CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200313

Synthesis and Conformation of Fluorinated β-Peptidic Compounds

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Abstract: Experimental and theoretical data indicate that, for α-fluoroamides, the F–C–C(O)–N(H) moiety adopts an antiperiplanar conformation. In addition, a *gauche* conformation is favoured between the vicinal C–F and C–N(CO) bonds in *N*-β-fluoroethylamides. This study details the synthesis of a series of fluorinated β-peptides (**1**–**8**) designed to use these stereoelectronic effects to control the conformation of β-peptide bonds. X-ray crystal structures of these compounds revealed the expected conformations: with fluorine β to a nitrogen adopting a *gauche* conformation, and fluorine α to a C=O group adopting an antiperiplanar conformation. Thus, the strategic placement of fluorine can control the conformation of a β-peptide bond, with the possibility of directing the secondary structures of β-peptides.

Keywords: amino acids · conformation analysis · organofluorine · peptides · X-ray diffraction

Introduction

It has recently been reported that β-peptides, which differ only in the absolute configuration of a centrally located α-fluoro-β-homoalanine unit, adopt different secondary structures.[1] In particular, when the β-heptapeptide containing (2*R*,3*S*)-α-fluoro-β-homoalanine adopts an extended 3_{14}-helix the analogous peptide containing (2*S*,3*S*)-α-fluoro-β-homoalanine does not. In this case the peptide assumes a structure with two quasi-helical termini separated by a central turn with a ten-membered hydrogen-bonded ring. The difference in the two structures was attributed to the F–C–C(O)–N(H) moiety in both peptides adopting an energetically favourable antiperiplanar conformation between the C–F and C=O bonds.[2] This conformation is compatible, and in fact stabilises, the helical conformation observed for the former peptide. However, a helical structure for the latter peptide is incompatible with an antiperiplanar conformation between the C–F and C=O bonds. This energetic preference for the antiperiplanar conformation outweighs the benefits associated with complete helix formation, such as hydrogen-bonding and side-chain interactions; the result is a "bend" in the backbone. Thus, the introduction of a single fluorine into the backbone of a peptide can influence the secondary structure of peptides, in this case either to stabilise or disrupt a 3_{14}-helix. The thermodynamic advantage of forming a helix overcomes the conformational effect of the fluorine in β-peptides containing greater than thirteen residues. This results in the fluorine being 90° to the carbonyl oxygen, and helix formation occurring over the entire length of the peptide.[3]

In addition, Raines and co-workers have reported hyperstable analogues of collagen in which natural 4(*R*)-hydroxyproline residues are replaced with 4(*R*)-fluoro-L-proline (Flp).[4] The enhanced stability imparted by Flp is attributed to the *gauche* effect between the amide nitrogen and the fluorine, which dictates the pyrrolidine ring pucker and pre-organises the three main-chain torsion angles to facilitate triple helix formation.[5] This effect has been observed in a number of other structures that contain two vicinal electronegative substituents. For example, O'Hagan and colleagues have shown that the fluorine–amide *gauche* effect in *N*-β-fluoroethylamides is especially strong.[6] A theoretical analysis of *N*-β-fluoroethylamides revealed an energy difference of approximately 1.8 kcal mol^{-1} between the antiperiplanar and *gauche* conformations of the C–N and C–F bonds.

More detailed fundamental structural information on the secondary structure preferences of fluoro-substituted β-peptides is required if we are to better define and understand the influence of these fluorine stereoelectronic effects on peptide conformation. To date detailed X-ray data on the conformational effects associated with the C–F bond in fluoroamide structures have been largely limited to simple amides, or involve structures containing vicinal fluorine

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200313.

atoms.[2,6–7] In this study we report the synthesis and X-ray structure of a series of monofluorinated β-amino acids and peptides derived from them in order gain systematic insight into the associated conformational preferences. This is the first comprehensive study of this type and it helps pave the way for the design of β-peptides with predictable and controllable conformations. The effect of fluorine adds to our ability to control the conformation of peptides based on natural effects.

Results and Discussion

We chose to incorporate β-fluoroethylamine and α-fluoropropionic acid units into a variety of fluorinated and nonfluorinated β^2- and β^3-amino acids in order to investigate the influence of the fluorine conformational effects on the peptide backbone conformation (Figure 1). As discussed, these

