The Influence of Fluoroalkyl-Group Electronegativity on Stereocontrol in the Synthesis of Ψ[CH(R_F)NH]Gly Peptides

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Abstract: New peptidomimetics featuring CH(R_F)NH units, having different degree of fluorination, as peptide-bond surrogates have been synthesized. The key step in the synthesis consists of a stereoselective aza-Michael addition of chiral α-amino acid esters to β-fluoroalkyl-α-nitroethenes. The diastereoselection of the process was influenced by the electronegativity, rather than by the steric bulk, of the fluorinated residue R_F in β-position of the nitroalkene acceptors. Replacement of a single F atom of R_F by a hydrogen or methyl group brings about a dramatic drop of stereocontrol, whereas Br, Cl, and CF_3, albeit bulkier than F, provide poorer results in terms of stereocontrol.

Key words: peptidomimetics, fluorine, electronegativity, peptide bond surrogate, fluoroalkyl

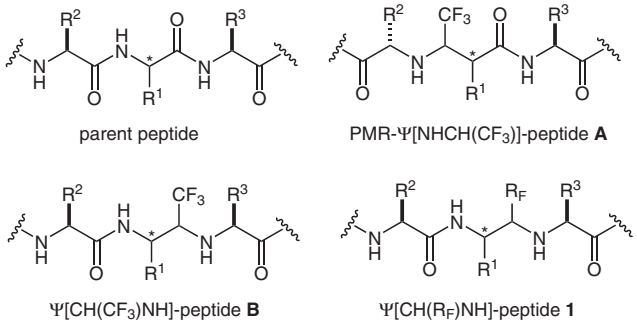

Figure 1 Structure of Ψ[CH(R_F)NH] peptides

Replacement of a scissile peptide bond by a surrogate function represents a viable and popular approach in the rational design of peptidomimetics[1] when: 1) the peptide bond surrogate is more stable to enzymatic hydrolysis than the native peptide bond;[2] 2) it is able to mimic either the original peptide bond or the transition state of amide-bond hydrolysis at the substrate cleavage site;[3] 3) it influences the conformational preference of contiguous residues; 4) modifying the electronic properties, the peptide-bond surrogate affects significantly the transport properties of the parent peptides.[4]

Recently, we proposed the trifluoroethylamino unit[5] as a peptide bond replacement, and we described its incorporation into partially modified retro (PMR)-peptides **A**[6] and into native peptide chains **B**[7] (Figure 1).

We also suggested that this unit might be seen as a hybrid between a peptide-bond mimic and a proteolytic transition-state analogue, as it combines some of the properties of a peptidyl CONH group [very low NH basicity, a CH(CF_3)NHCH backbone angle close to 120°, a C–CF_3 bond substantially isopolar with the C=O] with properties of the tetrahedral intermediate involved in the protease-mediated hydrolysis reaction of a peptide bond (high electron density on the CF_3 group, tetrahedral backbone carbon). Moreover, the presence of the bulky CF_3 group is probably the driving force for the high stability of turnlike conformation of appropriately configured retropeptides **A** both in low polarity organic-solvent solutions and in solid state. Recently, this conceptually new peptide bond surrogate has found the first validations in drug discovery.[8]

To investigate further the biomedicinal properties, as well as the effect and the capacity of the fluorinated residue to induce and stabilize secondary structures in peptide mimics, we undertook a research program aimed at the synthesis of Ψ[CH(R_F)NH]Gly peptides **1** (R = H) having different degrees of fluorination, namely $R_F = CF_2H$, CF_2CH_3, CF_2Cl, CF_2Br, and C_2F_5. Moreover, following the same synthetic strategy used for the synthesis of Ψ[CH(CF_3)NH]Gly peptides **B** ($R_F = CF_3$) from the nitroalkene **2** (Table 2),[7] we decided to investigate the role of the different fluorinated residues R_F on the diastereoselectivity of the key aza-Michael addition of α-amino acid esters **8** to β-fluoroalkyl-α-nitroethenes **3**–**7** (see Table 2). Clearly, the differences among the various R_F groups do not arise only from the different steric bulk (quantified here by means of the Bondi volumes) and shape of the R_F groups, but also from their electronegativities (Table 1).[9] More specifically, if one considers $R_F = CF_2X$, then the difference between the six R_F groups studied herein depends on the X substituent. Thus, in terms of electronegativity, the CF_3 group (X = F) is the most electronegative R_F group, followed by the C_2F_5 (X = CF_3), which in turn is more electronegative than the CF_2Cl (X = Cl) and CF_2Br (X = Br). The CF_2CH_3 (X = CH_3) and CF_2H (X = H) occupy the last positions of the list. Sterically, the C_2F_5 group is the bulkiest, followed by the CF_2Br, which in turn is only slightly bulkier than CF_2CH_3 and CF_2Cl, but remarkably bulkier than the CF_3 (X = F) and CF_2H, respectively. One should also note that the CF_3 is rotationally symmetrical around the axis of its C–C bond, in

