Published in final edited form as:
J Am Chem Soc. 2010 June 16; 132(23): 7868–7869. doi:10.1021/ja103233a.

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

Abstract

We report the first high-resolution structural data for the β/γ-peptide 13-helix (*i*,*i*+3 C=O···H-N H-bonds), a secondary structure that is formed by oligomers with a 1:1 alternation of β- and γ-amino acid residues. Our characterization includes both crystallophaphic and 2D NMR data. Previous studies suggested that β/γ-peptides constructed from conformationally flexible residues adopt a different helical secondary structure in solution. Our design features preorganized β- and γ-residues, which strongly promote 13-helical folding by the 1:1β:γ backbone.

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.[1e] Most examples involve combination of α-amino acid residues with other types of subunits, including those derived from β-[4] or γ-amino acids[5] 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 (C=O(i)--H-N(i+3)) that are analogous to the 13-membered ring backbone H-bonds characteristic of the α-helix (C=O(i)--H-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 $C_\alpha-C_\beta$ (ζ) and $C_\beta-C_\gamma$ (θ) bonds in the γ-residues and a $C_\alpha-C_\beta$ torsion angle of ~90° 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*

gellman@chem.wisc.edu .

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

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 [N--O distance~ 4.9Å]; instead, each molecule contains an 8-atom ring H-bond involving the carbonyl of the first γ-residue and the NH group of 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 of the possible C=O(i)--H-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 $C_\alpha-C_\beta$ (ζ) and $C_\beta-C_\gamma$ (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 pattern with two types of interaction: $C{=}O_\gamma$ (i)--H-N_γ (i−1) and $C{=}O_\gamma$ (i)--H-N_γ (i+3).

Hexamer **5** did not produce high-quality crystals, but 2D ^{1}H 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_βH(1)--NH(3), C_βH(1)--C_αH(3), C_γH(2)--NH(4), C_βH(3)--NH(5), C_βH(3)--C_αH(5), and C_γH(4)--NH(6) (Figure 3). These NOEs are consistent with intramolecular proton-proton distances in the crystal structure of pentamer **4**: C_βH(1)--NH(3) = 3.5 Å, C_βH(1)--C_αH(3) = 2.7 Å, C_γH(2)--NH(4) = 2.8 Å, C_βH(3)--NH(5) = 2.3 Å and C_βH(3)--C_αH(5) = 2.2 Å. Thus, the three NOE patterns observed for **5**, C_βH(i)--NH(i+2) and C_βH(i)--C_αH(i+2) for β-residues and C_γH(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 β-γ 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,e,10] and the present studies highlight the prospect that constrained γ-amino acid residues will be similarly useful in controlling molecular shape.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