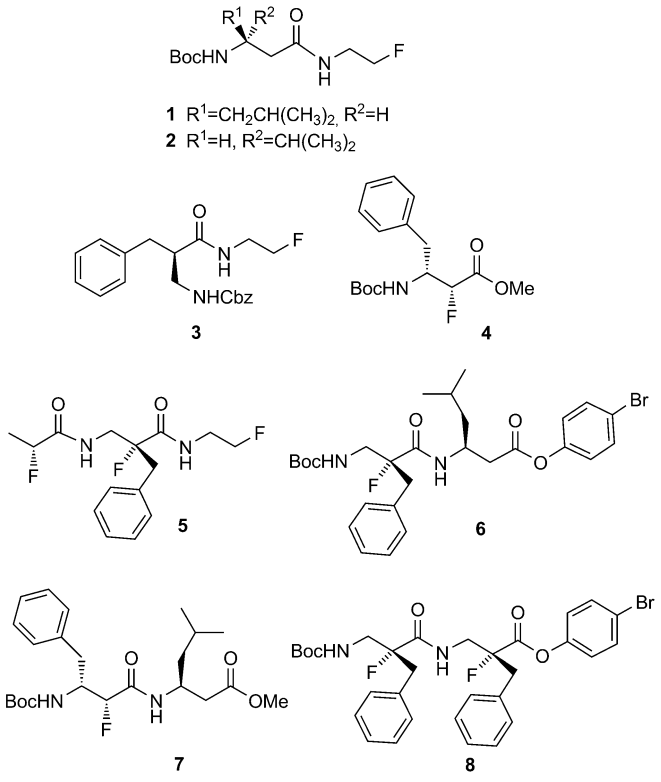


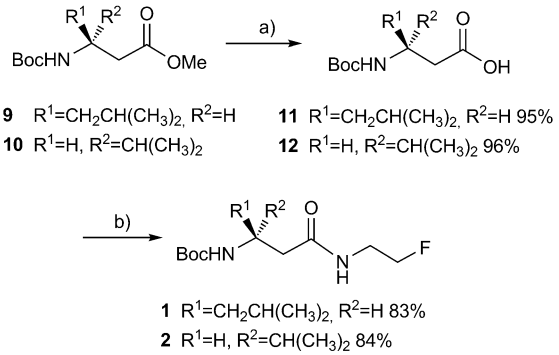
Figure 1. Target compounds.

two units have been reported to define *gauche* and antiperiplanar conformational preferences in simple fluoroamides, and as such provide a point of reference.[2,6]

Here we report the attachment of β-fluoroethylamine to β-amino acids to examine the *gauche* effect in peptidic *N*-β-fluoroethylamide. Both β^2- and β^3-amino acids (**3** and **1**–**2**, respectively) were used to investigate whether or not the position of the amino acid side chain influences the conformation of the fluoroamide backbone. A fluorine was also positioned β to a nitrogen and α to a C=O group in an α-fluoro-β-amino acid (see compound **4**). This combines the interactions present in both *N*-β-fluoroethylamides and α-fluoroamides into the one structure. The antiperiplanar preference of peptide-based α-fluoroamides was investigated by attaching α-fluoropropionic acid to α-fluoro-β^2-amino acid. The further attachment of β-fluoroethylamine to the C terminus resulted in compound **5**, which has two amide groups, each with two adjacent fluorine atoms, one positioned α to the carbonyl group, and the other β to the nitrogen of the amide. This derivative thus provides potential for a combination of both the antiperiplanar and *gauche* conformational effects to define the conformation of the constituent amides.

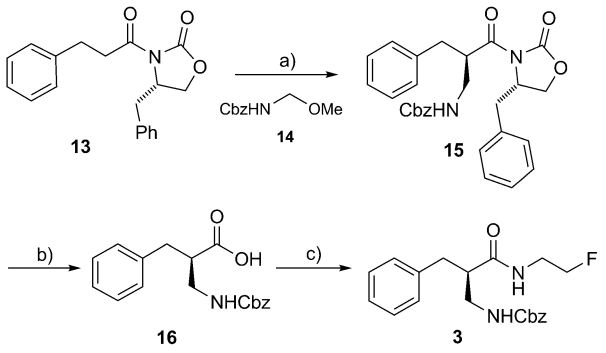
Dipeptides incorporating α-fluoro-β-amino acids were synthesised (see structures **6**, **7**, and **8**). Coupling an α-fluoro-β-amino acid unit to a second amino acid, as in **6** and **7**, provides an opportunity to define the influence on a true peptide bond. The dipeptide **8**, containing two α-fluoro-β^2-homophenylalanine units, was also investigated. The terminal amine in **8** is vicinal to fluorine, and the carbonyl of the bromophenyl ester is positioned α to fluorine. The conformational influence of fluorine on esters is known to be less pronounced than the corresponding amide.[8] This structure provides an example with a number of contributing conformational influences. The bromophenyl ester was introduced to facilitate crystallisation.

Synthesis: β-Fluoroethylamine·HCl was coupled to the β^3-amino acids, *N*-Boc-β^3hLeu-OH (**11**) and *N*-Boc-β^3hVal-OH (**12**), in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and *N*,*N*-diisopropylethylamine (DIPEA) to give **1** and **2**, respectively (Scheme 1).[9,10] Crystals of **1** and **2** suitable for X-ray crystallography were grown by slow evaporation in ethyl acetate. The acids **11** and **12** were conveniently prepared by hydrolysis of their corresponding methyl esters **9**[11] and **10**,[11] respectively.



Scheme 1. Reagents and conditions: a) LiOH, 3:1 MeOH/H_2O; b) β-fluoroethylamine·HCl, HATU, DIPEA, DMF.

