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γ- and β-Peptide Foldamers from Common Multifaceted Building Blocks: Synthesis and Structural Characterization

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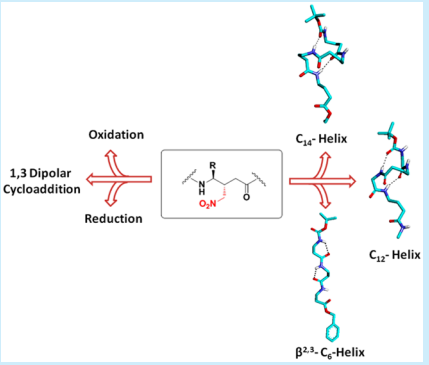
Supporting Information

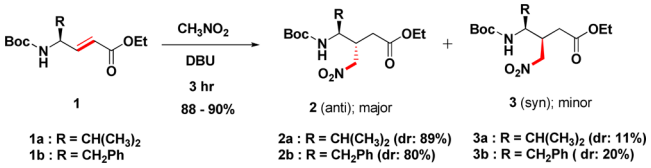
ABSTRACT: Structural characterization of 3,4-disubstituted γ-peptide and 2,3-disubstituted β-peptide foldamers derived from common multifaceted β-nitromethyl γ-amino acids and the chemical transformation of the β-nitromethyl group in γ-peptides into various functional derivatives are reported. The $\gamma^{3,4}$-oligomers and α,γ-hybrid peptides showed characteristic C_{14}-and C_{12}-helical conformations in single crystals. Further, the new 2,3-disubstituted acyclic β-peptide showed the C_6-helical conformation despite the poor geometry of H-bonds.



The relationship between a well-defined structure and function of proteins inspire the creation of foldamers from non-natural building blocks.[1] Among them, the most widely studied foldamers are constructed from β- and γ-amino acid subunits.[2] The oligomers of β- and γ-amino acids displayed a variety of helical structures with different H-bond pseudocycles. The remarkable helical structures and side-chain projections of β- and α,β-hybrid peptides have been exploited in designing inhibitors for various protein−protein interactions,[3] antimicrobials,[4] and biomaterials.[5] Despite the excellent biological activities of γ-amino acids such as pregabalin[6] and gabapentin,[7] the biological activities of γ- and hybrid γ-peptides have yet to be explored. Nevertheless, several bacteria are reported to produce poly-γ-glutamate, which allowed bacteria to survive at high salt concentrations and was also suspected of playing a role in virulence.[8] In the course of our investigation on structure and reactivity of α,β-unsaturated γ-amino acids, we recently reported the synthesis of β-nitromethyl γ-amino acids through highly diastereoselective Michael addition of nitromethane.[9] The literature search revealed that the alkyl nitro group can be transformed into a variety of functional groups including amines, carboxylic acids, aldehydes, ketones, alkenes, oximes, hydroxyl amines, 1,3-dipolar addition products, etc. under mild conditions.[10] With these multifaceted properties of alkyl nitro groups, we anticipated that the β-nitromethyl γ-amino acids may serve as excellent building blocks to construct 3,4-disubstituted γ-peptide foldamers, 2,3-disubstituted β-peptide foldamers, as well as intermediates to introduce various chemical modifications on foldamers. Moreover, to the best of our knowledge, peptides with alkyl nitro group functionality have not been systematically investigated to date. The notable properties of alkyl nitro groups encouraged us to investigate their structural and functional properties in peptides. Herein, we report the synthesis and structural characterization of homooligomers (**P1**−**P3**), heterooligomers (**P4** and **P5**) of β-nitromethyl $\gamma^{3,4}$-peptide foldamers, mild transformation of the β-nitromethyl group in $\gamma^{3,4}$-peptides into the corresponding peptide acid (**P6**), amine (**P7**), and 1,3-diploar cycloaddition product (**P8**), transformation of β-nitromethyl γ-amino acids into 2,3-disubstituted β-amino acids, and the crystal conformation of the 2,3-disubstituted β-peptide foldamer (**P9**). The structural characterization, chemical diversity, and mild chemistry reported here can be further explored to build novel functional foldamers.

