

Helix Formation in Preorganized β/γ -Peptide Foldamers: Hydrogen-Bond Analogy to the α -Helix without α -Amino Acid Residues

Li Guo, Aaron M. Almeida, Weicheng Zhang, Andrew G. Reidenbach, Soo Hyuk Choi, Ilia A. Guzei, and Samuel H. Gellman*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received April 16, 2010; E-mail: gellman@chem.wisc.edu

Identification of new types of foldamers with strong and discrete secondary structural propensities is a subject of ongoing research.¹ These studies enhance our understanding of the relationship between local conformational preferences and molecular shape. In addition, new folding patterns can be valuable for specific applications.^{2,3} Foldamers that contain more than one type of subunit, i.e., oligomers that have heterogeneous backbones, have been a subject of extensive recent interest.^{1c} Most examples involve a combination of α -amino acid residues with other types of subunits, including those derived from β -⁴ or γ -amino acids⁵ or other building blocks.⁶ Heterogeneous backbones that do not include α -amino acid residues have received relatively limited attention,^{5e,7} perhaps because α -amino acids are far more available than are other building blocks. Backbones with alternating β - and γ -amino acid residues (β/γ -peptides) are of particular interest because a β/γ -dipeptide has the same number of atoms between the N- and C-termini as an α -tripeptide.^{5b} An extended β/γ -peptide can in principle form a helix containing 13-membered ring backbone H-bonds ($\text{C}=\text{O}(i)\cdots\text{H}-\text{N}(i+3)$) that are analogous to the 13-membered ring backbone H-bonds characteristic of the α -helix ($\text{C}=\text{O}(i)\cdots\text{H}-\text{N}(i+4)$). However, Sharma, Kunwar et al.^{5e} have recently reported that flexible β/γ -peptides adopt a different type of helical conformation in solution. Here we show that β/γ -peptides containing appropriately preorganized subunits do indeed adopt the 13-helix in solution and the solid state.

The β/γ -peptide 13-helix is predicted by Hofmann et al.^{5d} to have g^+, g^+ or g^-, g^- local conformations about the $\text{C}_\alpha\text{--C}_\beta$ (ζ) and $\text{C}_\beta\text{--C}_\gamma$ (θ) bonds in the γ -residues and a $\text{C}_\alpha\text{--C}_\beta$ torsion angle of $\sim 90^\circ$ in the β -residues. Based on these predictions and available data for the conformational propensities of constrained β - and γ -residues in other contexts, we concluded that combining (*R,R,R*) γ -residue **1** (Figure 1), which has recently become available,^{5i,8} with (*R,R*)-*trans*-2-aminocyclopentanecarboxylic acid (ACPC, **2**) should favor formation of the left-handed β/γ -peptide 13-helix (the right-handed helix should be favored by residues with *S* configurations). This hypothesis was tested by preparation and analysis of tetramer **3**, pentamer **4**, and hexamer **5** (Figure 1).

The crystal structure of β/γ -peptide **3** contains two molecules in the asymmetric unit; the two conformations are very similar (Figure 2). Each independent molecule forms one 13-atom H-bonded ring, involving the NH group of the second ACPC residue and the carbonyl of the N-terminal Boc group. The other possible 13-atom ring H-bond does not form in either case [$\text{N}\cdots\text{O}$ distance ~ 4.9 Å]; instead, each molecule contains an 8-atom ring H-bond involving the carbonyl of the first γ -residue and the NH group of the second γ -residue. Despite this deviation from the 13-helical H-bonding pattern, the backbone torsion angles for the β - and γ -residues in **3** generally fall in ranges predicted by Hofmann et al.^{5d} for the β/γ -peptide 13-helix.⁹

Pentamer **4**, containing β - and γ -residues with *S* configurations, adopts the right-handed 13-helix in the crystalline state. All three

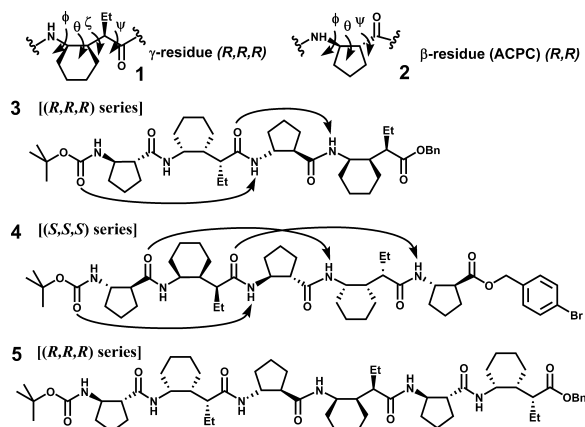


Figure 1. Structures of β/γ -peptides **3**, **4**, **5** (arrows indicate H-bonds in the crystal structures of **3** and **4**).

