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A γ-Amino Acid That Favors 12/10-Helical Secondary Structure in α/γ-Peptides

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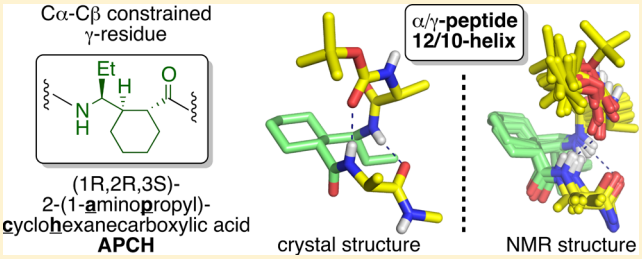
Supporting Information

ABSTRACT: H-bonded helices in conventional peptides (containing exclusively homochiral α-amino acid residues) feature a uniform H-bonding directionality, N-terminal side C═O to C-terminal side NH. In contrast, heterochiral α-peptides can form helices in which the H-bond directionality alternates along the backbone because neighboring amide groups are oriented in opposite directions. Alternating H-bond directions are seen also in helices formed by unnatural peptidic backbones, e.g., those containing β- or γ-amino acid residues. In the present study, we used NMR spectroscopy and crystallography to evaluate the conformational preferences of the novel γ-amino acid (1*R*,2*R*,3*S*)-2-(1-*a*mino*p*ropyl)-*c*yclo*h*exanecarboxylic acid (APCH), which is constrained by a six-membered ring across its Cα−Cβ bond. These studies were made possible by the development of a stereoselective synthesis of N-protected APCH. APCH strongly enforces the α/γ-peptide 12/10-helical secondary structure, which features alternating H-bond directionality. Thus, APCH residues appear to have a conformational propensity distinct from those of other cyclically constrained γ-amino acid residues.



INTRODUCTION

Biology relies on oligomers and polymers of α-amino acids to carry out an enormous range of tasks necessary for life. The fulfillment of these tasks often depends on the ability of the polypeptide chain to adopt a specific conformation. The relationship between folding and function among proteins has inspired exploration of the conformational properties of oligomers with unnatural backbones ("foldamers"),[1] including oligoamides containing subunits with extended backbones such as β- or γ-amino acid residues (Figure 1a).[1d,e,2−8] This building block diversification creates two dimensions of variation that transcend possibilities among proteins themselves. First, the peptidic foldamer sequence is defined not only by the identity of the side chain at each position, but also by the identity of the backbone at each position. Unnatural oligomers can parallel natural polypeptides in having homogeneous backbones, i.e., only one type of subunit. Exclusive use of β-amino acids, for example, generates β-peptides,[1d,2] and exclusive use of γ-amino acids generates γ-peptides.[3−8] Alternatively, unnatural oligomers can depart from the natural precedent by containing mixtures of subunit types, as exemplified by α/β-, α/γ-, β/γ-, and α/β/γ-peptides.[9]

The second distinctive feature of foldamers that contain extended amino acid residues arises because the presence of two or more carbon atoms between the nitrogen and carbonyl carbon enables the encoding of strong local conformational preferences in ways that have no analogue among α-amino acid residues. Among β-peptides, for example, the use of a ring to constrain the torsional preferences about the Cα−Cβ bond can enhance the stability of secondary structures favored by flexible residues or enforce a new secondary structure, depending on the ring size and stereochemistry.[2,10] Similar effects of ring-constrained β-residues have been observed among α/β-peptides, involving either stabilization of intrinsic conformational preferences or the emergence of new secondary structures.[11] Even in the absence of a ring, specific substitution patterns can exert profound effects on β-peptide conformation, as dramatically illustrated by the discovery of 12/10-helical secondary structure from sequences with an alternating β^2/β^3 pattern, as reported by Seebach and co-workers.[12] This helix departs from protein precedents in that H-bonds formed by nearest-neighbor amide groups along the backbone have opposite orientations [C═O(*i*)···H−N(*i*+3) vs C═O(*i*)···H−N(*i*−1)], and the designation "12/10-helix" is based on the alternating H-bond ring sizes.

γ-Amino acid residues offer considerable opportunity to influence local conformational propensity within foldamer backbones because there are three backbone carbon atoms that can bear side chains. "Foldameric potential" has been evaluated for some γ-amino acid substitution patterns in the context of both homogeneous and heterogeneous backbones.[3−8] More comprehensive exploration of γ-residue conformational propensities, however, is hindered by the substantial synthetic challenge of generating stereochemically