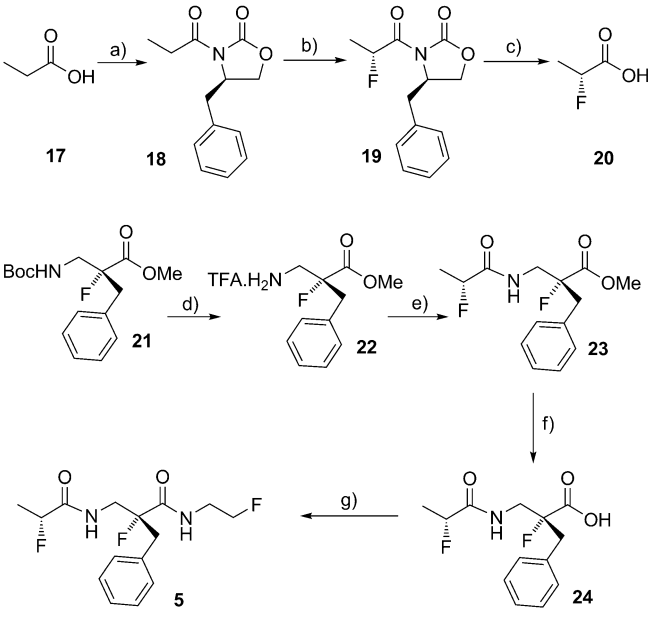
Derivative **3** was prepared as outlined in Scheme 2. The key synthesis precursor (β^2-amino acid **16**) was prepared by an initial diastereoselective aminomethylation of the Ti-eno-



Scheme 2. Reagents and conditions: a) $TiCl_4$, Et_3N, DCM, −20 °C, then $MeOCH_2NHCbz$ (**14**), $TiCl_4$, DCM, 0 °C, (42 %); b) LiOH, H_2O_2, 4:1 THF/H_2O, 0 °C to room temperature (62 %); c) β-fluoroethylamine·HCl, HATU, DIPEA, DMF (69 %).

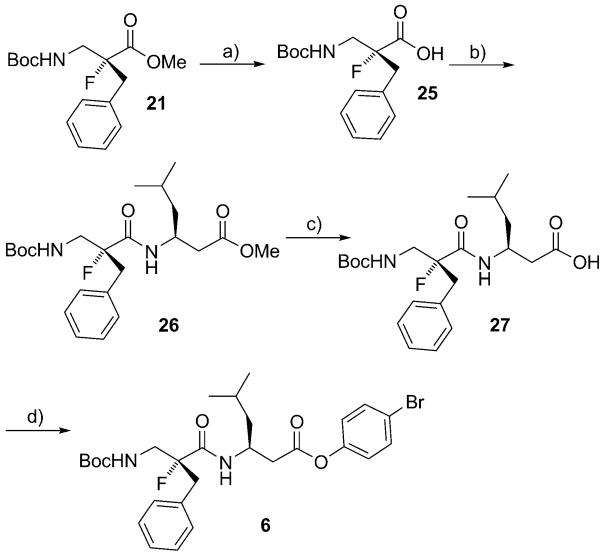
late of **13**[12] with benzyl *N*-(methoxymethyl)carbamate (**14**)[13] to give **15** in 42 % yield (>95 % *de* as determined by ^{1}H NMR spectroscopy).[14] Removal of the oxazolidinone auxiliary on treatment with LiOOH (formed in situ) gave **16** in 62 % yield. This acid was then coupled to β-fluoroethylamine·HCl, in the presence of HATU, to give **3** in 69 % yield. Crystals of **3** were grown by recrystallisation from petroleum ether/ethyl acetate.

The trifluorinated analogue **5** was prepared as shown in Scheme 3. The acid chloride of propionic acid **17** was treated with (4*R*)-4-benzyl-2-oxazolidinone to give the oxazolidinone **18** in 78 % yield. This was deprotonated with LDA and the corresponding enolate was treated with *N*-fluorobenzenesulfonimide (NFSI) to give **19** in 54 % yield and >95 % diastereometric excess, as determined by ^{19}F NMR spectroscopy. The bulky oxazolidinone chiral auxiliary of **19** was then removed on treatment with LiOOH to give the key starting material **20**. This acid was coupled with the amine salt **22** (prepared from **21**[15] as shown) in the presence of HATU, to give **23**. The methyl ester of **23** was hydrolysed, and the resulting acid **24** coupled to β-fluoroethylamine·HCl to give **5** in 47 % yield. Recrystallisation, by slow evaporation in ethyl acetate solution, gave crystals of **5** suitable for X-ray crystallography.



Scheme 3. Reagents and conditions: a) (4*R*)-benzyl-2-oxazolidinone, pivaloyl chloride, EtN_3, DMAP, THF, −78 to 0 °C (78 %); b) LDA, NFSI, THF, −78 to 0 °C (54 %); c) LiOOH, 4:1 THF/H_2O, 0 °C to room temperature (58 %); d) TFA, DCM (100 %); e) **22**, HATU, DIPEA, DMF, (35 %); f) LiOH, 3:1 MeOH/H_2O (99 %); g) β-fluoroethylamine·HCl, HATU, DIPEA, DMF (47 %).