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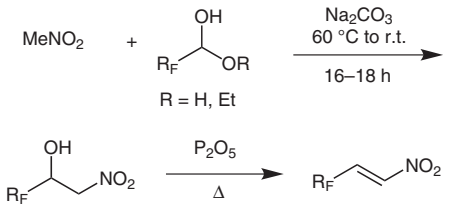
Table 1 Empirical Electronegativities and Bondi Volumes for X Substituents ($R_F = CF_2X$)

X Substituent	Electronegativity	Bondi volume (cm^3 mol^{-1})
H	2.28	3.3
CH_3	2.30	13.7
F	3.95	5.8
Cl	3.03	12.0
Br	2.80	15.1
CF_3	3.35	21.3

analogy with the CH_3 group, whereas the C_2F_5, CF_2Cl, CF_2Br, and CF_2CH_3 groups do not feature such rotational symmetry. In terms of 'effective bulk' the isotropic CF_3 is expected to occupy an even smaller volume than the anisotropic C_2F_5, CF_2Cl, and CF_2Br.[10] Thus, if steric bulk would be the dominating factor in the stereoselectivity of the aza-Michael reaction, one would expect a much higher diastereocontrol when R_F is a C_2F_5 or CF_2Br, rather than CF_3.

β-Fluoroalkyl-α-nitroethenes **2**–**7**, having CF_3, CF_2H, CF_2CH_3, CF_2Cl, CF_2Br, and CF_2CF_3 as R_F groups at the β-position, respectively, were prepared in multigram amounts by reacting the corresponding aldehyde hydrates or hemiacetals with nitromethane and a catalytic amount of Na_2CO_3 affording β-nitro alcohol intermediates that were dehydrated by refluxing in the presence of P_2O_5 (Scheme 1).[11]

The aza-Michael reactions between nitroalkene acceptors **3**–**7** and α-amino acid ester hydrochlorides **8a**–**d** were performed using the protocol previously optimized to achieve the best diastereoselectivity with **2**,[7] namely using 1.1 equivalents of DIPEA (the first equivalent is needed to quench the hydrochloric acid of **8**) in toluene at room temperature, producing a mixture of *syn*-**9** (major diastereoisomer) and *anti*-**10** (minor diastereoisomer),[12] which resulted to be easily separable by simple flash chromatography, in excellent overall yields (Table 2).



2: $R_F = CF_3$, 70%; **3**: $R_F = CF_2H$, 40%;
4: $R_F = CF_2Me$, 44%; **5**: $R_F = CF_2Cl$, 39%;
6: $R_F = CF_2Br$, 48%; **7**: $R_F = CF_2CF_2$, 37%

Scheme 1 Synthesis of nitroalkenes **2**–**7**

Under these conditions the diastereoselection of the process depends only on the nature of the R amino acidic side chain of **8**, and the fluorinated residue R_F on the nitroethene acceptors **2**–**7**. The results of the additions of **8a**–**d** to the trifluoro derivative **2** ($R_F = CF_3$) have been previously published,[7] and are summarized for the sake of comparison in entries 1–4 (Table 2).

When $R_F = CF_2H$ (nitroethene **3**, entries 5–8, Table 2), which is both the less electronegative and the least bulky R_F group among those examined herein, a dramatic drop of diastereoselectivity was observed in comparison with **2** ($R_F = CF_3$). The additions of the α-amino esters **8a**–**d** to **4** ($R_F = CF_2CH_3$, entries 9–12, Table 2) resulted in only slighly more diastereoselectivity than those obtained with **3** ($R_F = CF_2H$), and still much less diastereoselective than those with **2** ($R_F = CF_3$). Generally higher diastereoselectivities were observed with **5** ($R_F = CF_2Cl$, entries 13–16, Table 2) as the Michael acceptor, but still slightly worse as compared with those achieved with **2** ($R_F = CF_3$). The results obtained with the nitroalkene **6** ($R_F = CF_2Br$, entries 17–20, Table 2), were in all cases comparable with those of the nitroalkene **5** ($R_F = CF_2Cl$). To our surprise, even the diastereoselectivity of the reactions performed with the nitroethene **7** ($R_F = C_2F_5$, entries 21–24, Table 2), having the most sterically demanding R_F group (see Table 1), resulted less stereoselective than the reactions involving **2** ($R_F = CF_3$), and very similar to those obtained with the nitroalkenes **5** and **6** ($R_F = CF_2Cl$ and CF_2Br, respectively).