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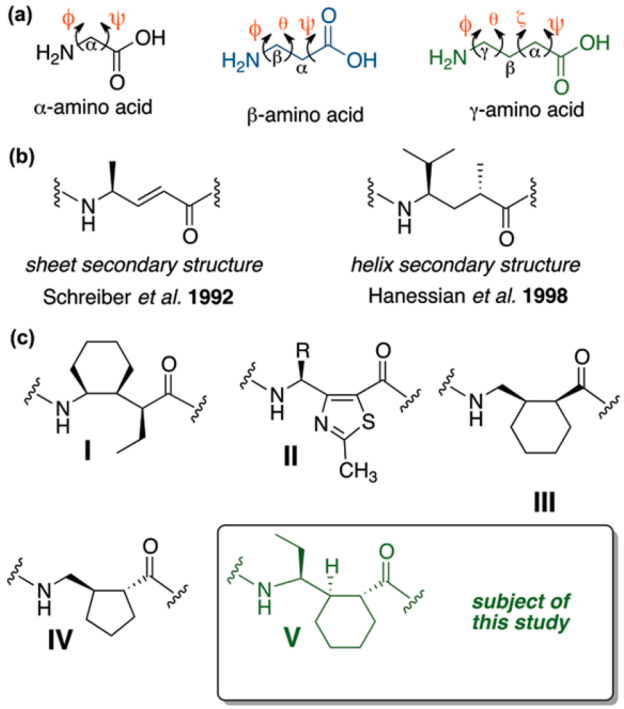


Figure 1. (a) Classes of amino acids. (b) γ-Residues studied by Schreiber[3] and Hanessian.[4] (c) Types of ring-constrained γ-residues found to promote helical secondary structures.[16−18]

pure building blocks with diverse and specific substitution patterns.

The pioneering work of Schreiber and co-workers with α/β-unsaturated γ-residues suggested conformational diversity for this class, with evidence of both sheet and helix secondary structures (Figure 1b).[3] The groups of Hanessian[4] and Seebach[5] showed that γ-residues bearing one, two, or three side chains could support the formation of a specific helical conformation that features a C═O(*i*)···H−N(*i*+3) H-bonding pattern. Hanessian et al. provided an important early example of backbone engineering by demonstrating that altering the relative configurations at Cα and Cγ in 2,4-disubstituted γ-amino acid residues ($\gamma^{2,4}$ residues) causes a switch from helix to reverse-turn secondary structure.[4] Sharma, Kunwar, and co-workers found that α/γ-peptides containing γ^4 residues with a bulky side chain form a 12/10-helix, a secondary structure in which neighboring amide groups form H-bonds with opposite orientations, as described above for the β-peptide 12/10-helix.[12,14] Gopi and co-workers[15a] and Balaram and co-workers[15b,c] recently showed that α/γ-peptides containing γ^4 residues bearing proteinogenic side chains adopt a different helical conformation in which all of the H-bonds have the same orientation [C═O(*i*)···H−N(*i*+3)].

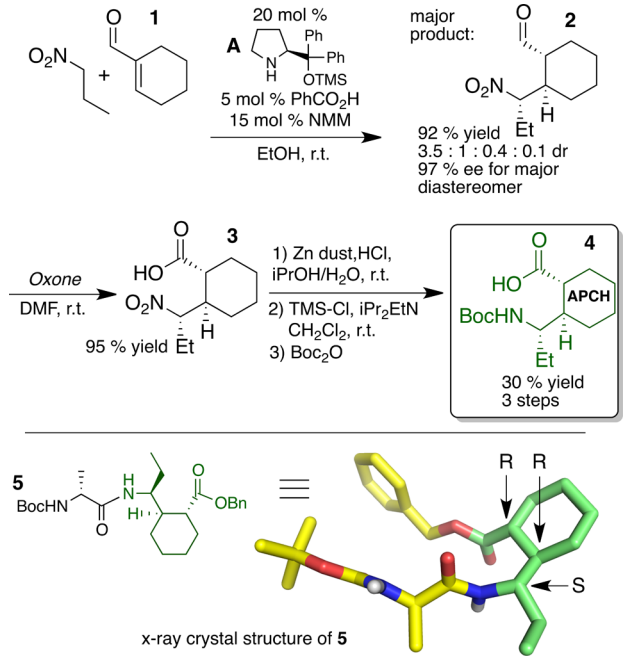
Several types of ring-constrained γ-residues have been evaluated (Figure 1c). In some cases the ring promotes extended backbone conformations that lead to sheet secondary structures,[6,7] while in other cases the conformational propensities of ring-constrained residues are consistent with helical secondary structures.[6,7] In particular, we have found that substitution pattern **I** is associated with the formation of helices containing the C═O(*i*)···H−N(*i*+3) H-bonding pattern in γ-, α/γ-, and β/γ-peptides.[16a−c] In contrast, Maillard and co-workers have shown that γ-peptides containing residues of type **II** favor a helix with the C═O(*i*)···H−N(*i*+2) H-bonding.[17] α/γ-Peptides containing residue **III** can access at least two helical conformations, one containing C═O(*i*)···H−N(*i*+3) H-bonds (12-helix) and the other containing an alternating pattern of C═O(*i*)···H−N(*i*+3) and C═O(*i*)···H−N(*i*−1) H-bonds (12/10-helix).[16d] Residue **IV** seems to have a weak propensity to adopt the 12/10-helix.[18]

In this work, we evaluated the foldameric potential of a new type of cyclic γ-residue, **V**, in the context of an α/γ-backbone. As a prelude to conformational analysis, we developed a short synthetic route to the protected γ-amino acid that is necessary for the preparation of oligomers containing subunit **V**. This building block is generated from achiral starting materials in five steps, with all three stereogenic centers set in a single operation. The route should be versatile, allowing future preparation of analogues bearing side chains other than ethyl at Cγ. The resulting α/γ-peptides display a preference for the 12/10-helical secondary structure.