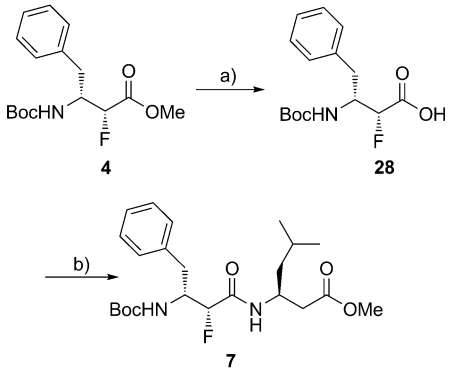
The α-fluoro-β^2-amino acid derivative **21** was also used to prepare **6** (Scheme 4). Hydrolysis of the methyl ester of **21**, with LiOH, gave the free acid **25** and this was coupled to H-β^3-hLeu-OMe,[11] in the presence of HATU, to give **26** in 72 % yield. The methyl ester of **26** was hydrolysed, and the resulting acid **27** was re-esterified with *p*-bromophenol to give **6** in 70 % yield. This material was crystallised from ethyl acetate to give crystals suitable for X-ray crystallographic analysis.



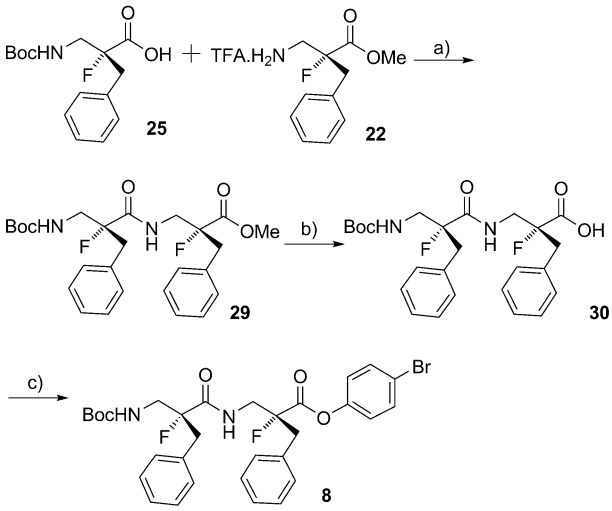
Scheme 4. Reagents and conditions: a) LiOH, 3:1 MeOH/H_2O (100 %); b) TFA-(*S*)-β^{3}hLeu methyl ester, HATU, DIPEA, DMF, (72 %); c) LiOH, 3:1 MeOH/H_2O (100 %); d) EDCI, DMAP, *p*-bromophenol, DCM (77 %).

Derivative **7** was prepared from α-fluoro-β^3-amino acid **4**[15] (Scheme 5). Ester hydrolysis of the α-fluoro-β^3-amino methyl ester **4** gave the acid **28** in 92 % yield. HATU-mediated coupling of this acid to H-β^3-hLeu-OMe[11] then gave the dipeptide **7** in 76 % yield. This dipeptide was recrystallised by slow evaporation in dichloromethane to give crystals suitable for X-ray crystallography.

The dipeptide **8**, consisting of two α-fluoro-β^2-amino acids, was prepared (Scheme 6). HATU mediated coupling of **22** with **25** (prepared as shown in Schemes 3 and 4, respectively) gave **29**. The methyl ester of **29** was hydrolysed on treatment with LiOH to give **30** and this was esterified



Scheme 5. Reagents and conditions: a) LiOH, 3:1 MeOH/H_2O (92%); b) H-β[3]hLeu-OMe, HATU, DIPEA, DMF (76%).



Scheme 6. Reagents and conditions: a) HATU, DIPEA, DMF, (79%); b) LiOH, 3:1 MeOH/H_2O (100%): c) EDCI, DMAP, *p*-bromophenol, DCM (43%).

with *p*-bromophenol to give **8** in order to aid the formation of single crystals suitable for X-ray crystallography.

Structure studies: X-ray crystal structures of compounds **1**–**8** were determined in order to define the associated conformational preferences, and also to confirm the relative stereochemistry.[15,16] The presence of a bromine, in compounds **6** and **8** allowed assignment of the absolute configuration of these compounds by using the Flack parameter.

The structures of **2**, **3** and **4** were obtained without disorder and with a single molecule in the asymmetric unit. However, the structure obtained for compound **1** had disorder in the amino acid side chain and three molecules in the asymmetric unit. The structure of **5** also contained disorder, in the *N*-β-fluoroethylamide group (Figure 2). The F3 fluorine on carbon 15 occupies three different positions in the crystal structure. The ratio for the three positions, F3A, F3B and F3C, is 0.387(4):0.268(16):0.345(16).

