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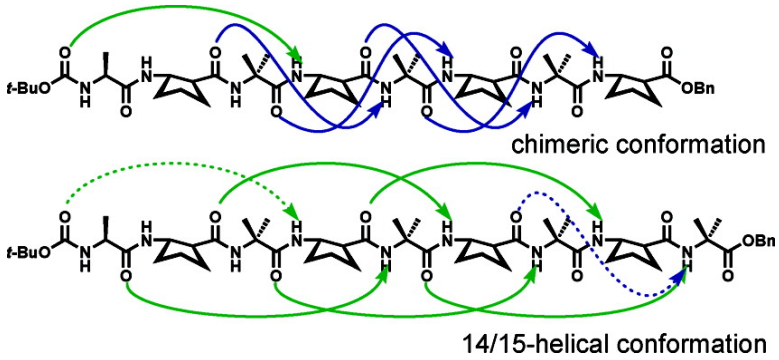

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Crystallographic Characterization of the α/β-Peptide 14/15-Helix

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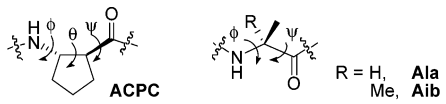
The search for oligomers that adopt specific conformations ("foldamers")[1] has recently included many efforts to identify backbones containing more than one class of subunit. Combinations involving α- and β-amino acids have been especially popular,[2−12] and other systems have been examined as well.[13−17] In early studies, we found that folding of short α/β-peptides with a 1:1 alternation of α- and β-residues is promoted by β-residues that have a five-membered ring constraint, such as *trans*-2-aminocyclopentanecarboxylic acid (ACPC).[4a−c] Short ACPC-containing α/β-peptides display numerous NOEs between protons on non-adjacent residues, which can be rationalized by proposing the adoption of two different helical conformations that interconvert rapidly on the NMR time scale, one containing *i*,*i*+3 C═O···H−N H-bonds and the other containing *i*,*i*+4 C═O···H−N H-bonds.[4a] These secondary structures were designated the "11-helix" and the "14/15-helix", respectively, based on the number of atoms in the H-bonded rings. Contemporaneous studies by Reiser et al. revealed a different type of helical folding, involving *i*,*i*−2 C═O···H−N H-bonds, by α/β-peptides containing *cis*-2-aminocyclopropanecarboxylic acid residues.[3] Subsequent work of Sharma, Kunwar, and co-workers has identified a "mixed" helix, containing both *i*,*i*+3 C═O···H−N and *i*,*i*−1 C═O···H−N H-bonds, in α/β-peptides lacking cyclically constrained residues.[5] Hofmann et al. have provided a comprehensive computational evaluation of helix types available to α/β-peptides containing a 1:1 backbone alternation.[6]

To date, the only reported crystallographic data for a 1:1 α/β-peptide have been obtained for octamer **1**, which contains ACPC and α-aminoisobutyric acid (Aib).[4c] α/β-Peptide **1** displays an 11-helical conformation in the solid state. Since that structure was reported, Seebach et al. have presented 2D NMR results for α/β-peptides containing Aib and acyclic β-residues, which were deduced to adopt 14/15-helix-like conformations lacking internal H-bonds.[7] Jagadeesh et al. have reported 2D NMR analysis of α/β-peptides containing L-Ala and *cis*-β-furanoid sugar amino acid residues.[9] These workers have concluded that 11- and 14/15-helix H-bond patterns are adopted simultaneously, that is, helical folding involves the formation of bifurcated H-bonds (simultaneous *i*,*i*+3 and *i*,*i*+4 C═O···H−N interactions). We considered this type of hybrid helix when we originally observed that neither the 11- nor the 14/15-helix could entirely explain the NOE patterns observed for short ACPC-containing α/β-peptides, but we discarded this hypothesis in favor of rapid interconversion between 11- and 14/15-helical conformations.[4a] In light of subsequent developments,[7,9] however, the existence of an internally H-bonded 14/15-helix as originally proposed may seem uncertain. This issue is important because the 14/15-helical secondary structure has been used as a basis for function-oriented foldamer design.[4b,d,f,g] Here we resolve this uncertainty by reporting the first crystal structure of an α/β-peptide in the 14/15-helical conformation.

We wondered whether the Aib residues in **1** might favor the 11-helix over the 14/15-helix. As a first step toward addressing this question, we prepared and crystallized **2**, the analogue of **1** in



1 Boc-Aib-ACPC-Aib-ACPC-Aib-ACPC-Aib-ACPC-OBn
2 Boc-Ala-ACPC-Aib-ACPC-Aib-ACPC-Aib-ACPC-OBn
3 Boc-Ala-ACPC-Aib-ACPC-Aib-ACPC-Aib-ACPC-Aib-OBn

which the N-terminal Aib residue is replaced by alanine. α/β-Peptide **2** adopts a chimeric conformation in the solid state (Figure 1). The carbonyl of the N-terminal Boc group forms an *i*,*i*+4 C═O···H−N H-bond (14-membered ring), but the remainder of the backbone amide groups are involved in *i*,*i*+3 C═O···H−N H-bonds (11-helix). This observation suggested that **2** might represent an α/β-peptide on the brink of forming a full-fledged 14/15-helix.

Among α-amino acid oligomers, the α-helix (*i*,*i*+4 C═O···H−N H-bonding) is favored over the 3_{10}-helix (*i*,*i*+3 C═O···H−N H-bonding) by increasing peptide length,[18] and 2D NMR evidence suggests a similar trend among α/β-peptides containing ACPC.[4b,g] We therefore examined **3**, the homologue of **2** containing one additional residue at the C-terminus. We reasoned that the *i*,*i*+4 C═O···H−N H-bonding observed at the N-terminus of **2** might be induced to propagate throughout the entire molecule if the backbone were lengthened. Indeed, the crystal structure of **3** revealed a fully 14/15-helical conformation.