RESULTS AND DISCUSSION

Synthesis. Previously, the building block necessary for incorporation of residue **III** was generated via a route in which the key step involved Michael addition of nitromethane to cyclohexene-1-carboxaldehyde (**1**), a process catalyzed by chiral pyrrolidine **A** (Scheme 1).[20] This reaction generated mostly the trans-disubstituted cyclohexane product, but the cis product that led to residue **III** was formed in sufficient quantity to enable further study. Both of the diastereomeric Michael adducts were generated with >95% ee.[16d] We adapted this approach to prepare the γ-amino acid necessary for residue **V**.

Scheme 1. (top) Synthesis of *N*-Boc-(1*R*,2*R*)-2-((*S*)-1-*amino*propyl)*cyclo*hexanecarboxylic Acid (APCH); (bottom) APCH (Shown in Green) in the Crystal Structure of α/γ-Dipeptide 5



The target γ-amino acid represents a greater challenge than the γ-amino acid that leads to **III**[16d] because there is an additional stereogenic center in **V**, at Cγ. Careful exploration of the reaction conditions revealed that Michael addition of 1-nitropropane to enal **1** could be accomplished with reasonably

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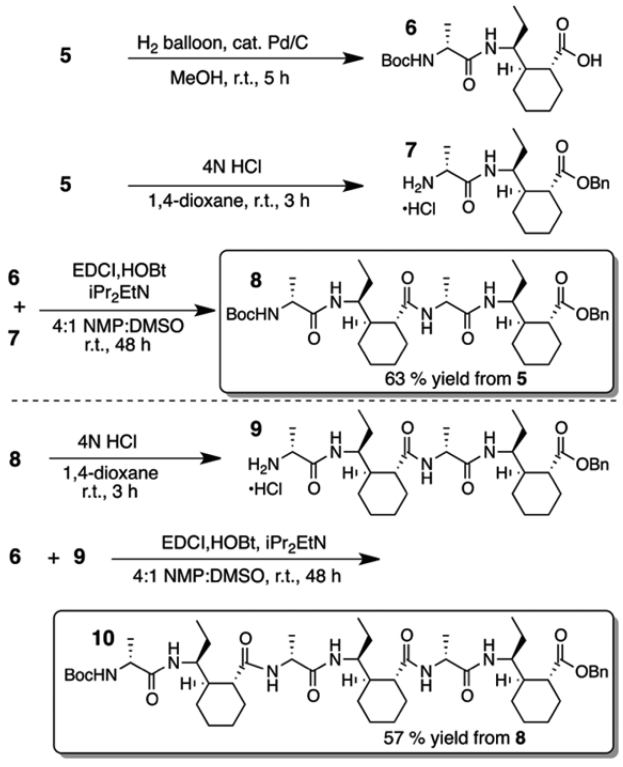
good diastereoselectivity and excellent enantioselectivity if a 1:3 benzoic acid/*N*-methylmorpholine (NMM) mixture was used along with catalyst **A** in ethanol (Scheme 1).[20,21] γ-Nitro aldehyde **2**, the major product, could be prepared on a multigram scale via this method. This compound is susceptible to epimerization at both Cα and Cγ, so oxidation to γ-nitro acid **3** was performed without purification.[22] Attempts to reduce the nitro group of **3** via hydrogenation over Raney Ni led to extensive epimerization at Cγ. After screening many alternative methods (Table S1 in the Supporting Information), we found that epimerization could be avoided by reduction with a large excess of zinc dust in acidified iPrOH/H_2O.[23] Amino group protection provided *N*-Boc-(1*R*,2*R*)-2-((*S*)-1-*a*mino*p*ropyl)*c*yclo*h*exanecarboxylic acid (APCH, **4**). The absolute configuration of this protected γ-amino acid was established by generating the benzyl ester, removing the Boc group, and coupling to Boc-protected D-alanine to generate dipeptide **5**. The crystal structure of **5** revealed a Cγ,Cβ,Cα configuration sequence of *S*,*R*,*R* for the APCH γ-residue (see the Supporting Information).

α/γ-Peptide tetramer **8** and hexamer **10** were prepared from dipeptide **5** (Scheme 2). Coupling reactions were carried out in

Scheme 2. Solution-Phase Synthesis of Alternating α/γ-Peptides Containing (*S*,*R*,*R*)-APCH



4:1 *N*-methylpyrrolidone (NMP)/dimethyl sulfoxide (DMSO) utilizing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt). When more common solvents such as CH_2Cl_2 and DMF, were used for these reactions, precipitation occurred within 30 min. We obtained α/γ-peptide tetramer **8** as a white semicrystalline solid in 63% yield from dipeptide **5** following recrystallization. α/γ-Peptide hexamer **10** was obtained from tetramer **9** and dimer **6** in 57% yield as a white amorphous solid.