The X-ray crystal structures of **6** and **7** each contained two molecules in the asymmetric unit without disorder. The

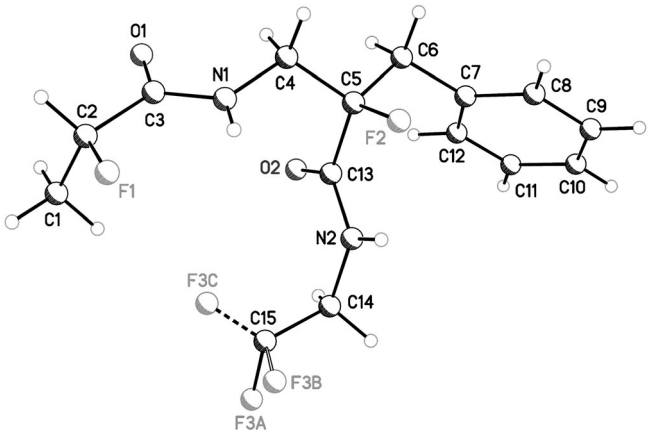


Figure 2. X-ray crystal structure of **5**. The disorder is shown by hollow and dashed bonds.

structure of **8** was obtained with disorder in the bromophenyl ring, with two different possible positions of its ring.

Torsion angles of the F–C–C–N(H) moiety: The crystal structures of **1**–**4** and **6**–**8** all reveal the F–C–C–N moiety in the expected *gauche* conformation for the C–F and C–N bonds as shown by the torsion angles in Table 1 and Table 2. The X-ray structure of **5** reveals disorder in the terminal F–C–C–N(H) moiety, without a preference for a particular conformation. Although literature indicates that the *gauche* conformation for the F–C–C–N(H) moiety is favoured over the *anti* conformation by 1.8 kcal mol^{-1},[6a] this small energy difference can be overcome by the crystal packing of **5** to

Table 1. Torsion angles of N–C–C–F in crystal structures with an internal fluorine.

Compound	N–C–C–F	Torsion angle [°]
4	N–C(6)–C(14)–F	61.5(2)
5	N(1)–C(4)–C(5)–F(2)	–73.7(6)
6a[a]	N(1A)–C(11B)–C(9A)–F(1A)	–73.9
6b[a]	N(1B)–C(11B)–C(9B)–F(1B)	–68.5
7a[a]	N(1A)–C(6A)–C(14A)–F(1A)	60.2(10)
7b[a]	N(1B)–C(6B)–C(14B)–F(1B)	62.3(10)
8	N(1)–C(6)–C(7)–F(1)	59.5(11)
	N(2)–C(16)–C(17)–F(2)	53.5(13)

[a] Refers to more than one distinct molecule in the asymmetric unit.

Table 2. Torsion angles of N–C–C–F in crystal structures with a terminal fluorine.

Compound	N–C–C–F	Torsion angle [°]
1a[a]	N(2A)–C(13A)–C(14A)–F(1A)	–69.9(8)
1b[a]	N(2B)–C(13B)–C(14B)–F(1B)	–70.1(8)
1c[a]	N(2C) –C(13C)–C(14C)–F(1C)	–70.3(9)
2	N(2)–C(12)–C(13)–F	71.7(8)
3	N(2)–C(19)–C(20)–F	–66.5(10)
5	N(2)–C(14)–C(15)–F(3A)	–178.4(10)
	N(2)–C(14)–C(15)–F(3B)	–78.4(13)
	N(2)–C(14)–C(15)–F(3C)	58.7(17)

[a] Refers to more than one distinct molecule in the asymmetric unit.

allow the fluorine to occupy all three possible positions. The terminal location of fluorine might be expected to result in a greater influence due to crystal packing forces. The internal F–C–C–N(H) moiety in **5** adopts the expected *gauche* conformation with a torsion angle of −73.7°. It might also be possible that additional dipole–dipole interactions within the molecule, due to the presence of the three C–F bonds, overrule the *gauche* effect in the terminal F–C–C–N(H) moiety.

Torsion angles of the F–C–C=O moiety: The crystal structures of **4**–**7** all show an antiperiplanar conformation between the C–F and C=O bonds, with torsion angles for F–C–C=O ranging from 172.4 to 179.7° (Table 3). The F–C–C=O torsion angle for the α-fluoroester in **8** was 154.5°. This slight deviation from the antiperiplanar conformation might be due to steric clash, between the phenyl rings of the bromophenyl ester and the phenylalanine side chain, overcoming the conformational preference. It is also important to note that the conformational preference for the C–F bond to be antiperiplanar to the C=O bond, a conformation in which the C–F dipole opposes the carbonyl dipole, is less pronounced for an α-fluoroester than an α-fluoroamide.[8] This is due to a reduced dipole moment for the ester carbonyl group. The energy difference between the *trans* and *cis* conformers for an ester is reported to be approximately 3–3.5 kcal mol^{-1} lower than for the corresponding amides.[8] Thus, the weaker antiperiplanar conformational preference of the α-fluoroester in **8** is likely overcome by steric effects and crystal packing. The α-fluoroamide moiety in **8** exhibited a classic antiperiplanar conformation between the C–F and C=O bonds, with a torsion angle for F–C–C=O of 177.3°.

Table 3. Torsion angles of F–C–C–O in crystal structures.