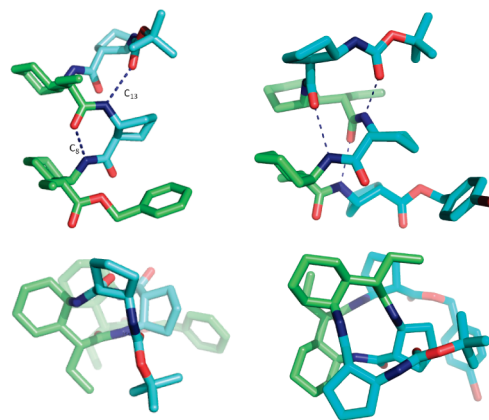


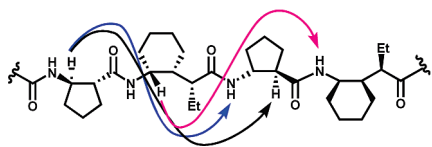
Figure 2. Crystal structures of **3** (left) and **4** (right): (top) views perpendicular to helical axis; (bottom) views along the helical axis.

of the possible $\text{C}=\text{O}(i)\cdots\text{H}-\text{N}(i+3)$ H-bonds are formed (Figure 2). Table 1 compares backbone torsion angles for the β - and γ -residues in pentamer **4** with analogous values from the computational work of Hofmann et al.^{5d} and from the NMR analysis of flexible β/γ -peptides in organic solvent by Sharma, Kunwar et al.^{5e} The preorganized γ -residues in **4** display g^+, g^+ local conformations about the $\text{C}_\alpha\text{--C}_\beta$ (ζ) and $\text{C}_\beta\text{--C}_\gamma$ (θ) bonds and ψ and ϕ near -120° , with a somewhat wider distribution for the latter torsion angle. These values are consistent with the predictions for the 13-helical conformation from Hofmann et al.^{5d} In contrast, the helical conformations deduced via NMR for flexible β/γ -peptides feature opposite signs for the ζ and θ torsion angles (g^-, g^+) and opposite signs for the ψ and ϕ torsion angles. The helical conformation deduced for these flexible β/γ -peptides has a distinctive H-bonding

Table 1. Backbone Torsion Angles (deg)^a of Helical β/γ -Peptides

Peptides	residues	ϕ	θ	ζ	ψ
β/γ pentamer 4	$\beta 1$	-107.7	93.3		-128.3
	$\gamma 2$	-134.7	60.1	59.8	-121.0
	$\beta 3$	-133.6	113.5		-85.7
	$\gamma 4$	-147.3	57.9	46.5	-129.8
	$\beta 5$	-167.9	141.4		-155.0
computational study ^{b,5d}	β	89.1	-94.1		121.9
	γ	124.9	-60.4	-62.2	132.0
flexible β/γ tetramer (NMR) ^{5e}	β	120	60		0
	γ	120	-60	60	-120

^a Nomenclature for the backbone torsion angles in β/γ -peptides is described in Figure 1. ^b Average backbone torsion angles.

**Figure 3.** Characteristic NOE patterns observed for the 1:1 β/γ -peptide hexamer **5** in pyridine- d_5 .

pattern with two types of interaction: $C=O_{\gamma(i)}-H-N_{\beta(i-1)}$ and $C=O_{\beta(i)}-H-N_{\gamma(i+3)}$.