Structural Characterization of α/γ-Peptides Containing (*S*,*R*,*R*)-APCH. Diffraction-quality crystals of α/γ-peptide tetramer **8** were obtained from 4:1 heptane/$CHCl_3$. The crystal structure reveals that **8** adopts a 12/10-helical conformation across the first three residues (Figure 2; see the Supporting

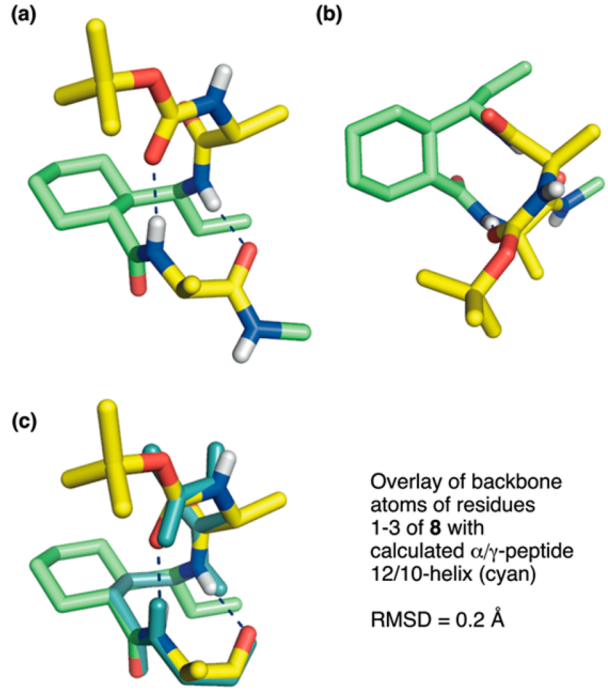


Figure 2. (a) Side view of the crystal structure of α/γ-tetramer **8** (residues 1–3). (b) Top view of crystal structure of α/γ-tetramer **8**. (c) Overlay of tetramer **8** with the calculated 12/10-helix from Hofmann and co-workers.[24] α-Residues and protecting groups are shown in yellow; the γ-residue APCH is shown in green and the Hofmann structure in cyan. The C-terminal APCH residue has been omitted for clarity.

Information for full structures). The C-terminal APCH residue cannot participate in the helical H-bonding pattern because the C-terminal group is an ester rather than a secondary amide. The crystal structure features two intramolecular H-bonds: one C═O(i)···H–N(i+3) (12-membered ring) H-bond between the Boc carbonyl oxygen and the NH proton of ^{D}Ala(3) and one C═O(i)···H–N(i–1) (10-membered ring) H-bond between the carbonyl oxygen of ^{D}Ala(3) and the NH proton of APCH(2). The backbone atoms of the three helical residues of **8** overlay with the corresponding atoms from the calculated α/γ-peptide 12/10-helix of Hofmann and co-workers with a root-mean-square deviation (RMSD) of 0.2 Å (Figure 2c).[24] Comparable conformations have previously been reported for an $\alpha\gamma\alpha\alpha$-tetramer containing gabapentin[25] and for an $\alpha\gamma\alpha\gamma$-tetramer containing residue **III**.[16d] However, an $\alpha\gamma\alpha\gamma\alpha\gamma$-hexamer containing **III** crystallized in a 12-helical conformation (all intramolecular H-bonds oriented in the same direction).

We assessed the folding behavior of tetramer **8** in $CDCl_3$ solution via NMR spectroscopy. Excellent dispersion among the proton resonances (Figure 3a,b) allowed nearly full assignment based on ^{1}H–^{1}H COSY, TOCSY, and ROESY spectra.[26] However, chemical shift overlap prevented assignment of the ring protons, HCβ, and HCγ(β') (methylene of the Cγ side chain) of APCH residues. We observe several nuclear Overhauser effects (NOEs) involving protons on

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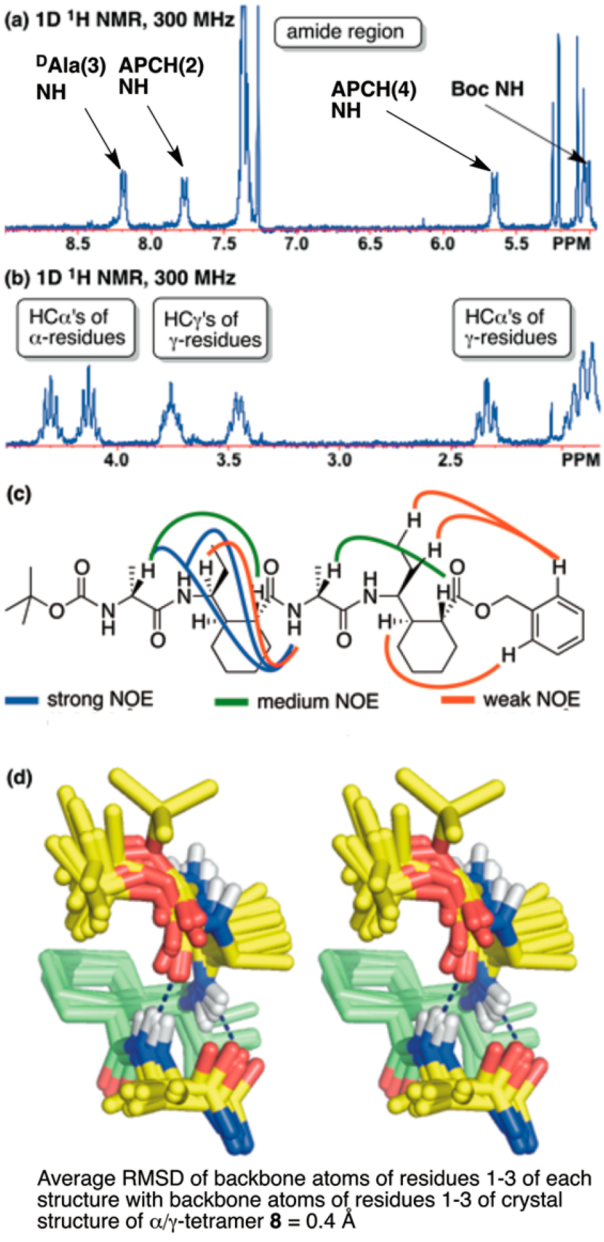