Compound	F–C–C=O	Torsion angle [°]
4	F–C(14)–C(15)–O(3)	174.8(2)
5	F(1)–C(2)–C(3)–O(1)	−172.4(6)
	F(2)–C(5)–C(13)–O(2)	−179.7(4)
6a[a]	F(1A)–C(9A)–C(8A)–O(3A)	177.6
6b[a]	F(1B)–C(9B)–C(8B)–O(3B)	179.4
7a[a]	F(1A)–C(14A)–C(15A)–O(3A)	−175.2(9)
7b[a]	F(1B)–C(14B)–C(15B)–O(3B)	−175.3(10)
8	F(1)–C(7)–C(15)–O(3)	177.3(11)
	F(2)–C(17)–C(25)–O(4)	154.5(12)

[a] Refers to more than one distinct molecule in the asymmetric unit.

There are other reports of X-ray crystal structures of backbone fluorinated peptidic compounds (Figure 3). O'Hagan has reported the synthesis and X-ray structures of the peptides **31** and **32** that contain 2,3-difluororosuccinic acid cores.[7a,b] Here different conformations were observed for the *syn* and *anti* vicinal fluorine stereochemistries. For the *syn* isomer (**31**) one α-fluoroamide group deviates from the expected antiperiplanar arrangement between the C–F and C=O bond to a similar extent to that seen for compound **8**. The F–C–C–O torsion angle was observed to be

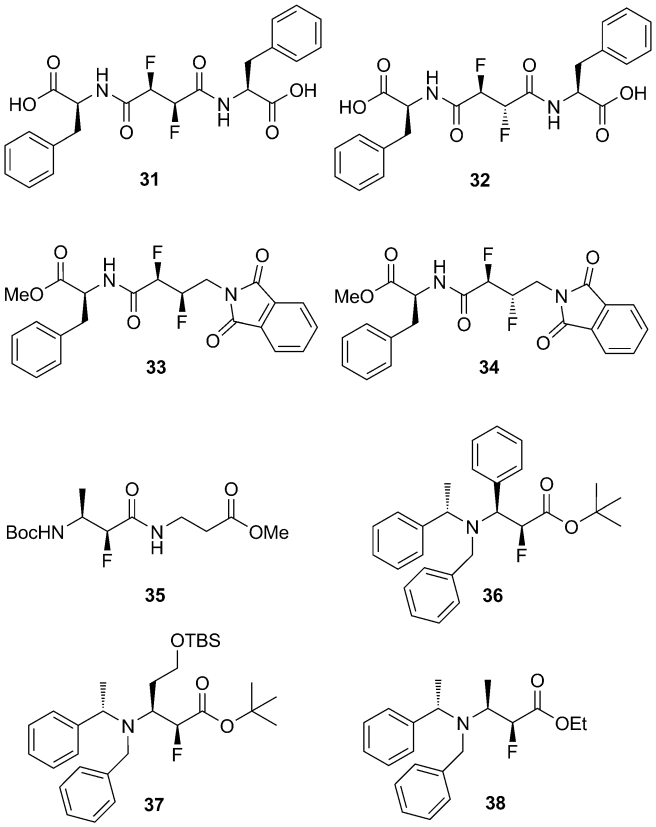


Figure 3. Literature backbone fluorinated peptidic compounds with X-ray crystal structures.

155.4(6)°, with distortion from the ideal antiperiplanar conformation being attributed to crystal packing interactions. In the crystal packing diagram the N–H group of the amide is involved in an intermolecular hydrogen bond with the carbonyl of another amide and this results in a small deviation from the ideal antiplanar geometry. Both the *syn* and *anti* isomers adopt the preferred *gauche* conformation between the two fluorine atoms, and in the *anti* isomer (**32**) both fluorine atoms align antiperiplanar to the amide carbonyls. To accommodate these conformational preferences the two diastereoisomers adopt very different backbone conformations; the *syn* isomer adopts an *anti*-zig-zag conformation, whereas the *anti* isomer has a bend in the carbon backbone.

Hunter et al. reported the stereoselective synthesis of *syn* and *anti* diastereoisomers of an α,β-difluoro-γ-amino acid, which were then incorporated into short peptides **33** and **34** (Figure 3).[7e] X-ray crystal structures of these peptides revealed different backbone conformations, within accordance with the known conformational effects of fluorine: the α-C–F bond aligns antiparallel to the adjacent amide carbonyl, the β-C–F bond is *gauche* to the vicinal γ-C–N bond, and the two vicinal fluorine atoms are *gauche* to each other. To maintain these conformations the diastereoisomers must adopt very different structures; the *syn* isomer forms an extended zig-zag structure, whereas the *anti* isomer has a bend in the carbon backbone.

The X-ray crystal structure of the Boc-β-dipeptide methyl ester containing an α-fluoro-β^3 homoalanine unit (**35**) reveals an antiperiplanar arrangement of the F and carbonyl atom with a torsion angle of 173.3°. In addition, the F–C–C–N torsion angle was observed to be −59.5°, as for a *gauche* conformation.[1c] This compound is very similar to **7** as both contain a *syn*-α-fluoro-β^3-amino acid attached to a β-amino acid, and both exhibit the expected conformations based on the conformational preferences seen in fluoroamide groups.