To begin with, the β-nitromethyl-substituted γ-amino acids (**2a** and **2b**) were synthesized starting from (*E*)-α,β-unsaturated γ-amino esters (**1a** and **1b**) through highly diastereoselective Michael addition of nitromethane in the presence of DBU as shown in Scheme 1. The major *anti* addition products were isolated in excellent yields after the column chromatography and subjected for the construction of peptides and chemical transformations. In order to understand the conformations of β-nitromethyl $\gamma^{3,4}$- peptides, we synthesized homooligomers (**P1**−**P3**) and heterooligomers (**P4** and **P5**) in solution-phase

Scheme 1. Synthesis of *N*-Boc-β-Nitromethyl-Substituted γ-Amino Esters



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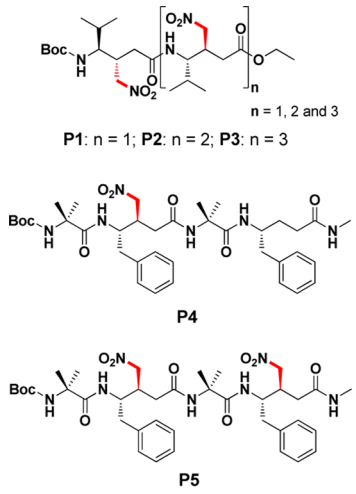
synthesis using standard DCC/HOBt coupling conditions. The sequences of the peptides are shown in Scheme 2. The

Scheme 2. Sequences of $\gamma^{3,4}$-Peptides and $\alpha, \gamma^{3,4}$-Hybrid Peptides Derived from the Major *Anti*-Isomers



deprotection of *N*-Boc and ethyl esters was carried out using TFA and NaOH, respectively. We adopted stepwise couplings from the C- to N-terminus to avoid unexpected impurities during the hydrolysis of peptide esters. All pure peptides were subjected to growth of X-ray quality crystals in various solvent combinations to understand their unambiguous conformations. In contrast to the γ^4-, $\gamma^{2,4}$-, $\gamma^{3,3}$, $\gamma^{4,4}$-, and $\gamma^{2,3,4}$-peptides,[11] the conformations of $\gamma^{3,4}$-peptides have not been systematically investigated. We speculated greater helical propensity from $\gamma^{3,4}$-peptides due to the favorable *gauche* interactions of side chains similar to the tetrasubstituted ethanes.[12]

Single-crystal structures of **P1**, **P2**, and **P3** are shown in Figure 1. Analysis of the crystal structure of **P1** reveals that it adopted a

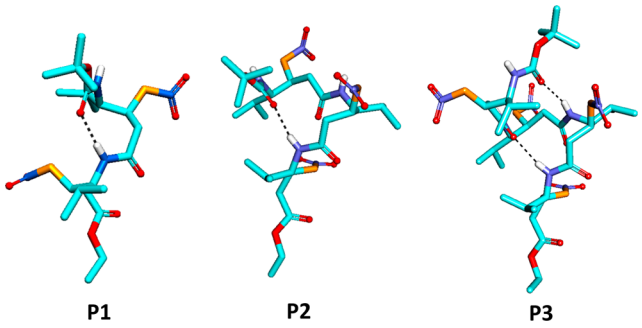


Figure 1. Single-crystal conformations of **P1**, **P2**, and **P3**.

