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Helix Formation in Preorganized *βlγ*-Peptide Foldamers: Hydrogen-Bond Analogy to the α-Helix without α-Amino Acid Residues

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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 a 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* 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 ~4.9 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

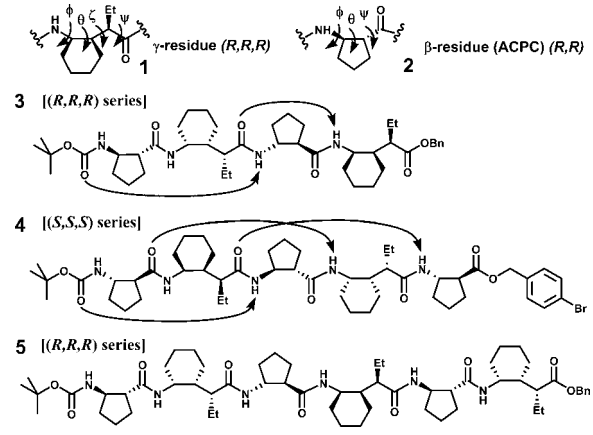

Figure 1. Structures of *β*/*γ*-peptides **3**, **4**, **5** (arrows indicate H-bonds in the crystal structures of **3** and **4**).

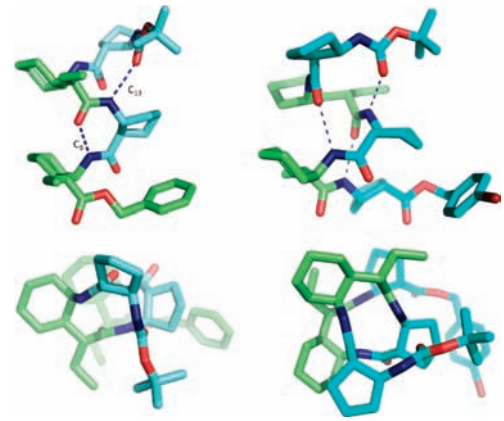

Figure 2. Crystal structures of **3** (left) and **4** (right): (top) views perpendicular to helical axis; (bottom) views along the helical axis.

of the possible 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

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

Peptides	residues	ϕ	θ	ζ	ψ
β/γ pentamer **4**	β1	−107.7	93.3		−128.3
	γ2	−134.7	60.1	59.8	−121.0
	β3	−133.6	113.5		−85.7
	γ4	−147.3	57.9	46.5	−129.8
	β5	−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.

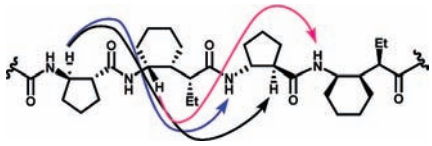

Figure 3. Characteristic NOE patterns observed for the 1:1 β/γ-peptide hexamer **5** in pyridine-d_5.

pattern with two types of interaction: C═O_γ(i)--H—N_β(i−1) and C═O_β(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 $\beta-\gamma$ 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,e,10] and the present studies highlight the prospect that constrained γ-amino acid residues will be similarly useful in controlling molecular shape.

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

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