

Non-classical Helices with *cis* Carbon–Carbon Double Bonds in the Backbone: Structural Features of α,γ -Hybrid Peptide Foldamers

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Abstract: The impact of geometrically constrained *cis* α,β -unsaturated γ -amino acids on the folding of α,γ -hybrid peptides was investigated. Structure analysis in single crystals and in solution revealed that the *cis* carbon–carbon double bonds can be accommodated into the 12-helix without deviation from the overall helical conformation. The helical structures are stabilized by 4 $\rightarrow$ 1 hydrogen bonding in a similar manner to the 12-helices of β -peptides and the 3_{10} helices of α -peptides. These results show that functional *cis* carbon–carbon double bonds can be accommodated into the backbone of helical peptides.

Despite backbone conformational freedom, β - and γ -peptides, along with hybrid α,β -, α,γ -, and β,γ -peptide sequences, display a variety of distinct helical structures.^[1] Indeed, by carefully controlling the sequence of these non-natural oligomers, it is possible to mimic protein secondary structures, and this structural mimicry can be exploited to design inhibitors for protein–protein interactions^[2] as well as antimicrobials.^[3] In comparison to β -peptides, greater foldameric potential is expected from γ -residues owing to the presence of three backbone carbon atoms.^[1d] Indeed, the helical folding of γ -amino acid oligomers was first examined by Rydon using the natural polymer poly- γ -D-glutamate.^[4] In early work, Schreiber and co-workers demonstrated the formation of extended β -sheet and helical structures from peptides composed of naturally occurring (*E*)- α,β -unsaturated γ -amino acids.^[5] More convincing evidence on the folding of γ -peptides came from the groups of Seebach^[6] and Hanessian,^[7] and they independently showed well-defined 14-helical organizations from homooligomers of γ^4 -, $\gamma^{2,4}$ - and $\gamma^{2,3,4}$ -amino acids. Furthermore, the foldameric potential of γ - and hybrid γ -peptides have been thoroughly investigated through *ab initio* theoretical calculations.^[8] Balaram et al. demonstrated the utility of γ^4 - and spiro $\gamma^{3,3}$ -amino acids (gabapentin) in the design of helices.^[1i,9,10] Recently, Gellman and colleagues have reported a variety of helical structures

from γ - and hybrid γ -peptides composed of stereochemically constrained cyclic γ -amino acids.^[11] In addition, a variety of γ -amino acids have been explored in the design of foldamers.^[12] However, little is known about the utilization of geometrically constrained α,β -unsaturated γ -amino acids in foldamers design. Nevertheless, Hofmann and co-workers have provided a comprehensive overview on the helix types available to the *E*- and *Z*-vinylogous homooligomers using theoretical calculations.^[13] Recently Maillard and co-workers showed C_9 helices from γ -peptides composed of thiazole-based amino acids, which mimic the *Z*-vinylogous residues.^[14] Grison et al. and others also reported turn mimetics using *Z*-vinylogous amino acids.^[15] Recently, we demonstrated the design of stable β -hairpins, three-stranded β -sheets, and miniature β -meander mimetics (Figure 1) through selective incorporation

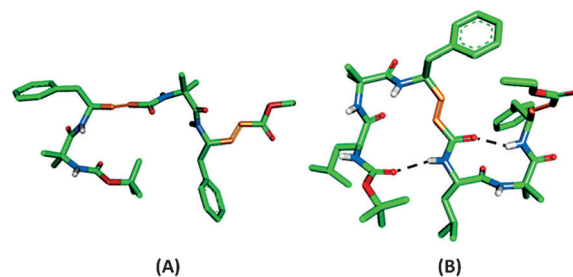


Figure 1. A) The unusual planar structure resulting from 1:1 alternating α -residues and *E*-vinylogous residues (Boc-Aib-E γ Phe-Aib-E γ Phe-OEt).^[17] B) A miniature β -meander mimetic consisting of an α,α,γ -hybrid peptide (Boc-Leu-Aib-E γ Phe-Leu-Aib-E γ Phe-OEt).^[16b] Aib = 2-aminoisobutyric acid. C green, O red, N blue, H white, vinyl group orange.