helical type of conformation with a single nine-membered H-bond between Boc-amide CO and the NH of C-terminal residue ($i \rightarrow i+2$), resembling the γ-turn in α-peptides.[13] Similar types of 9-helices have also been observed in the homooligomers of gabapentin, however, with mirror image torsional values.[14] The torsional variables of γ-amino acid derivatives were analyzed by introducing two new additional variables θ_1(N−C$^\gamma$−C$^\beta$−C$^\alpha$) and θ_2(C$^\gamma$−C$^\beta$−C$^\alpha$−C′) along with ϕ (C′−N−C$^\gamma$−C$^\beta$) and ψ (C$^\alpha$−C$^\beta$−C′−N).[14] The torsional values are tabulated in the Supporting Information (Table S1). Inspection of the crystal structure reveals that the β-nitromethyl γ-amino acids adopted the g^+, g^+ ($\theta_1 \approx \theta_2 \approx \sim 60°$) backbone conformations along the C$^\gamma$−C$^\beta$ and C$^\beta$−C$^\alpha$ bonds. Intriguingly, the extension of dipeptide to tri (**P2**) and tetrapeptide (**P3**) leads to (P)-14-helical conformations similar to those of the γ^4-peptides.[11a] The helical conformation in **P2** and **P3** is stabilized by one and two intramolecular H-bonds between the i and i+3 residues, respectively. The H-bond parameters are tabulated in the Supporting Information (Tables S4−S6 and S8). The helical structure in **P2** is stabilized by the 14-membered H-bond between the Boc amide CO (i) and the NH of the C-terminal γ-residue (i+3), while **P3** structure is stabilized by two intramolecular 14-membered H-bonds between Boc amide CO (i) and NH of $\gamma^{3,4}$ Val3 (i+3) and between the Val1 CO (i) and $\gamma^{3,4}$ Val4 NH (i+3). Though there is a possibility to attain C_9-helices similar to the **P1**, both **P2** and **P3** attained the C_{14}-helix conformation. Crystal structure analysis of **P2** and **P3** reveal that except the C-terminal $\gamma^{3,4}$-residue, the other $\gamma^{3,4}$-residues adopted g^+, g^+ conformations. The directionality and the pattern of H-bonding ($i \rightarrow i+3$) observed in the $\gamma^{3,4}$- tri and tetrapeptides resemble the 3_{10}-helix in α-peptides as well as 14-helix of γ^4-peptides.[15,11a] The torsional angles of **P2** and **P3** are given in Tables S3 and S7, respectively. Careful analysis of the intramolecular H-bonds in **P1**−**P3** revealed that the H-bond distance is relatively larger in the 14-helix compared to the C_9-helix. Overall, these novel $\gamma^{3,4}$-disubstituted amino acids favor the helical conformation even in simple dipeptides.

These results motivated us to design **P4** and **P5** to understand the conformations of $\gamma^{3,4}$-amino acids in 1:1 α,γ-hybrid peptides. The sequences of the peptides are shown in Scheme 2. Peptide **P4** consists of both $\gamma^{3,4}$ and γ^4-amino acids along with Aib, while **P5** composed of alternating $\gamma^{3,4}$ amino acids. Peptides were synthesized in solution-phase chemistry and pure peptides were subjected to crystallization. Single crystals of **P4** obtained from the methanol solution gave the X-ray structure as shown in the Figure 2A. The 12-helical structure of **P4** is stabilized by three intramolecular H-bonds between i and i+3 residues similar to the other α,γ-hybrid peptides.[16] Both γ^4-Phe and $\gamma^{3,4}$-Phe adopted required g^+, g^+ conformations along C$^\gamma$−C$^\beta$ and C$^\beta$−C$^\alpha$ bonds to accommodate into the 12-helix. The H-bond parameters and torsion angles are tabulated in the Supporting Information (Tables S9−S12). Enormous efforts have been made to crystallize **P5** in various solvent combinations; however, it gave single crystals only in 2-propanol solution. The X-ray structure of **P5** is shown in Figure 2A. The 12-helical conformation of **P5** is stabilized by two 12-membered H-bonds. Analysis reveals that instead of participating into the canonical intramolecular H-bonding the terminal amide NH is involved in strong intermolecular H-bonding with the solvent 2-propanol. In contrast to **P4**, the nitro and the CO groups of $\gamma^{3,4}$Phe2 in **P5** are involved in intermolecular H-bonding with NH of the $\gamma^{3,4}$ Phe2 and Boc-amide NH of the other helix. These intermolecular interactions lead to the arrangement of 12-helices into a spectacular right-handed superhelix with the pore diameter of 7.3 Å. Solvent 2-propanol occupied the helical groove of the super helix in the crystal packing, suggesting its important role in peptide crystallization. A well-organized helical assembly of **P5** is shown in Figures 2B. The tubular arrangement of the hybrid 12-helix, **P5**, resembles the arrangement of β-sheets in β-helix, however, through noncovalent interactions.[17] Recently, the tubular porous organic and peptide structures have attracted considerable attention due to their applications in the separation science, catalysis, and nanobiotechnology.[18] We hypothesize that the tubular architecture of **P5** may serve as a new template to design soft biomaterials. In contrast, the **P4** 12- helix with single