References

1. (a) Gellman SH. Acc Chem Res 1998;31:173. (b) Seebach D, Beck AK, Bierbaum DJ. Chem Biodivers 2004;1:1111. [PubMed: 17191902] (c) Hecht, S.; Huc, I., editors. Foldamers: Structure, Properties and Applications. Wiley-VCH Weinheim; Germany: 2007. (d) Goodman CM, Choi S, Shandler S, DeGrado WF. Nat Chem Biol 2007;3:252. [PubMed: 17438550] (e) Horne WS, Gellman SH. Acc Chem Res 2009;41:1399. [PubMed: 18590282]
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 WS, Johnson LM, Ketas TJ, Klasse PJ, Lu M, Moore JP, Gellman SH. Proc Natl Acad Sci USA 2009;106:14751. [PubMed: 19706443] (c) Jochim AL, Miller SE, Angelo NG, Arora PS. Bioorg Med Chem Lett 2009;19:6023. [PubMed: 19800230] (d) Choi S, Isaacs A, Clements D, Liu DH, Kim H, Scott RW, Winkler JD, DeGrado WF. Proc Natl Acad Sci USA 2009;106:6968. [PubMed: 19359494] (e) Bautista AD, Stephens OM, Wang LG, Domaoal RA, Anderson KS, Schepartz A. Bioorg Med Chem Lett 2009;19:3736. [PubMed: 19497744] (f) Brown NJ, Wu CW, Seurynck-Servoss SL, Barron AE. Biochemistry 2008;47:1808. [PubMed: 18197709] (g) For earlier examples, see ref. [1d].
3. Sadowsky JD, Fairlie WD, Hadley EB, Lee HS, Umezawa N, Nikolovska-Coleska Z, Wang SM, Huang DCS, Tomita Y, Gellman SH. J Am Chem Soc 2007;129:139. [PubMed: 17199293]
4. (a) De Pol S, Zorn C, Klein CD, Zerbe O, Reiser O. Angew Chem, Int Ed 2004;43:511. (b) Hayen A, Schmitt MA, Ngassa FN, Thomasson KA, Gellman SH. Angew Chem, Int Ed 2004;43:505. (c) Sharma GVM, Nagendar P, Jayaprakash P, Krishna PR, Ramakrishna KVS, Kunwar AC. Angew Chem, Int Ed 2005;44:5878. (d) Mandity IM, Weber E, Martinek TA, Olajos G, Toth GK, 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 NJ, Stout TJ, Clardy J, Schreiber SL. J Am Chem Soc 1992;114:6568. (b) Karle IL, Pramanik A, Banerjee A, Bhattacharjya S, Balaram P. J Am Chem Soc 1997;119:9087. (c) Ananda K, Vasudev PG, Sengupta A, Raja KMP, Shamala N, Balaram P. J Am Chem Soc 2005;127:16668. [PubMed: 16305256] (d) Baldauf C, Gunther R, Hofmann HJ. J Org Chem 2006;71:1200. [PubMed: 16438538] (e) Sharma GVM, Jadhav VB, Ramakrishna KVS, Narsimulu K, Subash V, Kunwar AC. J Am Chem Soc 2006;128:14657. [PubMed: 17090052] (f) Baruah PK, Sreedevi NK, Gonnade R, Ravindranathan S, Damodaran K, Hofmann HJ, Sanjayan GJ. J Org Chem 2007;72:636. [PubMed: 17221986] (g) Vasudev PG, Ananda K, Chatterjee S, Aravinda S, Shamala N, Balaram P. J Am Chem Soc 2007;129:4039. [PubMed: 17348653] (h) Chatterjee S, Vasudev PG, Raghothama S, Ramakrishnan C, Shamala N, Balaram P. J Am Chem Soc 2009;131:5956. [PubMed: 19341285] (i) Guo L, Chi Y, Almeida AM, Guzei IA, Parker BK, Gellman SH. J Am Chem Soc 2009;131:16018. [PubMed: 19886693] (j) Chakraborty TK, Rao KS, Kiran MU, Jagadeesh B. Tetrahedron Lett 2009;50:4350. (k) Araghi RR, Jackel C, Cofen H, Salwiczek M, Vokel A, Wagner SC, Wieczorek S, Baldauf C, Koksch B. ChemBioChem 2010;11:335. [PubMed: 20039254]
6. (a) Yang D, Li W, Qu J, Luo SW, Wu YD. J Am Chem Soc 2003;125:13018. [PubMed: 14570462] (b) Chowdhury S, Schatte G, Kraatz HB. Angew Chem, Int Ed 2006;45:6882. (c) Olsen CA, Bonke G, Vedel L, Adsersen A, Witt M, Franzhk H, Jaroszewski JW. Org Lett 2007;9:1549. [PubMed: 17352488] (d) Zhao Y, Zhong ZQ, Ryu EH. J Am Chem Soc 2007;129:218. [PubMed: 17199302] (e) Angelici G, Luppi G, Kaptein B, Broxterman QB, Hofmann HJ, Tomasini C. Eur J Org Chem 2007:2713. (f) Sakai N, Mareda J, Matile S. Acc Chem Res 2008;41:1354. [PubMed: 18590283] (g) Sharma GVM, Babu BS, Ramakrishna KV, Nagendar P, Kunwar AC, Schramm P, Baldauf C, Hofmann HJ. Chem Eur J 2009;15:5552. (h) Sharma GVM, Babu BS, Chatterjee D, Ramakrishna

KVS, Kunwar AC, Schramm P, Hofmann HJ. J Org Chem 2009;74:6703. [PubMed: 19663475] (i) Hetenyi A, Toth GK, Somlai C, Vass E, Martinek TA, 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 RD, Kovalevsky AY, Mills JL, Skrzypczak-Jankun E, Martinovic S, Smith RD, Zheng C, Szyperski T, Zeng XC. Proc Natl Acad Sci USA 2002;99:11583. [PubMed: 12177422] (b) Delsuc N, Godde F, Kauffmann B, Leger JM, Huc I. J Am Chem Soc 2007;129:11348. [PubMed: 17718571]
8. A complementary example: Nodes WJ, Nutt DR, Chippindale AM, Cobb AJA. J Am Chem Soc 2009;131:16016. [PubMed: 19827809]
9. See the Supporting Information.
10. Schmitt MA, Choi SH, Guzei IA, Gellman SH. J Am Chem Soc 2005;127:13130. [PubMed: 16173725]