Figure 3. NMR analysis of α/γ-peptide **8** (2 mM in $CDCl_3$). (a) Amide proton region of the ^1H NMR spectrum. (b) HCα and HCγ proton region of the ^1H NMR spectrum. (c) Medium-range NOEs observed in the 2D $^1H-^1H$ ROESY spectrum. (d) Stereo view (side) of the 10 lowest-energy structures of α/γ-peptide **8**, residues 1−3, calculated in CNS.[27] The C-terminal APCH residue has been omitted for clarity. α-Residues are shown in yellow, and the γ-residue APCH is shown in green.

APCH(2) (Figure 3c). Three NOEs in particular correlate with NOE patterns reported by Sharma, Kunwar, and co-workers for α/γ-peptides that were deduced to adopt 12/10-helical conformations:[14] strong NOEs from the HCα of ^{D}Ala(1) to the NH of ^{D}Ala(3) and from the NH of APCH(2) to the NH of ^{D}Ala(3) and a weak NOE from the HCγ of γ-residue i to the NH of α-residue $i + 1$. In addition, we observe several weaker NOEs involving protons on APCH(4).

We used the observed NOEs as restraints to evaluate the solution conformation of α/γ-peptide **8** using the torsional force field molecular dynamics/simulated annealing protocol in Crystallography & NMR System (CNS) (Figure 3d; see the Supporting Information).[27] The NMR-based ensemble generated in this way is consistent with 12/10-helix formation across the first three residues, as seen in the crystal, with one 12-membered-ring H-bond and one 10-membered-ring H-bond. The amide protons that participate in these intramolecular H-bonds are the two that are furthest downfield, while the upfield NH resonances correspond to the Boc NH proton (~5 ppm) and the NH proton of APCH(4), which do not form intramoleculcar hydrogen bonds in the crystal.

The NMR-derived solution conformation appears to be very similar to the crystal structure of **8**. The backbone atoms of the first three residues for each member of the NMR ensemble overlay well with the corresponding atoms of the crystal structure (average RMSD of 0.4 Å). The NMR-derived conformation is highly ordered even at the termini, which is noteworthy for such a short oligomer. Overall, the data suggest that the APCH residue strongly enforces a 12/10-helical secondary structure in both solution and the crystalline state.

For α/γ-peptide hexamer **10**, the 1D ^1H NMR spectrum displays four downfield amide NH resonances, which were assigned to the four interior amide NH groups via COSY, TOCSY, and ROESY experiments. As was the case for tetramer **8**, the Boc NH resonance and the C-terminal γ-residue amide NH resonance of hexamer **10** were upfield relative to the resonances of the other amide protons (5−6 ppm; Figure 4a). The ^{D}AlaHCα, γ-residue HCγ, and γ-residue HCα resonances were all resolved at 4−5 ppm, 3−4 ppm, and 2−3 ppm, respectively (Figure 4b). We observed 15 nonsequential NOEs for α/γ-peptide hexamer **10** (Figure 4c). In particular, we observed strong NOEs from the HCα of α-residue i to the NH

