Foldamers

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

*Mothukuri Ganesh Kumar, Varsha J. Thombare, Mona M. Katariya, Kuruva Veeresh, K. Muruga Poopathi Raja, and Hosahudya N. Gopi**

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→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 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

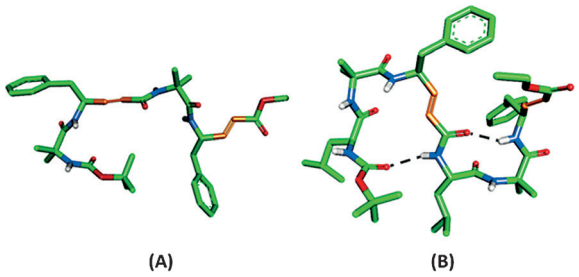

Figure 1. A) The unusual planar structure resulting from 1:1 alternating α-residues and *E*-vinylogous residues (Boc-Aib-*E*γPhe-Aib-*E*γPhe-OEt).[17] B) A miniature β-meander mimetic consisting of an α,α,γ-hybrid peptide (Boc-Leu-Aib-*E*γPhe-Leu-Aib-*E*γPhe-OEt).[16b] Aib = 2-aminoisobutyric acid. C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

[*] M. Ganesh Kumar, V. J. Thombare, M. M. Katariya, K. Veeresh, Prof. Dr. H. N. Gopi
Department of Chemistry
Indian Institute of Science Education and Research
Dr. Homi Bhabha Road, Pashan, Pune-411008 (India)
E-mail: hn.gopi@iiserpune.ac.in
Prof. Dr. K. M. P. Raja
Department of Physical Chemistry
School of Chemistry, Madurai Kamaraj University, Madurai-625 021 (India)

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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*-vinylogous 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^4Phe4 in **P6** was replaced with with *Z*γ^4Phe (*Z*-vinylogous γ^4-phenylalanine). The *Z*-vinylogous 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-residues can be measured by introducing two additional torsional variables, θ_1 and θ_2, along with ϕ and ψ (Scheme 1 A). Extensive theoretical[8b,13b] and experimental[8b,9,10,11a,e,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 ($\theta_1 \approx \theta_2 \approx \pm 60°$ and $\phi \approx \psi \approx \pm 120°$). As with peptide **P6**, the saturated γ^4-amino acids γ^4Leu2 and γ^4Leu6 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^4Phe4 also accommodated into the 12-helix, with an inherent *cis* double bond along the C^β–C^α bond ($\theta_2 \approx 0°$). The torsion angles of the *Z*γ^4Phe4 are listed in the Table 1. Instructively, θ_1 and θ_2 attained values of +95° and −2°, respectively, and ϕ and ψ showed the values of −122° and −79°, respectively. To determine whether any other *Z*-vinylogus residues can be accommodated into the helix, we designed peptides **P2** and **P3**, which contain *Z*γ^4Val4 and *Z*γ^4Leu4, respectively, and

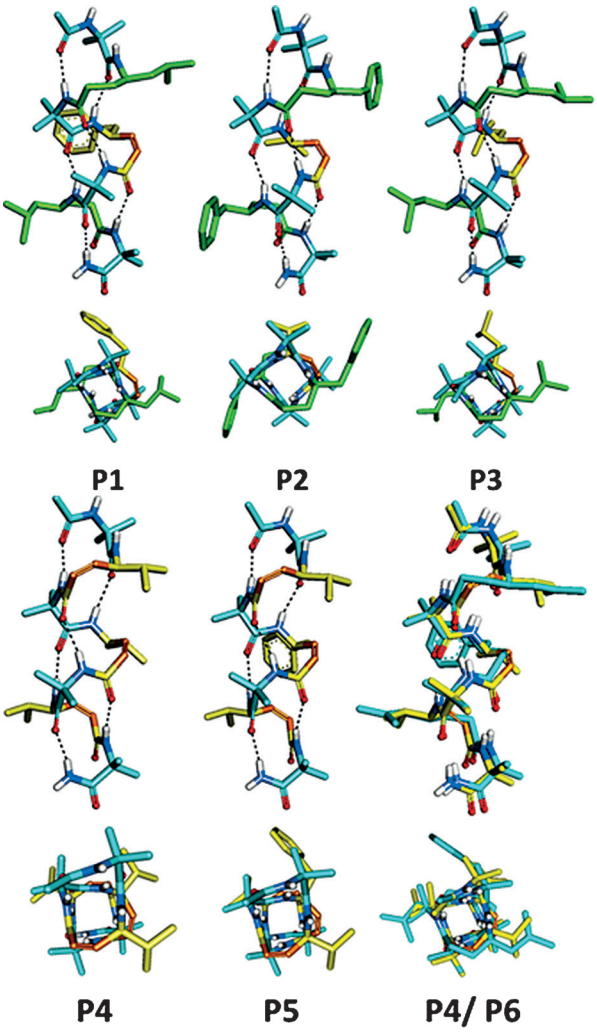
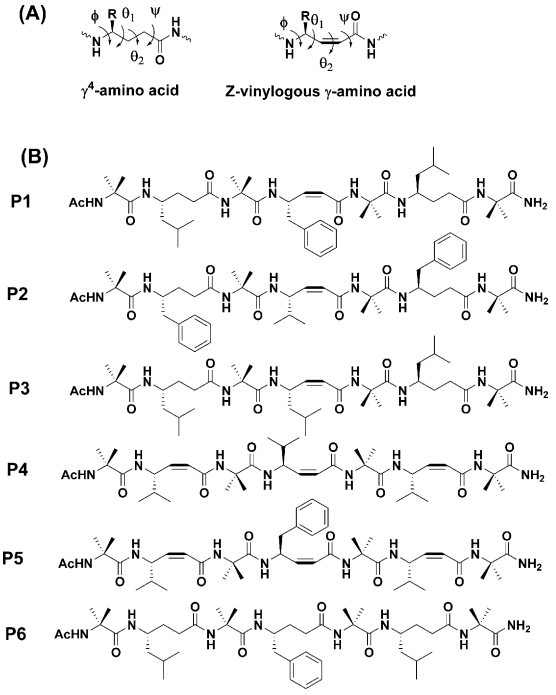