of *E*-vinylogous residues into hybrid peptides.^[16] Furthermore, we have shown an unusual planar structure from 1:1 alternating α -residues and *E*-vinylogous residues (Figure 1).^[17] By using mild catalytic hydrogenation, we transformed the unusual planar structure resulting from 1:1 alternating α -residues and *E*-vinylogous residues and miniature β -meanders into 12 [12-atom H-bond pseudocycle between C=O(*i*)...NH(*i* + 3)] and 10/12 [alternating 10-atom H-bond pseudocycle and 12-atom H-bond pseudocycle between C=O(*i*)...NH(*i* + 3)] α,γ^4 -hybrid peptide helices, respectively.^[16b,17] Since *E*-vinylogous amino acids promote β -sheet structures in hybrid peptides,^[16] we hypothesized that the geometrical constraints of *Z*-vinylogous amino acids could be utilized to design helical structures. Since conjugated double bonds have been extensively utilized as intermediates for various chemical transformations,^[18] we anticipate that

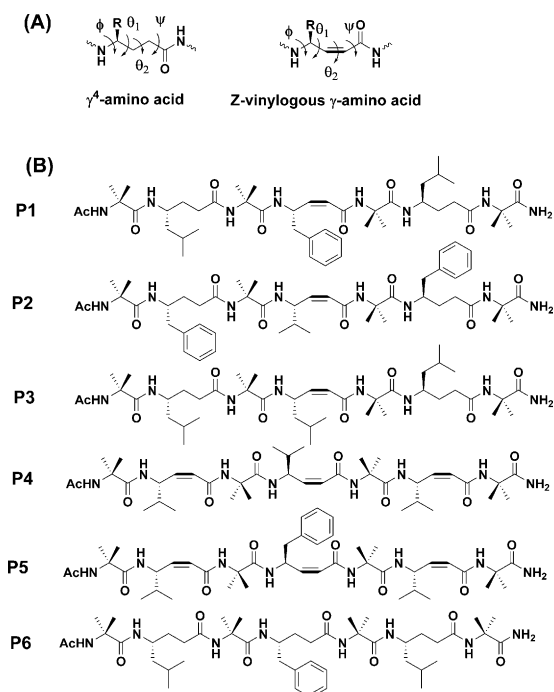
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helices with carbon–carbon double bonds may find potential applications in organic chemistry and chemical biology. Herein, we report the design, synthesis, and solution and single-crystal conformation of various α,γ -hybrid peptides (**P1–P5**) composed of *Z*-vinyllogous residues. Structural analysis shows that *cis* double bonds can be accommodated into an α,γ -hybrid 12-helix without deviation from the overall helix folding.

The sequences of the peptides are given in the Scheme 1. The design was based on the previously reported, well characterized α,γ^4 -hybrid peptide 12-helix **P6**, which is composed of alternating α - and γ^4 -amino acids.^[19] To determine whether the *cis* double bond can be accommodated into the helix, we designed **P1**, in which the γ^4 Phe4 in **P6** was replaced with *Z* γ^4 Phe (*Z*-vinyllogous γ^4 -phenylalanine). The *Z*-vinyllogous amino acid was synthesized by using the Horner–Wadsworth–Emmons (HWE) reaction.^[20] Peptide **P1** was synthesized through solid-phase synthesis with Fmoc chemistry. All coupling reactions were carried with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent. The pure peptide was subjected to crystallization to determine its conformation.

Diffraction-quality crystals of **P1** were obtained through slow evaporation of the peptide in aqueous methanol solution, and its X-ray structure is shown in Figure 2. Strikingly, the structure analysis of **P1** reveals that it adopts a right-handed 12-helix conformation similar to that of model peptide **P6**. The 12-helix conformation is stabilized by six intramolecular H-bonds between *i* (C=O) and *i*+3 (NH) residues. The H-bond parameters of **P1** are tabulated in the Supporting Information. The backbone conformations of γ -



Scheme 1. A) Local torsion variables of γ^4 -residues and *Z*-vinyllogous residues. B) Sequences of the α,γ -hybrid peptides **P1–P5**, along with the model α,γ^4 -hybrid peptide 12-helix **P6**.