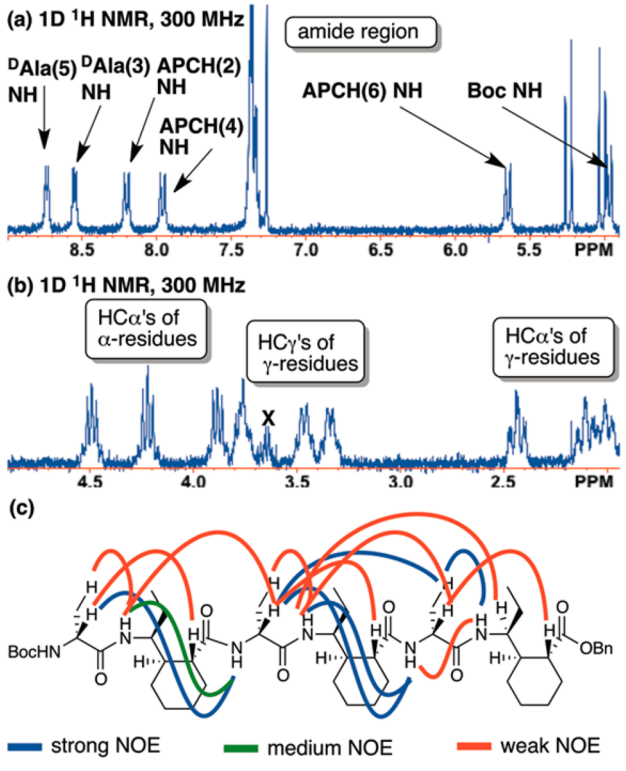

Figure 4. NMR analysis of α/γ-peptide **10** (3 mM in $CDCl_3$). (a) Amide proton region of the ^1H NMR spectrum. (b) HCα and HCγ proton region of the ^1H NMR spectrum. (c) Medium-range NOEs observed in the 2D $^1H-^1H$ ROESY spectrum. X is an unassigned resonance.[19]

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of α-residue i + 2 and from the NH of γ-residue i to the NH of α-residue i + 1 across both APCH(2) and APCH(4). In addition to these four characteristic 12/10-helical NOEs,[14,18] we observed 11 other interwoven NOEs along the length of the α/γ-peptide, suggestive of a compact, ordered conformation in solution. Such a pattern of NOEs was noticeably absent in previous studies of longer α/γ-oligomers containing γ-residue **IV**.[18]

We used the 15 observed medium-range NOEs as restraints to evaluate the solution conformation of α/γ-peptide **10** with CNS (Figure 5).[27] The 10 lowest-energy conformations of **10**

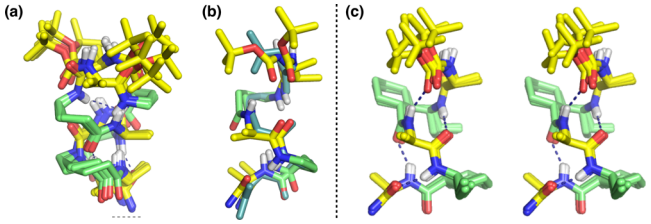
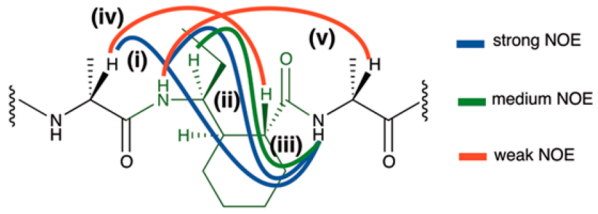


Figure 5. (a) Ten lowest-energy NMR structures of α/γ-peptide **10**, residues 1−5, calculated in CNS.[27] (b) Overlay of helices from population I and population II with the calculated α/γ-peptide 12/10-helix from Hofmann and co-workers.[24] (c) Stereo view of residues 1−5 of 12/10-helical population I structures. The C-terminal APCH residue has been omitted for clarity. α-Residues and protecting groups are shown in yellow; the γ-residue APCH is shown in green and the Hofmann structure in cyan. Side chains (a, b) and residue 6 have been omitted for clarity after calculation in (a) and (b).

are split into two sets of five structures. As was the case for the ensemble of tetramer **8**, the C-terminal APCH residue of hexamer **10** does not participate in the 12/10-helix in either population, presumably because the terminal ester group does not provide an H-bond donor site. Population I (Figure 5a,c) consists of two turns of the 12/10-helix. The members of this set contain 12-membered-ring H-bonds between the Boc carbonyl and the NH proton of ^{D}Ala(3) and between the carbonyl of APCH(2) and the NH proton of ^{D}Ala(5) and 10-membered-ring H-bonds between the carbonyl of ^{D}Ala(3) and the NH proton of APCH(2) and between the carbonyl of ^{D}Ala(3) and the NH proton of APCH(2). The members of population II are quite similar to the members of population I; however, the backbone of population II conformations is distorted in such a way that the putative H-bond donor−acceptor pairs are slightly misaligned, resulting in a lack of ideal H-bonding geometries in this population. Nevertheless, we believe that population II should be considered as a variant within the 12/10-helical conformational envelope. Backbone atoms from a representative structure in population I overlay with backbone atoms from a representative structure in population II with an RMSD of 0.8 Å. Moreover, a structure in population I overlays with an idealized 12/10-helix with an RMSD of 0.4 Å,[24] while a structure from population II overlays with an RMSD of 1.1 Å (Figure 5b). This analysis suggests that the entire NMR ensemble generated for hexamer **10** in $CDCl_3$ is consistent with a two-turn 12/10-helical conformation (Figure 5c).