All these experimental results suggest that the diastereoselectivity of the aza-Michael reaction is much more influenced by the electronegativity of the β-fluoroalkyl substituents R_F, rather than by their steric bulk. In fact, the dramatic drop of diastereocontrol observed with the nitroalkene **3** ($R_F = CF_2H$) and **4** ($R_F = CF_2CH_3$) as compared with that featured by **2** ($R_F = CF_3$) cannot be explained in terms of steric bulk, as the CF_2H group is quite close in size to the CF_3 (their Bondi volumes are 18.8 vs. 21.3 cm^3 mol^{-1}, respectively) while the CF_2CH_3 group is much bigger (Bondi volume = 29.2 cm^3 mol^{-1}). Thus, the striking effect on the stereocontrol observed by replacing a single F atom of the nitroalkene **2** with an H atom in **3** and a CH_3 in **4** must be ascribed to the considerably higher electronegativity of F with respect to H and CH_3. On the other hand, the CF_3 group is 'smaller' than the CF_2Cl, CF_2Br, and, in particular, the C_2F_5 groups (see Table 1 and discussion thereof), therefore the decreased stereoselectivities observed with nitroalkenes **5**–**7** as compared with the CF_3-nitroalkene **2**, cannot be explained as well in terms of steric bulk. One should therefore notice that, within the set of nitroalkenes **2**–**7**, the trend of stereoselectivity **2** > **7** ≈ **5** ≈ **6** > **4** > **3** in the aza-Michael reaction matches quite well the trend of electronegativity of the X group in R_F ($R_F = CF_2$-X) namely F > CF_3 > Cl > Br > CH_3 ≈ H.