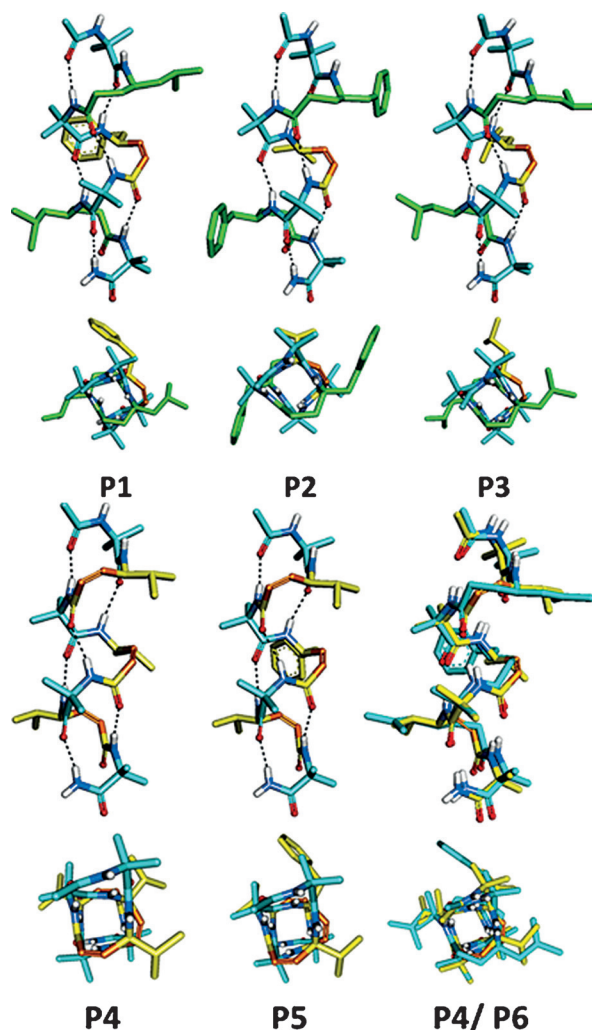


Figure 2. X-ray structures of the α,γ -hybrid peptides **P1–P5** (*Z*-vinyllogous residues are shown in yellow and C=C bonds in orange). A superposition of **P4** onto the α,γ^4 -hybrid peptide **P6** is also shown. Top views are shown below the side views.

residues can be measured by introducing two additional torsional variables, θ_1 and θ_2 , along with ϕ and ψ (Scheme 1A). Extensive theoretical^[8b,13b] and experimental^[8b,9,10,11a,c,12e,g] investigations suggested that saturated γ -residues prefer to adopt *gauche*⁺, *gauche*⁺ (*g*⁺, *g*⁺) conformation along C γ –C β (θ_1) and C β –C α (θ_2) bonds and anticlinal conformations along N–C γ (ϕ) and C α –C'(O) (ψ) bonds to accommodate into the helix ($\theta_1 \approx \theta_2 \approx \pm 60^\circ$ and $\phi \approx \psi \approx \pm 120^\circ$). As with peptide **P6**, the saturated γ^4 -amino acids γ^4 Leu2 and γ^4 Leu6 in **P1** adopted *g*⁺, *g*⁺ conformations along C γ –C β and C β –C α bonds and anticlinal conformation along N–C γ and C α –C'(O) bonds. Interestingly, the unsaturated amino acid *Z* γ^4 Phe4 also accommodated into the 12-helix, with an inherent *cis* double bond along the C β –C α bond ($\theta_2 \approx 0^\circ$). The torsion angles of the *Z* γ^4 Phe4 are listed in the Table 1. Instructively, θ_1 and θ_2 attained values of $+95^\circ$ and -2° , respectively, and ϕ and ψ showed the values of -122° and -79° , respectively. To determine whether any other *Z*-vinyllogous residues can be accommodated into the helix, we designed peptides **P2** and **P3**, which contain *Z* γ^4 Val4 and *Z* γ^4 Leu4, respectively, and

Table 1: Dihedral angles of the (Z)-vinyllogous residues in **P1–P5**.