Characteristics of the α/γ-Peptide 12/10-Helix Derived from Structural Study of APCH-Containing α/γ-Peptides. Our NMR analysis of **8** and **10** suggests that five medium-range NOE patterns are characteristic of the α/γ-peptide 12/10-helix conformation (Figure 6). Strong NOEs are



(i) HCα α-residue (i) to NH of α-residue (i+2) **strong**
(ii) NH of γ-residue (i) to NH of α-residue (i+1) **strong**
(iii) HCγ of γ-residue (i) to NH of α-residue (i+1) **medium**
(iv) HCα of α-residue (i) to HCα of γ-residue (i+1) **weak**
(v) NH of γ-residue (i) to HCα of α-residue (i+1) **weak**

NOE	designation	NMR distance (Å)	Crystal distance (Å)[b]
(i)	strong	2.6[a]	2.90
(ii)	strong	2.5[a]	2.65
(iii)	medium	3.5[a]	4.67
(iv)	weak	3.6[c]	3.79
(v)	weak	4.0[c]	4.11

Figure 6. Characteristic NOEs of the α/γ-peptide 12/10-helix. [a]Distance obtained from the NMR structure of tetramer **8**. [b]Distances obtained from the crystal structure of tetramer **8**. [c]Distance obtained from the NMR structure of hexamer **10**.

expected from the HCα of α-residue i to the NH of α-residue i + 2 and from the NH of γ-residue i to the NH of α-residue i + 1 [NOE types (i) and (ii)]. Medium NOEs are expected from the HCγ of γ-residue i to the NH of α-residue i + 1 [NOE type (iii)]. These three NOE patterns were detected by Sharma, Kunwar, and co-workers for α/γ-peptides that were assigned to adopt 12/10-helical conformations.[14] We detected NOE types (i) and (ii) but not type (iii) in α/γ-peptides containing **IV**, which suggested a weak folding propensity for this γ-residue.[14,18]

We observed additional medium/weak NOEs from the HCα of α-residue i to the HCα of γ-residue i + 1 and from the NH of γ-residue i to the HCα of α-residue i + 1 [NOE types (iv) and (v), respectively]. We note that this last NOE [type (v)] was observed only in the 2D ROESY spectrum of hexamer **10**, suggesting that it may be indicative of extended 12/10-helix formation. These characteristic NOE types are supported by comparison of the integrated distances we obtained to the corresponding measured distances in the crystal structure of **8** (Figure 6). In all but one case [type (iii)], we see excellent agreement between the measurements. NOE type (iii) was observed only in the NMR spectrum of tetramer **8** but was also observed consistently in the work of Sharma and Kunwar.[14] Therefore, despite this disagreement in our own data, we have included it in this analysis (designated as medium-strength) to accommodate residues other than APCH, which may vary in their substitution pattern and stereochemistry.

Comparisons of the APCH residues in the crystal structure of α/γ-peptide **8** and the NMR-derived structures of **8** and **10** suggest a consistent local conformation for this new foldamer building block. The Cβ−Cγ and Cα−Cβ torsion angles of APCH in these structures (θ and ζ, respectively) are consistent with the average values for γ-residues in a 12/10-helix calculated by Hofmann and co-workers[24] (Table 1). The ζ torsion angles are generally near gauche$^-$ values, as seen for cyclohexyl-constrained backbone bonds in previously studied γ-residues **I** and **III**. In contrast, the θ torsion angles in the structures of **8** and **10** are more acute than the corresponding θ

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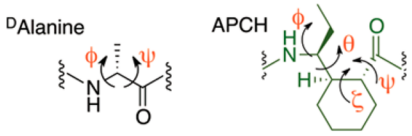
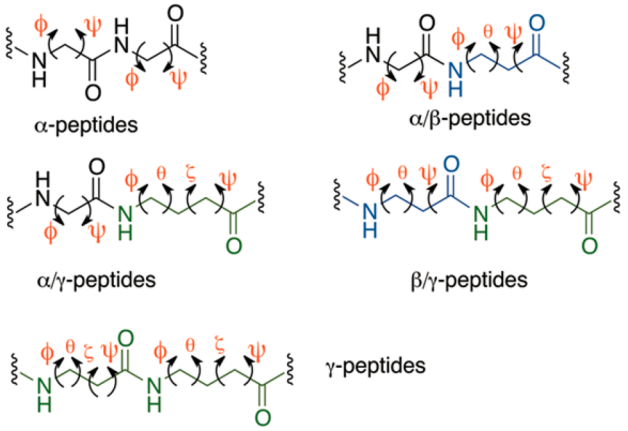
Table 1. Backbone Torsion Angles[a] for α/γ-Peptides 8 and 10