The crystallographic data suggest that most intramolecular H-bonds in **1**−**3** have standard geometries. Thus, in 11-helical **1**, the six *i*,*i*+3 C═O···H−N H-bonds display H···O distances of 1.9−2.1 Å, N···O distances of 2.8−2.9 Å, and N−H···O angles of 150−170°. In the folded conformation of **2**, the four *i*,*i*+3 C═O···H−N H-bonds have H···O distances of 2.0−2.1 Å, N···O distances of 2.8−2.9 Å, and N−H···O angles of 150−180°, and the lone *i*,*i*+4 C═O···H−N H-bond has an H···O distance of 2.3 Å, an N···O distance of 3.1 Å, and an N−H···O angle of 160°. In 14/15-helical **3**, five of the *i*,*i*+4 C═O···H−N H-bonds have standard geometries, H···O distances of 2.1−2.2 Å, N···O distances of 2.9−3.0 Å, and N−H···O angles of 140−160°, while the *i*,*i*+4 C═O···H−N interaction at the N-terminus, H···O distance = 2.8 Å and N···O distance = 3.5 Å, is a little longer than the conventional H-bond length limit (H···O distance < 2.5 Å, N···O < 3.9 Å).[19] In only one case is there the possibility of bifurcated H-bonding: in addition to the *i*,*i*+4 C═O···H−N H-bond at the C-terminus of **3**, the amide proton of the last Aib residue is involved in an *i*,*i*+3 C═O···H−N interaction with poorer geometry (H···O distance = 2.8 Å, N···O distance = 3.3 Å, N−H···O angle = 116°) (Figure 2). Average backbone torsion angles are given in Table 1.

The crystallographic data for **1**−**3** are consistent with the original hypothesis that ACPC-containing α/β-peptides can adopt two distinct helical conformations, the 11-helix and the 14/15-helix.[4a] It is perilous to extrapolate conformational behavior from the solid state to solution, but the fact that we see evidence for only one bifurcated H-bond in these structures appears to argue against the hypothesis of a regular hybrid helical conformation containing both *i*,*i*+3 and *i*,*i*+4 C═O···H−N H-bonds. The intriguing observation

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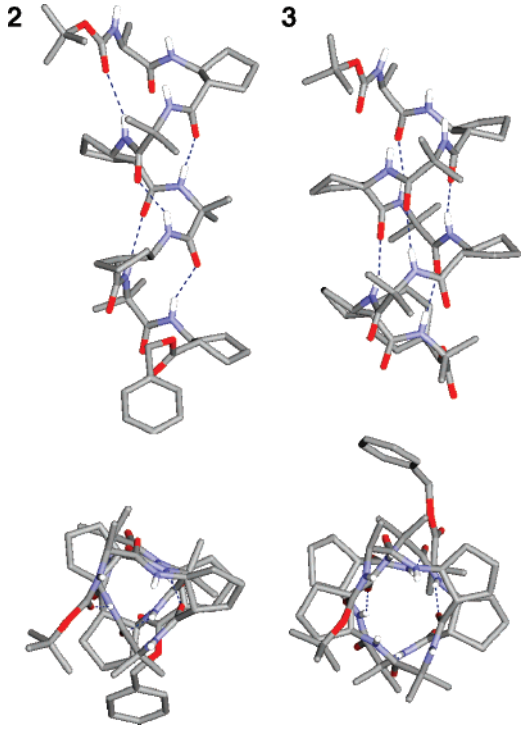

Figure 1. Crystal structures of **2** and **3**: (top) views perpendicular to helical axis; (bottom) views along the helical axis. Dotted lines indicate H-bonds. The solvent molecules, minor components of the disordered atoms, and non-amido hydrogen atoms are omitted for clarity.

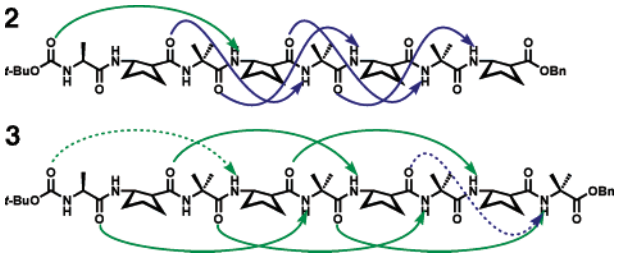

Figure 2. Intramolecular hydrogen bonding patterns in the crystal structures of **2** and **3**: (green) 14/15-helical, (blue) 11-helical. Dotted arrows indicate possible H-bonding interactions.

Table 1. Average Backbone Torsion Angles (deg) from α/β-Peptides **1**−**3**[a]

	α-residue		β-residue		
	ϕ	ψ	ϕ	θ	ψ
11-helix	−55(3)	−40(6)	−96(4)	94(6)	−88(7)
14/15-helix	−62(7)	−38(3)	−126(11)	83(6)	−119(15)

[a] Unfolded C-terminal residues were excluded.

of both H-bond patterns within octamer **2** seems to provide indirect support for the hypothesis that short α/β-peptides of this type can interconvert between 11- and 14/15-helical conformations in solution, as originally proposed.[4a] The high-resolution structural data we have provided for the 14/15-helix secondary structure should prove valuable for the design of α/β-peptides that are intended to perform specific functions.

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Supporting Information Available: Complete ref 14, experimental procedure, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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