Peptide	ϕ	θ_1	θ_2	ψ
P1	-122°	95°	-2°	-79°
P2	-124°	106°	0°	-74°
P3	-115°	98°	-4°	-83°
P4	$-119 \pm 3^\circ$	$99 \pm 4^\circ$	$3 \pm 1^\circ$	$-79 \pm 7^\circ$
P5	$-117 \pm 5^\circ$	$104 \pm 1^\circ$	$-1 \pm 2^\circ$	$-75 \pm 2^\circ$
Average	$-119 \pm 4^\circ$	$100 \pm 5^\circ$	$0 \pm 3^\circ$	$-78 \pm 4^\circ$

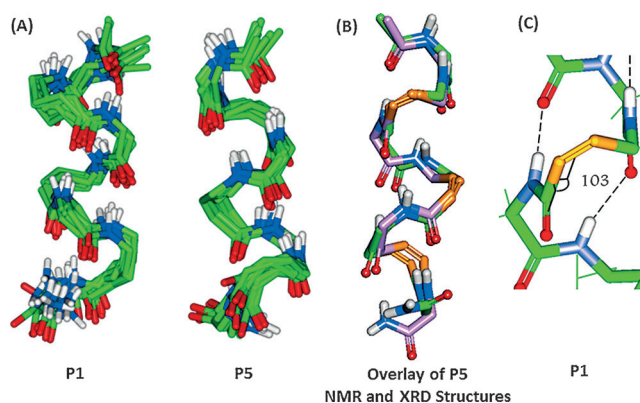
synthesized them in a similar manner to **P1**. The X-ray structures of **P2** and **P3** are shown in Figure 2. Both **P2** and **P3** adopt right-handed 12-helical conformations akin to **P1**. The structures are stabilized by six intramolecular H-bonds between i (CO) and $i+3$ (NH) residues. The torsion angles of the Z-vinyllogous residues are listed in the Table 1. Analysis revealed that $Z\gamma^4$ Val and $Z\gamma^4$ Leu adopt similar torsion values to those of $Z\gamma^4$ Phe in **P1**. Inspired by the successful accommodation of single *cis* double bonds into the hybrid peptide helices **P1–P3**, we designed **P4** and **P5**, which have 1:1 alternating α -residues and Z-vinyllogous residues. The X-ray structures of **P4** and **P5** are shown in Figure 2. Remarkably, peptides **P4** and **P5** adopt right-handed 12-helical conformations in single crystals. In sharp contrast to the unusual planar conformation of hybrid tetrapeptides composed of 1:1 alternating α -residues and E-vinyllogous residues (Figure 1),^[17] hybrid peptides with 1:1 alternating α -residues and Z-vinyllogous residues adopt a 12-helix conformation. The average dihedral angles of Z-vinyllogous residues are listed in the Table 1. The 12-helix conformation in both **P4** and **P5** is stabilized by six intramolecular H-bonds between residues i and $i+3$. The 4 $\rightarrow$ 1 H-bonding pattern observed in the α,γ -hybrid peptides resembles that of the 12-helix conformation of β -peptides,^[21a] which is analogous to the 3₁₀-helix of α -peptides.^[21b] The H-bonding parameters of all the peptides are tabulated and given in the Supporting Information. Intriguingly, structural analysis of **P1–P5** revealed that Z-vinyllogous residues attain unique and distinct dihedral angles to accommodate into the helix compared to other γ^4 -, $\gamma^{2,4}$ -, $\gamma^{3,4}$ -, $\gamma^{3,3}$ - and $\gamma^{2,3,4}$ -residues, as well as cyclic γ -residues. Table 2 shows a comparison of four torsion angles of Z-vinyllogous residues and other γ -residues in various α,γ -hybrid 12-helices. Examination of all the crystal structures (**P1–P5**) revealed that the Aib residues display average ϕ and ψ values of $-56 \pm 6^\circ$ and $-44 \pm 6^\circ$, respectively. Further, we superimposed the structures of **P4** and **P6** to compare their backbone conformations

Table 2: Comparison of the backbone torsion angles of the Z-vinyllogous γ -amino acids with other γ -residues in α,γ -hybrid 12-helices.