The crystal structures of α-fluoro-β-amino acids **36**, **37** and **38** have also been reported, with only **36** exhibiting the expected *gauche* conformation between the fluorine and amine nitrogen (F–C–C–N torsion angle of −53.0°).[17] The F–C–C–N torsion angle in **37** is −75.7°, a slight deviation from the *gauche* conformation, and −171.9° in **38**; this corresponds to an antiperiplanar arrangement between the fluorine and nitrogen. In all three structures, the α-fluoroester functionalities do not adopt the expected antiperiplanar arrangement between the C–F and C=O bonds. The F–C–C–O torsion angles were −2.8° and −11.9° for compounds **36** and **37**, respectively, showing synperiplanar arrangements, and 127.4° for compound **38**, an anticlinal conformation. These observations contrast with those obtained for the α-fluoro-β-amino acid **4**, which exhibits all the expected conformational preferences. The deviations from the expected conformations for **36**–**38** could be attributed to π stacking between the phenyl rings in the structures, and to the steric clash between the bulky groups in the molecules distorting the conformations.

The results in this study and comparison made with other literature reports shed further light on the backbone conformations of fluorinated peptidic compounds. The results also demonstrate that these conformations persist in the solid state as defined in X-ray crystal structures; the F–C–C(O)–N(H) moiety adopts an antiperiplanar conformation, and a *gauche* conformation is exhibited between the vicinal C–F and C–N(CO) bonds. However, these conformational preferences can be overridden by interactions in the crystal structure, such as crystal packing, steric interactions and hydrogen bonding.

Conclusion

A series of fluorinated β-peptides (**1**–**8**) were designed and synthesised to investigate how the associated stereoelectronic effects might influence the conformation of β-peptide bonds through the strategic placement of fluorine. X-ray crystal structures were obtained for eight compounds, with structures **1**–**4** and **6**–**8** all exhibiting the expected *gauche* conformation between the vicinal C–F and C–N bonds, and structures **4**–**7** showing an antiperiplanar conformation for the F–C–C(O)–N(H) moiety.

The reduced dipole moment for an ester carbonyl group, compared to an amide, results in a decreased preference for a C–F bond to be antiperiplanar to the C=O bond. This was apparent for the C-terminal ester of the α-fluoroester **8** exhibiting a torsion angle of 154.5° between the C–F and C=O bonds.

Thus, the conformational effects associated with fluoroamides can be used to control the conformation of peptide bonds in small fluorinated β-peptides. These studies are important to future efforts to exploit the biological properties of these structures, as conformation is implicitly linked to biological function.[18] This complements other approaches for controlling and influencing the conformation of peptides and peptidomimetics.[19]

Experimental Section

Synthesis: Detailed synthetic procedures for all compounds and characterisation data can be found in the Supporting Information.

X-ray diffraction analysis: Table 4 and Table 5 contain selected crystallographic data for compounds **1**–**8**. X-ray crystallographic data for **1**–**5**, **7** and **8** were collected on a Bruker APEXII diffractometer employing

Table 4. Crystal data for compounds **1**–**4**.

	1	**2**	**3**	**4**
formula	$C_{14}H_{27}FN_2O_3$	$C_{13}H_{25}FN_2O_3$	$C_{20}H_{23}FN_2O_3$	$C_{16}H_{22}FNO_4$
M_r	290.38	276.35	358.40	311.35
temperature [K]	133(2)	98(2)	133(2)	135(2)
crystal system	monoclinic	monoclinic	orthorhombic	orthorhombic
space group	*C*2	*C*2	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)
a [Å]	23.647(19)	21.349(5)	4.9335(19)	5.2431(2)
b [Å]	15.056(12)	5.0311(8)	10.106(7)	9.1728(3)
c [Å]	14.321(12)	15.514(3)	37.26(2)	33.9923(13)
α [°]	90	90	90	90
β [°]	90	109.19(2)	90	90
γ [°]	90	90	90	90
V [Å^3]	4955(7)	1573.7(5)	1857.6(18)	1634.82(10)
Z	12	4	4	4
ρ_{calcd} [g cm^{-3}]	1.168	1.166	1.282	1.265
μ [mm^{-1}]	0.089	0.090	0.093	0.098
crystal size [mm]	1.30×0.25×0.12	0.80×0.78×0.02	0.75×0.25×0.08	0.50×0.35×0.25
θ range	1.62 to 24.71	2.78 to 25.24	2.19 to 24.99	1.20 to 30.21
total reflns	11783	9940	3164	38535
independent reflns	4389 [R_{int} = 0.0867]	1584 [R_{int} = 0.2118]	1894 [R_{int} = 0.0840]	2805 [R_{int} = 0.0393]
max. and min. transmission	0.7456 and 0.4084	1 and 0.658196	1 and 0.018256	0.7460 and 0.6377
parameters	647	177	235	203
goodness-of-fit on F^2	1.015	0.931	1.009	1.210
$R(F)(I>2\sigma(I))$	0.1125	0.0628	0.0741	0.0372
$wR(F^2)$ (all data)	0.3941	0.1775	0.2204	0.1127
largest diff. peak and hole [eÅ^{-3}]	0.688 and −0.615	0.294 and −0.324	0.325 and −0.348	0.352 and −0.196

Table 5. Crystal data for compounds **5**–**8**.