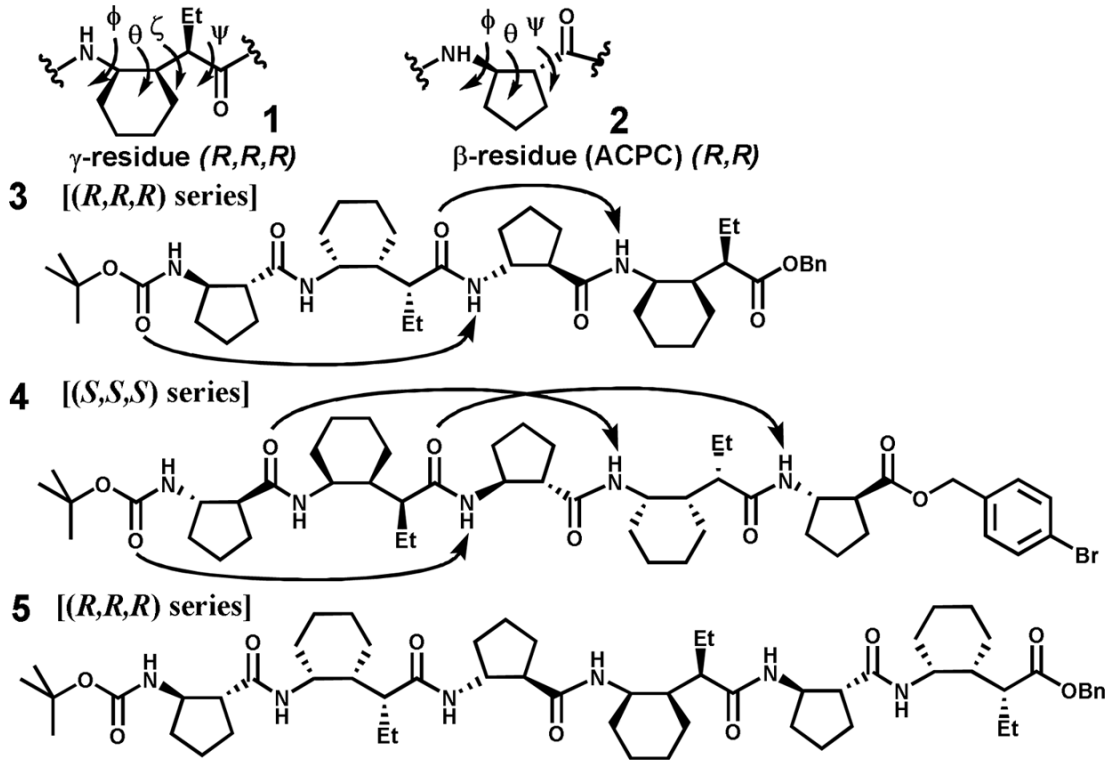

Figure 1.
Structures of β/γ peptides **3, 4, 5** (arrows indicate H-bonds in the crystal structures of **3** and **4**)