peptide residue	ϕ (deg)	θ (deg)	ζ (deg)	ψ (deg)
		8 (Crystal Structure)		
^{D}Ala(1)	**66.4**	–	–	**−137.3**
APCH(2)	**−84.2**	**−20.5**	**−56.1**	**130.2**
^{D}Ala(3)	**73.9**	–	–	**−153.7**
APCH(4)	−93.7	169.2	−51.2	−66.9
		8 (NMR Ensemble)		
^{D}Ala(1)	**110 ± 10**	–	–	**−137 ± 7**
APCH(2)	**−80 ± 10**	**−20 ± 10**	**−70 ± 2**	**130 ± 20**
^{D}Ala(3)	**120 ± 10**	–	–	**−144 ± 3**
APCH(4)	−120 ± 9	−30 ± 1	−71 ± 1	−52 ± 4
		10 (NMR Ensemble)		
^{D}Ala(1)	**110 ± 10**	–	–	**−132 ± 3**
APCH(2)	**−85 ± 9**	**−10 ± 10**	**−70 ± 8**	**135 ± 2**
^{D}Ala(3)	**110 ± 20**	–	–	**−140 ± 1**
APCH(4)	**−110 ± 10**	**9 ± 9**	**−75 ± 8**	**122 ± 1**
^{D}Ala(5)	**85 ± 1**	–	–	**−157 ± 1**
APCH(6)	−129 ± 6	−20 ± 30	−90 ± 30	50 ± 90
		Averages (All Helical Residues)		
^{D}Ala	**110 ± 20**	–	–	**−140 ± 9**
APCH	**−90 ± 10**	**−7 ± 20**	**−71 ± 9**	**130 ± 10**
		Hofmann Values[b]		
α	68 ± 2	–	–	−148 ± 1
γ	−64 ± 1	−32 ± 1	−48 ± 1	132 ± 5

[a]Values set in bold type indicate residues observed to participate in 12/10-helices. [b]Hofmann values are averages for α- and γ-residues calculated from 12/10-helix conformer I, available in the Supporting Information of ref 24.

Table 2. Relative Signs of the ϕ and ψ Dihedral Angles for α-Peptide Helices and Selected Helices of Peptidic Foldamers[a]



helix (oligomer type)	residue i, sign ϕ, sign ψ	residue i + 1, sign ϕ, sign ψ	H-bond direction
α-helix[28] (α-peptides)	α, −, −	α, −, −	uniform
3_{10}-helix[28] (α-peptides)	α, −, −	α, −, −	uniform
12-helix[15a] (α/γ-peptides)	α, −, −	γ, −, −	uniform
13-helix[15b] (β/γ-peptides)	β, −, −	γ, −, −	uniform
14-helix[15c] (γ-peptides)	γ, −, −	γ, −, −	uniform
16/18-helix[13b] (α/β-peptides)	α, −, −	β, +, +	alternating
11/9-helix[13c] (α/β-peptides)	α, +, −	β, −, +	alternating
12/10-helix (α/γ-peptides)	α, +, −	γ, −, +	alternating

[a]In the scheme at the top of the table, α-residues are shown in black, β-residues in blue, and γ-residues in green.

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torsion angles in oligomers containing γ-residue **I** or **III**.[16a,d] We propose that the ability of APCH to accommodate relatively small θ values is related to its apparent propensity for the 12/10-helix in the α/γ-peptide context.

Martinek, Fülöp, and co-workers have noted that the relationships between the ϕ and ψ angles of adjacent residues in α/β- and β-peptides are correlated with the observed helical conformations.[13a,b] Specifically, these workers have noted that for a given backbone amide bond between residue *i* and residue *i* + 1, the ψ angle of residue *i* and the ϕ angle of residue *i* + 1 must have the same sign for a helical secondary structure to form. If successive $\psi(i)/\phi(i+1)$ pairs have the same sign, then the helix has all of the amide−amide H-bonds oriented in one direction. In contrast, if successive $\psi(i)/\phi(i+1)$ pairs have opposite signs, then the amide−amide H-bonds alternate in their directionality relative to the helix axis.[13b] This latter pattern is observed for the α/γ-peptide 12/10-helix, and sign alternation between neighboring $\psi(i)/\phi(i+1)$ torsion angle pairs is evident in Table 1. Table 2 compares a number of helical secondary structures observed among peptidic backbones containing α-, β-, and/or γ-residues, showing that even foldamers containing γ-residues follow the trends identified by Martinek, Fülöp, and co-workers.[13b]

CONCLUSIONS

We envisioned that APCH might have a high propensity for helix formation because of the six-membered-ring constraint on the Cα−Cβ bond and the substituent at Cγ. We observed 12/10-helical conformations in both solution and the crystalline state for α/γ-peptide tetramer **8** and in solution for hexamer **10**. We therefore conclude that γ-residue APCH possesses a significant propensity for the α/γ-peptide 12/10-helix, and we speculate that this residue may support other helical secondary structures with alternating H-bonding direction in the context of different peptidic backbones. The observed APCH propensity appears to be related to this residue's ability to accommodate relatively small θ dihedral angles and opposite relative signs of the ϕ and ψ dihedral angles. Our findings support the proposal of Martinek, Fülöp, and co-workers[13a,b] that the relative signs of $\psi(i)/\phi(i+1)$ torsion angle pairs is an important consideration for foldamer design.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures for synthetic reactions, 2D NMR data collection, and NOE-restrained molecular dynamics calculations; reaction screening tables with accompanying discussion of the optimized conjugate addition utilized in the synthesis of γ-residue APCH; ^{1}H and ^{13}C NMR spectra for all new compounds; tabulated 2D NMR data with associated spectra for all peptides; aggregation control experiment for α/γ-peptide **10**; tabulated dihedral angle measurements used in Table 1; crystallographic data (CIF); and images of the crystal structure of **8** and the NMR structures of **8** and **10** without the C-terminal residues omitted. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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