Hexamer **5** did not produce high-quality crystals, but 2D 1H NMR analysis in pyridine- d_5 solution indicated that the 13-helix is significantly populated under these conditions. Among the unambiguous NOEs involving backbone protons, six strong NOEs were observed between protons from residues that are not adjacent in the sequence: $C_{\beta}H(1)-NH(3)$, $C_{\beta}H(1)-C_{\alpha}H(3)$, $C_{\gamma}H(2)-NH(4)$, $C_{\beta}H(3)-NH(5)$, $C_{\beta}H(3)-C_{\alpha}H(5)$, and $C_{\gamma}H(4)-NH(6)$ (Figure 3). These NOEs are consistent with intramolecular proton–proton distances in the crystal structure of pentamer **4**: $C_{\beta}H(1)-NH(3) = 3.5$ Å, $C_{\beta}H(1)-C_{\alpha}H(3) = 2.7$ Å, $C_{\gamma}H(2)-NH(4) = 2.8$ Å, $C_{\beta}H(3)-NH(5) = 2.3$ Å, and $C_{\beta}H(3)-C_{\alpha}H(5) = 2.2$ Å. Thus, the three NOE patterns observed for **5**, $C_{\beta}H(i)-NH(i+2)$ and $C_{\beta}H(i)-C_{\alpha}H(i+2)$ for β -residues and $C_{\gamma}H(i)-NH(i+2)$ for γ -residues, appear to be general indicators of β/γ -peptide 13-helical secondary structure.

The β/γ -peptide helix we have documented is interesting because of its relationship to the α -helix formed by pure α -residue backbones. Both helices contain 13-atom ring H-bonds. Detailed comparison of the two helices reveals further similarities: both have a rise-per-turn of 5.4 Å, and the radii are similar (2.5 vs 2.3 Å).⁹ These parameters suggest that the β/γ -peptide 13-helix may be a promising scaffold for functional mimicry of natural α -helices.^{2b,3}

Our results show that appropriately preorganized residues promote the formation of the 13-helical conformation in short β/γ -peptides. This secondary structure was anticipated (along with alternative helices) in computational studies,^{5c,d} and hints of 13-helical propensity can be found in the local conformations observed in crystal structures for isolated $\beta-\gamma$ segments,^{5b,g} but the only previous analysis of β/γ -peptide oligomer folding indicated the formation of a different helical conformation, containing both 11- and 13-membered ring H-bonds.^{5e} Conformationally constrained β -amino acid residues have been shown to induce novel secondary structures,^{1a,c,10} and the present studies highlight the prospect that constrained γ -amino acid residues will be similarly useful in controlling molecular shape.

Acknowledgment. This research was supported by the NSF (CHE-0848847). NMR spectrometers were purchased with partial support from the NIH and NSF.

Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111. (c) Hecht, S.; Huc, I., Eds. *Foldamers: Structure, Properties and Applications*; Wiley-VCH Weinheim: Germany, 2007. (d) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252. (e) Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2009**, *41*, 1399.
- (2) Recent examples of biologically active foldamers: (a) Claudon, P.; Violette, A.; Lamour, K.; Decossas, M.; Fournel, S.; Heurtault, B.; Godet, J.; Mely, Y.; Jamart-Gregoire, B.; Averlant-Petit, M.-C.; Briand, J.-P.; Duportail, G.; Monteil, H.; Guichard, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 333. (b) Horne, W. S.; Johnson, L. M.; Ketas, T. J.; Klasse, P. J.; Lu, M.; Moore, J. P.; Gellman, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 14751. (c) Jochim, A. L.; Miller, S. E.; Angelo, N. G.; Arora, P. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6023. (d) Choi, S.; Isaacs, A.; Clements, D.; Liu, D. H.; Kim, H.; Scott, R. W.; Winkler, J. D.; DeGrado, W. F. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 6968. (e) Bautista, A. D.; Stephens, O. M.; Wang, L. G.; Domaoal, R. A.; Anderson, K. S.; Schepartz, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3736. (f) Brown, N. J.; Wu, C. W.; Seurynck-Servoss, S. L.; Barron, A. E. *Biochemistry* **2008**, *47*, 1808. (g) For earlier examples, see ref 1d.
- (3) Sadowsky, J. D.; Fairlie, W. D.; Hadley, E. B.; Lee, H. S.; Umezawa, N.; Nikolovska-Coleska, Z.; Wang, S. M.; Huang, D. C. S.; Tomita, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 139.
- (4) (a) De Pol, S.; Zorn, C.; Klein, C. D.; Zerbe, O.; Reiser, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 511. (b) Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 505. (c) Sharma, G. V. M.; Nagendar, P.; Jayaprakash, P.; Krishna, P. R.; Ramakrishna, K. V. S.; Kunwar, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 5878. (d) Mandity, I. M.; Weber, E.; Martinek, T. A.; Olajos, G.; Toth, G. K.; Vass, E.; Fulop, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 2171. (e) For a heterogeneous backbone review, see ref 1e.
- (5) (a) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568. (b) Karle, I. L.; Pramanik, A.; Banerjee, A.; Bhattacharjya, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 9087. (c) Ananda, K.; Vasudev, P. G.; Sengupta, A.; Raja, K. M. P.; Shamala, N.; Balaram, P. *J. Am. Chem. Soc.* **2005**, *127*, 16668. (d) Baldauf, C.; Gunther, R.; Hofmann, H. J. *J. Org. Chem.* **2006**, *71*, 1200. (e) Sharma, G. V. M.; Jadhav, V. B.; Ramakrishna, K. V. S.; Narsimulu, K.; Subash, V.; Kunwar, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 14657. (f) Baruah, P. K.; Sreedevi, N. K.; Gonnade, R.; Ravindranathan, S.; Damodaran, K.; Hofmann, H. J.; Sanjayam, G. J. *J. Org. Chem.* **2007**, *72*, 636. (g) Vasudev, P. G.; Ananda, K.; Chatterjee, S.; Aravinda, S.; Shamala, N.; Balaram, P. *J. Am. Chem. Soc.* **2007**, *129*, 4039. (h) Chatterjee, S.; Vasudev, P. G.; Raghothama, S.; Ramakrishnan, C.; Shamala, N.; Balaram, P. *J. Am. Chem. Soc.* **2009**, *131*, 5956. (i) Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, I. A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018. (j) Chakraborty, T. K.; Rao, K. S.; Kiran, M. U.; Jagadeesh, B. *Tetrahedron Lett.* **2009**, *50*, 4350. (k) Araghi, R. R.; Jackel, C.; Cofen, H.; Salwiczek, M.; Vokel, A.; Wagner, S. C.; Wiczorek, S.; Baldauf, C.; Koksche, B. *ChemBioChem* **2010**, *11*, 335.
- (6) (a) Yang, D.; Li, W.; Qu, J.; Luo, S. W.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 13018. (b) Chowdhury, S.; Schatte, G.; Kraatz, H. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6882. (c) Olsen, C. A.; Bonke, G.; Vedel, L.; Adersen, A.; Witt, M.; Franzhk, H.; Jaroszewski, J. W. *Org. Lett.* **2007**, *9*, 1549. (d) Zhao, Y.; Zhong, Z. Q.; Ryu, E. H. *J. Am. Chem. Soc.* **2007**, *129*, 218. (e) Angelici, G.; Luppi, G.; Kaptein, B.; Broxterman, Q. B.; Hofmann, H. J.; Tomasini, C. *Eur. J. Org. Chem.* **2007**, 2713. (f) Sakai, N.; Mareda, J.; Matile, S. *Acc. Chem. Res.* **2008**, *41*, 1354. (g) Sharma, G. V. M.; Babu, B. S.; Ramakrishna, K. V.; Nagendar, P.; Kunwar, A. C.; Schramm, P.; Baldauf, C.; Hofmann, H. J. *Chem.—Eur. J.* **2009**, *15*, 5552. (h) Sharma, G. V. M.; Babu, B. S.; Chatterjee, D.; Ramakrishna, K. V. S.; Kunwar, A. C.; Schramm, P.; Hofmann, H. J. *J. Org. Chem.* **2009**, *74*, 6703. (i) Hetenyi, A.; Toth, G. K.; Somlai, C.; Vass, E.; Martinek, T. A.; Fulop, F. *Chem.—Eur. J.* **2009**, *15*, 10736.
- (7) (a) Gong, B.; Zeng, H.; Zhu, J.; Yuan, L.; Han, Y.; Cheng, S.; Furukawa, M.; Parra, R. D.; Kovalevsky, A. Y.; Mills, J. L.; Skrzypczak-Jankun, E.; Martinovic, S.; Smith, R. D.; Zheng, C.; Szyperski, T.; Zeng, X. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583. (b) Delsuc, N.; Godde, F.; Kauffmann, B.; Leger, J. M.; Huc, I. *J. Am. Chem. Soc.* **2007**, *129*, 11348.
- (8) A complementary example: Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 16016.
- (9) See the Supporting Information.
- (10) Schmitt, M. A.; Choi, S. H.; Guzei, I. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 13130.

JA103233A