α,γ -hybrid 12-Helix	ϕ	θ_1	θ_2	ψ
γ^4 -AA ^[12g]	$-124 \pm 6^\circ$	$51 \pm 2^\circ$	$62 \pm 3^\circ$	$-122 \pm 9^\circ$
$\gamma^{3,3}$ -AA ^[10]	$-124 \pm 4^\circ$	$56 \pm 6^\circ$	$64 \pm 8^\circ$	$-112 \pm 10^\circ$
$\gamma^{2,3,4}$ -AA (cyclic) ^[11a]	$140 \pm 10^\circ$	$-56 \pm 2^\circ$	$-52 \pm 2^\circ$	$111 \pm 4^\circ$
Theoretical model ^[8b]	$-122 \pm 2^\circ$	$52 \pm 2^\circ$	$62 \pm 2^\circ$	$-125 \pm 4^\circ$
$\gamma^{2,3}$ -AA (cyclic) ^[11e]	$-129 \pm 9^\circ$	$56 \pm 2^\circ$	$55 \pm 2^\circ$	$-120 \pm 9^\circ$
$\gamma^{3,4}$ -AA ^[12]	$-120 \pm 2^\circ$	$50 \pm 5^\circ$	$64 \pm 2^\circ$	$-127 \pm 2^\circ$
Z- γ^4	$-119 \pm 4^\circ$	$100 \pm 5^\circ$	$0 \pm 3^\circ$	$-78 \pm 4^\circ$
(Present work)				

(Figure 2). The excellent backbone correlation between **P4** and **P6** suggests that Z-vinyllogous residues can be accommodated into a well folded 12-helix, with a new set of backbone torsional angles. Strikingly, despite the rigidity of backbone *cis* double bonds ($\theta_2 \approx 0^\circ$), the 12-helix fold is facilitated by notable deviations in the neighbored torsion angles θ_1 and ψ , which are different from those in other 12-helices (Table 2).

Careful analysis of the local conformations of Z-vinyllogous residues in 12-helices revealed very interesting features of the carbonyl-conjugated *cis* carbon-carbon double bonds. None of the *cis* double bonds of the Z-vinyllogous residues in the hybrid helices are π -conjugated to the carbonyl groups since they deviate from planarity (Figure 3C). The local torsion angles ($C^\beta-C^\alpha-C=O = 103^\circ$) of Z-vinyllogous residues revealed that the C=C double bonds are almost perpendicular to the carbonyl group, thus suggesting an absence of π conjugation (Figure 3C). We envisage that the absence of π conjugation may have an influence on the reactivity of double bonds.

**Figure 3.** A) Solution conformations of the α,γ -hybrid peptides **P1** and **P5**. B) An overlay of the X-ray and NMR structures of **P5**. C) The X-ray structure of peptide **P1**, illustrating the non-planarity of the C=C and C=O bonds ($C^\beta-C^\alpha-C=O = 103^\circ$) in the Z-vinyllogous residues.

To gain insight into their solution conformations, we subjected **P1** (a single Z-vinyllogous residue) and **P5** (three Z-vinyllogous residues) to 2D NMR analysis. Both **P1** and **P5** showed well resolved 1H NMR spectra in CD_3OH . The sequence of the amino acids was identified by using TOCSY and ROESY. Analysis of the ROESY spectra revealed characteristic NOEs between $C^H(i)$ and $NH(i+2)$, as well as between $C^H(i)$ and $NH(i+1)$. All unambiguous NOEs observed in the **P1** and **P5** are tabulated in the Supporting Information. The NOE pattern we observed is consistent with the NOEs observed for reported 12-helix solution structures.^[11e,22] Based on the experimentally deduced NOEs, calculation of solution structures were performed by using distance restrained molecular dynamic simulations as reported earlier.^[23] The overlay of 10 low-energy conformers of NMR-calculated structures of **P1** and **P5** are shown in Figure 3A. The solution structures showed excellent correlation with the conformation in single crystals.

A superimposition of the solution and crystal conformations of **P5** is shown in Figure 3B.

In conclusion, we present single-crystal and solution conformations of novel α,γ -hybrid peptide 12-helices composed of *Z*-vinyllogous amino acids. The results suggest that *Z*-vinyllogous residues show an intrinsic tendency to adopt helical conformation, however, with a distinct new set of backbone torsion angles compared to the other γ -amino acids. Remarkably, the *cis* double bonds and carbonyl groups in *Z*-vinyllogous residues showed no π conjugation compared to their (*E*)-isomers in hybrid peptides. The deviation from planarity of the carbonyl-conjugated double bonds in the helix may be dictated by the strength of canonical intramolecular H-bonds. These novel non-classical helices with functionalizable carbon-carbon double bonds in the backbone may provide new opportunities in the design of functional peptide foldamers. We are currently exploring the chemical reactivity of these unsaturated helices.

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