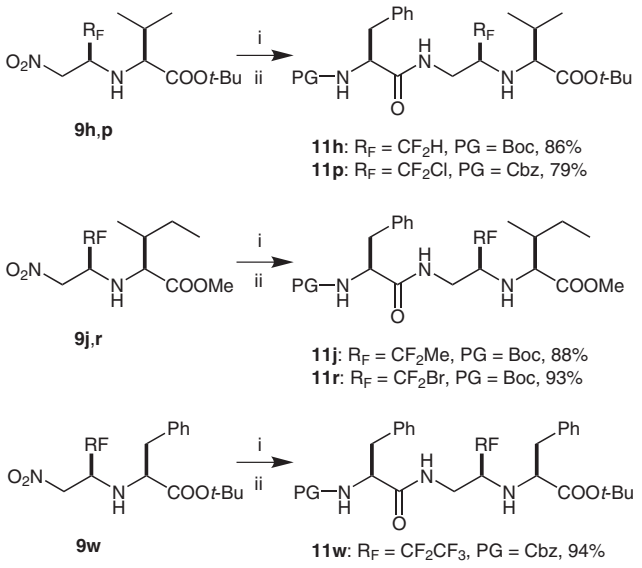
Table 2 The Aza-Michael Reaction

2–7 8 major **9** minor **10**

Entry	Nitroethene	R_F	α-Amino ester	Major product	R	X	Ratio **9/10**[b]	Yield (%)[c]
1[a]	**2**	CF_3	L-**8a**	**9a**	Me (Ala)	*t*-Bu	5.8:1.0	60
2[a]	**2**	CF_3	L-**8b**	**9b**	*s*-Bu (Ile)	Me	7.5:1.0	75
3[a]	**2**	CF_3	L-**8c**	**9c**	Bn (Phe)	*t*-Bu	8.5:1.0	60
4[a]	**2**	CF_3	L-**8d**	**9d**	*i*-Pr (Val)	*t*-Bu	11.7:1.0	65
5	**3**	CF_2H	L-**8a**	**9e**	Me (Ala)	*t*-Bu	1.1:1.0	77
6	**3**	CF_2H	L-**8b**	**9f**	*s*-Bu (Ile)	Me	1.4:1.0	96
7	**3**	CF_2H	L-**8c**	**9g**	Bn (Phe)	*t*-Bu	1.7:1.0	68
8	**3**	CF_2H	L-**8d**	**9h**	*i*-Pr (Val)	*t*-Bu	2.5:1.0	85
9	**4**	CF_2CH_3	L-**8a**	**9i**	Me (Ala)	*t*-Bu	2.3:1.0	80
10	**4**	CF_2CH_3	L-**8b**	**9j**	*s*-Bu (Ile)	Me	3.3:1.0	82
11	**4**	CF_2CH_3	L-**8c**	**9k**	Bn (Phe)	*t*-Bu	2.5:1.0	63
12	**4**	CF_2CH_3	L-**8d**	**9l**	*i*-Pr (Val)	*t*-Bu	4.2:1.0	74
13	**5**	CF_2Cl	L-**8a**	**9m**	Me (Ala)	*t*-Bu	4.0:1.0	74
14	**5**	CF_2Cl	L-**8b**	**9n**	*s*-Bu (Ile)	Me	8.8:1.0	69
15	**5**	CF_2Cl	L-**8c**	**9o**	Bn (Phe)	*t*-Bu	4.8:1.0	75
16	**5**	CF_2Cl	L-**8d**	**9p**	*i*-Pr (Val)	*t*-Bu	10.0:1.0	76
17	**6**	CF_2Br	L-**8a**	**9q**	Me (Ala)	*t*-Bu	4.2:1.0	77
18	**6**	CF_2Br	L-**8b**	**9r**	*s*-Bu (Ile)	Me	8.1:1.0	65
19	**6**	CF_2Br	L-**8c**	**9s**	Bn (Phe)	*t*-Bu	6.5:1.0	70
20	**6**	CF_2Br	L-**8d**	**9t**	*i*-Pr (Val)	*t*-Bu	10.3:1.0	93
21	**7**	CF_2CF_3	L-**8a**	**9u**	Me (Ala)	*t*-Bu	3.5:1.0	70
22	**7**	CF_2CF_3	L-**8b**	**9v**	*s*-Bu (Ile)	Me	8.1:1.0	66
23	**7**	CF_2CF_3	L-**8c**	**9w**	Bn (Phe)	*t*-Bu	5.9:1.0	74
24	**7**	CF_2CF_3	L-**8d**	**9y**	*i*-Pr (Val)	*t*-Bu	10.2:1.0	90

[a] See ref. 7.
[b] Determined by ^1H NMR and ^{19}F NMR.
[c] Overall isolated yields.

It is, in our opinion, quite remarkable that very subtle differences such as the presence of F instead of H, Cl, or Br in the R_F group of the nitroalkene acceptor bring about a striking effect in terms of stereocontrol of the process. Insufficient data exist at present to allow a detailed mechanistic discussion. However, based on the current experimental data, we can reliably assume that 1) the reaction is under kinetic control, 2) the amino ester nucleophile reacts with a rigid conformation due to the presence of an intramolecular hydrogen bond, 3) the fluorinated residue greatly stabilizes the LUMO of the nitroalkenes, making these Michael acceptors more electrophilic than the parent unfluorinated compounds, 4) the reaction involves a tight, polar transition state, which is destabilized and disrupted in polar solvents, decreasing the stereocontrol, and 5) the base DIPEA appears to play a fundamental catalytic role, presumably by promoting the formation of a ternary transition-state-involving nucleophile, Michael acceptor and amine base, in analogy with related processes we have studied in the recent past.[13] Clearly, these results demonstrate that electronic factors can overcome



Scheme 2 Elaboration of the aza-Michael adducts **9** into the targets peptidomimetics **11**. *Reagents and conditions*: i) H_2, $Pd(OH)_2$/C, aq HCl–MeOH; ii) PG-LPhe-OH, HATU and HOAt, TMP, DMF.

steric factors in the control of the diastereoselectivity of aza-Michael reactions.

Elaboration of the major adducts **9** into the target Ψ[CH(R_F)NH]Gly peptides **11** (Scheme 2) was addressed next. Reduction of the nitro group of **9** was accomplished by using Parlman's catalyst in the presence of aqueous 1 N HCl to trap the free amino function as hydrochloride salt. Coupling with Boc(Cbz)-L-Phe-OH using HOBt and EDC afforded Boc(Cbz)-L-Phe-Ψ[CH(R_F)NH]Gly-L-Val-O*t*-Bu (**11**), in very good yields.

