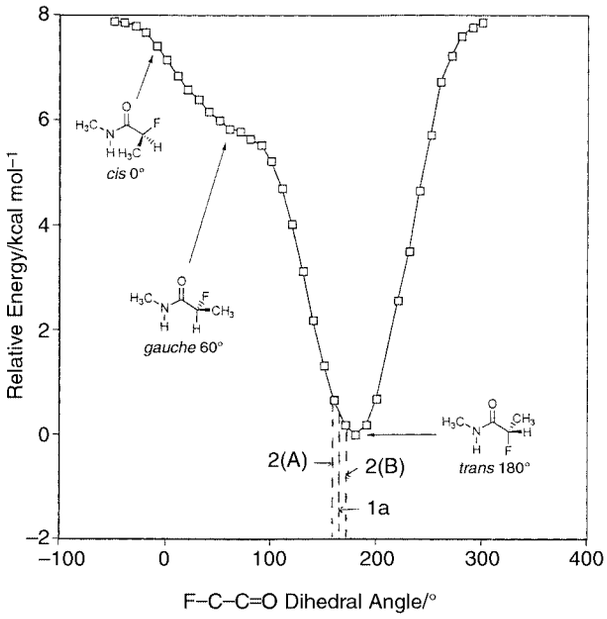

Fig. 4 Rotational energy profile of *N*-methyl-2-fluoropropionamide **4** monitoring rotation around the C–C(O) bond. *Ab initio* calculations were carried out at the B3LYP/6-31G*(d) level. Energies of conformations **1a** and **2** are indicated in the profile.

to H···H steric repulsions when the methyl group approaches N–H, the preferred methyl group location being in the hemisphere proximate to the carbonyl group. The plateau indicates some stabilisation of the *gauche* conformation, in which the C–H bond eclipses N–H. It is noteworthy that fluoroacetamide[7] shows a distinct potential minimum for this conformation, second deepest after that at $\tau = 180°$. The energy difference of *ca.* 7 kcal mol^{-1} between the *cis* ($\tau = 0$) and *trans* ($\tau = 180°$) conformers of **4** is similar to that in fluoroacetamide (7.5 kcal mol^{-1}) and at least four times greater in the other α-fluorocarbonyl systems studied earlier.[4–6] The stabilisation of the *trans* conformer is due mainly to the interaction between fluorine lone pairs and the N–H σ* orbital, which contributes 3.1 kcal mol^{-1}, according to NBO analysis[14] of the interaction energies. The rest of the energy difference is due to minor effects, *viz.* a greater interaction in the *trans* conformation between the C–F σ orbital and both the antiperiplanar C=O σ* orbital (1 kcal mol^{-1}) and the antiperiplanar methyl C–H σ* orbital (1 kcal mol^{-1}). The *trans* conformer also has the smaller dipole moment (2.1 D) since the C=O and C–F bond dipoles are opposed, compared to 4.8 D in the *cis* conformer where they re-inforce the charge separation.

It is important that the fluorine effect can *not* be explained simply by formation of an intramolecular hydrogen bond N–H···F, although the H(1N)···F distance observed in **1a** is typical for such bonds.[15,16] A survey of structural data[15,16] shows that a F atom bonded to carbon (in contrast with 'inorganic' fluorine) forms weak hydrogen bonds, *e.g.* 2.4 kcal mol^{-1} for $H_3CF \cdots HOH$ *vs.* 5 to 10 kcal mol^{-1} for H···O bonds.[15]

In general it has proven very difficult to prepare peptides containing α-fluorinated substituents within the amino acid residues, although there have been some limited successes[17,18] but clearly if synthetic methods were developed the current observations suggest that the substitution of the C–F bond into peptides could perhaps offer a valuable tool for controlling peptide conformation.

Notes and references

† X-Ray diffraction experiments on a Rigaku AFC6S 4-circle diffractometer (Cu-Kα radiation) for **1b** and **2**, SMART 1K CCD area detector diffractometer (Mo-Kα radiation) for **1a**; structure solution (direct methods) and least squares refinement (against F^2 of all data) with

SHELXTL software (G. M. Sheldrick, Bruker Analytical X-ray Systems, Madison, Wisconsin, USA, 1997). CCDC reference number 188/188.

1a: $C_{11}H_{12}FNO_3$, $M = 225.22$, $T = 120$ K, orthorhombic, space group $P2_12_12$ (No. 18), $a = 9.366(1)$, $b = 16.003(2)$, $c = 7.598(1)$ Å, $U = 1138.8(1)$ Å^3, $Z = 4$, $D_x = 1.314$ g cm^{-3}, $\bar{\lambda} = 0.71073$ Å, $\mu = 0.11$ mm^{-1}, 8013 reflections (2596 unique) with $2\theta \leq 55°$, 192 variables refined to $R = 0.032$ [2497 data, $I \geq 2\sigma(I)$], $wR(F^2) = 0.080$, $\Delta\rho_{max,min} = 0.19$, -0.24 e Å^{-3}. The phenyl ring disorder was rationalised as two positions (differing by an 18° libration) with 50% occupancies, which were refined with restraints to regular hexagonal ring and equal anisotropic ADP for two positions of each atom.

1b: $C_{12}H_{15}NO_3$, $M = 221.25$, $T = 150$ K, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 5.754(2)$, $b = 8.139(2)$, $c = 24.873(2)$ Å, $U = 1164.9(4)$ Å^3, $Z = 4$, $D_x = 1.262$ g cm^{-3}, $\bar{\lambda} = 1.54184$ Å, $\mu = 0.75$ mm^{-1}, 1899 reflections (1597 unique) with $2\theta \leq 150°$, 172 variables refined to $R = 0.036$ [1417 data, $I \geq 2\sigma(I)$], $wR(F^2) = 0.084$, $\Delta\rho_{max,min} = 0.15$, -0.15 e Å^{-3}. The absolute configuration was confirmed by anomalous scattering: Flack parameter $-0.16(33)$.

2: $C_9H_{10}FNO$, $M = 167.18$, $T = 150$ K, triclinic, space group $P\bar{1}$ (No. 1), $a = 5.367(1)$, $b = 8.821(4)$, $c = 9.893(3)$ Å, $\alpha = 106.65(2)$, $\beta = 101.84(2)$, $\gamma = 105.13(2)°$, $U = 412.8(2)$ Å^3, $Z = 2$, $D_x = 1.345$ g cm^{-3}, $\bar{\lambda} = 1.54184$ Å, $\mu = 0.87$ mm^{-1}, 1582 unique reflections with $2\theta \leq 150°$, 236 variables refined to $R = 0.043$ [1482 data, $I \geq 2\sigma(I)$], $wR(F^2) = 0.154$, $\Delta\rho_{max,min} = 0.22$, -0.29 e Å^{-3}. The absolute configuration was confirmed by anomalous scattering: Flack parameter 0.0(2).

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Communication 9/07452J