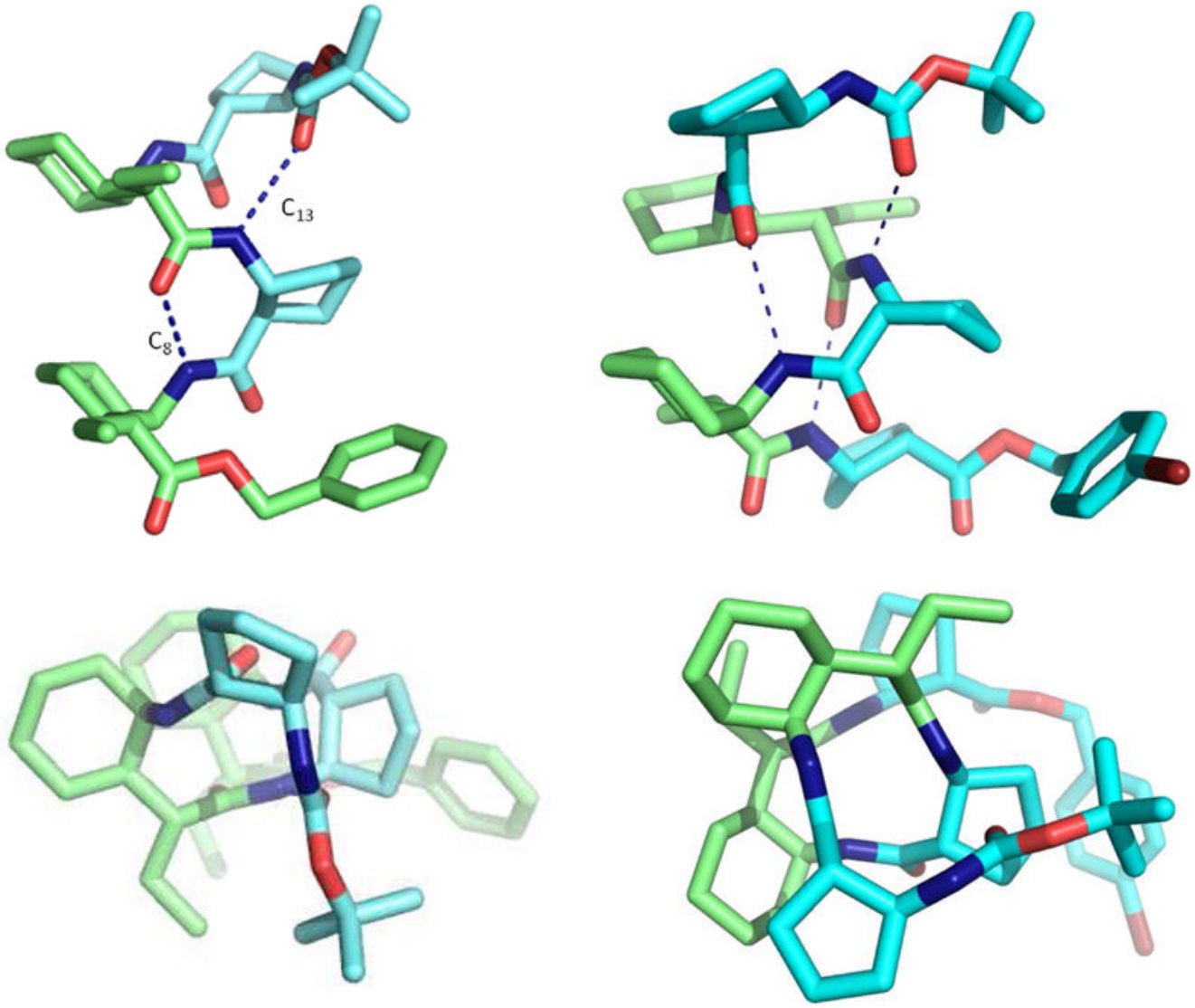

Figure 2.
Crystal structures of **3** (left) and **4** (right): (top) views perpendicular to helical axis; (bottom) views along the helical axis.

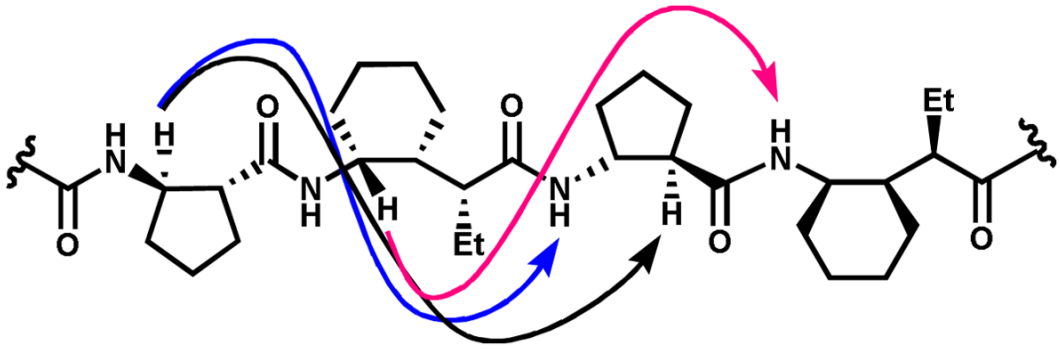

Figure 3.
Characteristic NOEs patterns observed for the 1:1 β/γ-peptide hexamer **5** in pyridine-d_5.

Table 1

Backbone Torsion Angles (deg) [†] from β/γ Peptides

Peptides	residues	*φ*	*θ*	*ζ*	*ψ*
β/γ pentamer **4**	β	−107.7	93.3		−128.3
	γ	−134.7	60.1	59.8	−121.0
	β	−133.6	113.5		−85.7
	γ	−147.3	57.9	46.5	−129.8
	β	−167.9	141.4		−155.0
computational Study [‡],5d	β	89.1	−94.1		121.9
	γ	124.9	−60.4	−62.2	132.0
flexible β/γ (NMR)5e	β	120	60		0
	γ	120	−60	60	−120

[†]Nomenclature for the backbone torsion angles in β,γ-residues is as described in Figure 1.

[‡]Average backbone torsion angles