Figure 2. X-ray structures of the α,γ-hybrid peptides **P1–P5** (Z-vinylogous residues are shown in yellow and C=C bonds in orange). A superposition of **P4** onto the α,γ^4-hybrid peptide **P6** is also shown. Top views are shown below the side views.



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

Table 1: Dihedral angles of the (*Z*)-vinylogous 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 ± 3°	99 ± 4°	3 ± 1°	−79 ± 7°
P5	−117 ± 5°	104 ± 1°	−1 ± 2°	−75 ± 2°
Average	−119 ± 4°	100 ± 5°	0 ± 3°	−78 ± 4°

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*-vinylogous 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*-vinylogous 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*-vinylogous residues (Figure 1),[17] hybrid peptides with 1:1 alternating α-residues and *Z*-vinylogous residues adopt a 12-helix conformation. The average dihedral angles of Z-vinylogous 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→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 3_{10}-helix of α-peptides.[21b] The H-bonding parameters of all the peptides are tabulated and given in the Supporting Information. Instructively, structural analysis of **P1**–**P5** revealed that *Z*-vinylogous 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*-vinylogous 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 ± 6° and −44 ± 6°, respectively. Further, we superimposed the structures of **P4** and **P6** to compare their backbone conformations (Figure 2). The excellent backbone correlation between **P4** and **P6** suggests that *Z*-vinylogous 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 ($\theta_2 \approx 0°$), 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).

Table 2: Comparison of the backbone torsion angles of the Z-vinylogous 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 ± 6°	51 ± 2°	62 ± 3°	−122 ± 9°
$\gamma^{3,3}$-AA[10]	−124 ± 4°	56 ± 6°	64 ± 8°	−112 ± 10°
$\gamma^{2,3,4}$-AA (cyclic)[11a]	140 ± 10°	−56 ± 2°	−52 ± 2°	111 ± 4°
Theoretical model[8b]	−122 ± 2°	52 ± 2°	62 ± 2°	−125 ± 4°
$\gamma^{2,3}$-AA (cyclic)[11e]	−129 ± 9°	56 ± 2°	55 ± 2°	−120 ± 9°
$\gamma^{3,4}$- AA[12i]	−120 ± 2°	50 ± 5°	64 ± 2°	−127 ± 2°
Z-γ^4 (Present work)	−119 ± 4°	100 ± 5°	0 ± 3°	−78 ± 4°

Careful analysis of the local conformations of *Z*-vinylogous 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*-vinylogous residues in the hybrid helices are π-conjugated to the carbonyl groups since they deviate from planarity (Figure 3C). The local torsion angles (C^{β}-C^{α}-C-O = 103°) of *Z*-vinylogous 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.

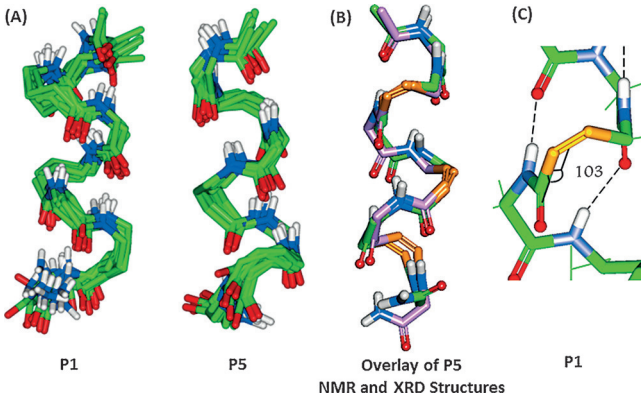


Figure 3. A) Solution conformations of the α,γ-hybrid peptides **P1** and **P5**. B) An overlay of the X-ray and NMR structures of **P5**. C) The X-ray structure of peptide **P1**, illustrating the non-planarity of the C=C and C=O bonds (C^{β}-C^{α}-C-O = 103°) in the Z-vinylogous residues.

To gain insight into their solution conformations, we subjected **P1** (a single *Z*-vinylogous residue) and **P5** (three *Z*-vinylogous residues) to 2D NMR analysis. Both **P1** and **P5** showed well resolved ^{1}H 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 $C^{\gamma}H$ (*i*) and NH (*i* + 2), as well as between $C^{\gamma}H$ (*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*-vinylogous amino acids. The results suggest that *Z*-vinylogous 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*-vinylogous 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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