	5	**6**	**7**	**8**
formula	$C_{15}H_{17}F_3N_2O_2$	$C_{28}H_{36}BrFN_2O_5$	$C_{23}H_{35}FN_2O_5$	$C_{31}H_{33}BrF_2N_2O_5$
M_r	314.31	579.50	438.53	631.50
temperature [K]	135(2)	100(2)	125(2)	125(2)
crystal system	monoclinic	orthorhombic	triclinic	orthorhombic
space group	*P*2(1)	*P*2(1)2(1)2(1)	*P*1	*P*2(1)2(1)2
a [Å]	10.946(3)	10.178(2)	5.1493(6)	10.5501(6)
b [Å]	5.1174(12)	20.341(4)	10.3220 (12)	53.765(3)
c [Å]	14.488(4)	27.274(6)	22.863(3)	5.1663(3)
α [°]	90	90	96.333(5)	90
β [°]	108.611(15)	90	92.157(8)	90
γ [°]	90	90	90.063(9)	90
V [Å^3]	769.1(3)	5647(2)	1206.8	2930.5(3)
Z	2	8	2	4
ρ_{calcd} [g cm^{-3}]	1.366	1.363	1.207	1.431
μ [mm^{-1}]	0.115	1.501	0.089	1.458
crystal size [mm]	0.57×0.10×0.03	0.10×0.01×0.01	0.51×0.09×0.01	0.78×0.07×0.05
θ range	2.97 to 25.00	1.96 to 26.66	0.90 to 23.25	0.76 to 25.10
total reflns	8096	25419	18132	36999
independent reflns	1506 [R_{int}=0.0835]	9090 [R_{int}=0.1054]	3478 [R_{int}=0.0954]	5186 [R_{int}=0.1282]
max. and min. transmission	0.7452 and 0.5710	n/a[a]	0.7456 and 0.5909	0.7460 and 0.2715
parameters	221	323	571	369
goodness-of-fit on F^2	0.929	1.077	1.110	1.169
$R(F)(I>2\sigma(I))$	0.0564	0.069	0.0936	0.1101,
$wR(F^2)$ (all data)	0.1567	0.1884	0.2589	0.2912
largest diff. peak and hole [eÅ^{-3}]	0.349 and −0.281	0.927 and −0.799	0.801 and −0.443	0.759 and −1.889

[a] Not available.

$Mo_{K\alpha}$ radiation (λ=0.71073 Å) with a graphite monochromator and CCD detector at the temperatures indicated in Tables 4 and 5.[20] Cell refinement and data reduction were undertaken with SAINT[20] and SADABS[21] for multiscan absorption correction. The structures were solved by direct methods by using SHELXS97,[22] and refined by full-matrix least squares calculations on F^2 by using SHELXL97.[22]

X-ray crystallographic data for **6** was collected on the MX2 beamline (λ=0.77345 Å) at the Australian Synchrotron, Victoria, Australia, at 100 K by using Blu-Ice software.[23] Cell refinement and data reduction were undertaken with XDS.[24] The structure was determined by direct methods by using SHELXS97, and refined by full-matrix least squares calculations on F^2 by using SHELXL97.

All H atoms bound to carbon were constrained to their expected geometries (C–H 0.98, 0.99, 1.00 Å). Methyl H atoms were refined with U_{iso}=1.5U_{eq}(C); all other H atoms were refined with U_{iso}=1.2U_{eq}(C,N). Hydrogen atoms on nitrogens in compound **6** were located from the difference maps and modelled with isotropic displacement parameters. A riding atom model was used for the remaining hydrogen atoms.

Acknowledgements

A.D.A. acknowledges financial support from the Australian Research Council (ARC). V.P. thanks the Tertiary Education Commission of New Zealand for funding. We also thank Dr. Graeme Gainsford and Dr. Matthew Polson (X-ray Crystallography), and Dr. Marie Squire (NMR spectroscopy and MS).

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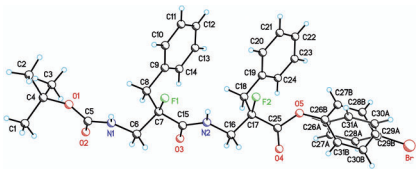
Received: January 29, 2012
Published online: ■■ ▮▮, 0000

Making moves: X-ray crystal structures were obtained for a series of α-fluoro-β-amino acids and small fluorinated β-peptides (see picture for an example). When fluorine was positioned α to a carbonyl group, the F–C–C=O moiety was found to adopt an antiperiplanar conformation; but when fluorine was positioned β to an amide nitrogen, a conformation in which C–F and C–N(CO) bonds are *gauche* was favoured.



Peptides

*V. Peddie, R. J. Butcher, W. T. Robinson, M. C. J. Wilce, D. A. K. Traore, A. D. Abell** ..... ▮▮▮▮–▮▮▮▮

Synthesis and Conformation of Fluorinated β-Peptidic Compounds