In summary, a new class of peptidomimetics having diverse [CH(R_F)NH] functions as surrogates of the scissile peptide bond, namely Ψ[CH(R_F)NH]Gly peptides are now available. The aza-Michael addition of α-amino acid esters **8** to fluoroalkyl nitroethenes **2**–**7** represents the key synthetic step. The diastereoselectivity of this reaction, which was already known to be dependent on the base and its stoichiometry, solvent, temperature, and R side chain of **8**, resulted to be strongly influenced also by the electronegativity, rather than the steric bulk, of the fluorinated R_F group in β-position to the nitroethene acceptors. The synthesis of more complex Ψ[CH(R_F)NH] peptides and the study of their conformation in solution, as well as calculations and mechanistic studies, are currently being addressed.

Typical Procedure for the Michael Addition

To a stirred solution of **2** (0.76 mmol, 107 mg) and **8b** (0.51 mmol, 92 mg) in toluene (7 mL) at r.t., DIPEA was added (0.56 mmol, 73 μL). After 30 min at r.t., the solvent was removed in vacuo, the crude residue was dissolved in EtOAc, and washed once with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude was purified by flash chromatography (hexane–diisopropyl ether, 9:1) affording 110 mg (75%) of the two pure diastereoisomers **9b** (R_f = 0.31, *n*-hexane–*i*-Pr_2O, 7:3) and **10b** (R_f = 0.41, *n*-hexane–*i*-Pr_2O, 7:3), in a ratio of 7.5:1.0.

Typical Procedure for the Synthesis of the Fluorinated Tripeptide Mimics 11

A solution of **9p** (0.11 mmol, 33 mg) and 1 N HCl (0.11 mmol, 110 μL), in MeOH (2 mL) and in the presence of a catalytic amount of $Pd(OH)_2$/C, was stirred at r.t. for 5 h under hydrogen atmosphere. Then, the mixture was filtered on a Celite pad, the solvent removed in vacuo. The crude was dissolved in 1 mL of dry DMF and Cbz-L-Phe-OH, (0.11 mmol, 32.9 mg) followed by *sym*-collidine (0.22 mmol, 30 μL), HOAt (0.11 mmol, 14.9 mg), HATU (0.11 mmol, 41.8 mg) were added at r.t. The mixture was stirred overnight, quenched with 1 N HCl, and extracted with Et_2O. The organic layer was washed once with H_2O and then dried on Na_2SO_4. The solvent was removed in vacuo, and the crude purified by flash chromatography (hexane–EtOAc, 70:30) affording 50.6 mg of **11p** (79%).

Compound 11p

R_f = 0.35 (hexane–EtOAc, 8:2); $[\alpha]_D^{20}$ +9 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.10 (m, 10 H), 5.52 (br s, 1 H), 5.11 (d, *J* = 12.3 Hz, 1 H), 5.00 (d, *J* = 12.3 Hz, 1 H), 4.56 (br s, 1 H), 3.49 (dt, *J* = 13.6, 4.3 Hz, 1 H), 3.39 (m, 1 H), 3.25 (d, *J* = 3.7 Hz, 1 H), 3.19 (dd, *J* = 13.7, 5.9 Hz, 1 H), 3.06 (br m, 1 H), 2.94 (br m, 1 H), 2.03 (m, 1 H), 1.55 (br s, 1 H), 1.46 (s, 9 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ = –60.2 (dd, *J* = 177.3, 6.0 Hz, 1 F), –60.8 (dd, *J* = 177.3, 8.6 Hz, 1 F). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.86, 172.01, 137.08, 136.76, 130.90 (t, *J* = 296.7 Hz), 129.75, 129.59, 129.19, 128.84 (d, *J* = 4.2 Hz), 128.45 (d, *J* = 8.5 Hz), 127.22, 82.63, 67.27, 66.45, 64.11 (t, *J* = 24.5 Hz), 56.66, 40.10, 40.06, 31.86, 28.48, 19.83, 17.59. ESI-MS: *m/z* (%) = 582.3 (15) [M^+ + H], 604.3 (100) [M^+ + Na], 620.2 (23) [M^+ + K].

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