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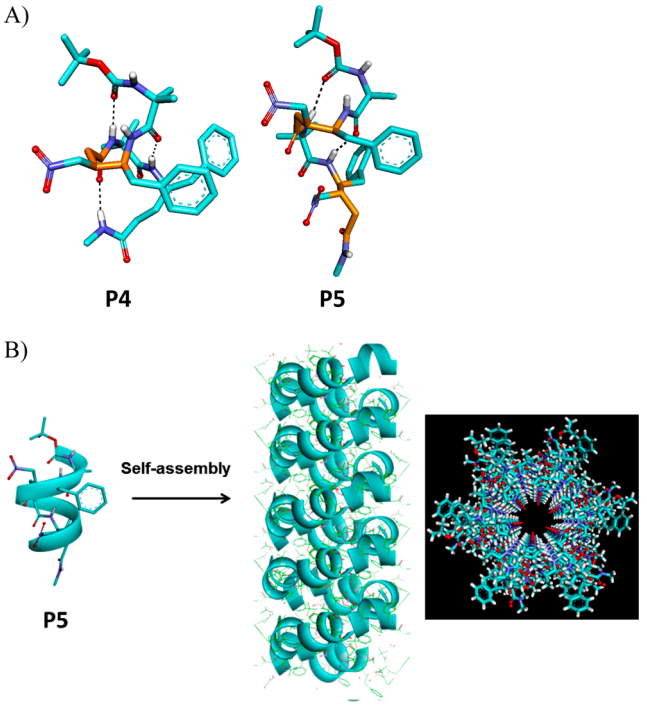
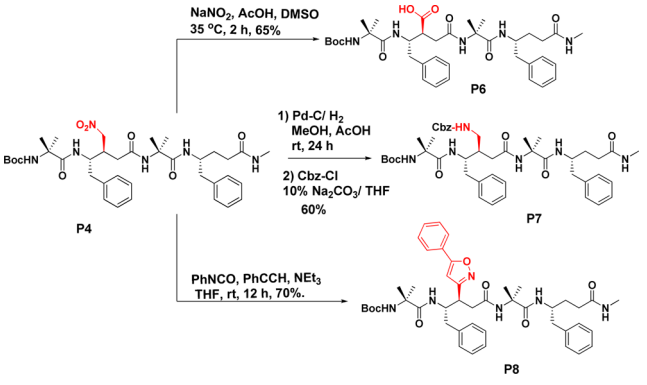


Figure 2. (A) X-ray structures of $\alpha,\gamma^{3,4}$-hybrid tetrapeptide 12-helices **P4** and **P5**. (B) Hierarchical assembly of $\alpha,\gamma^{3,4}$-hybrid 12-helix **P5** into right-handed superhelix along the *b*-axis and top view of the ordered self-organization of **P5** (along the *c*-axis).

nitro amino acid did not show helical pores in single crystals, suggesting the requirement of two nitro groups for the hierarchical tubular assembly. Overall the structural analysis of homo- and heterooligomers of β-nitromethyl-substituted γ-amino acids suggested that they readily adopt helical conformations and follow the trend of other γ-peptides. In addition, helical pores observed in **P5** offer the glimpse of potential of β-nitromethyl γ-amino acids and laid the foundation for further investigation.

To verify whether these nitropeptides can undergo organic transformations similar to the alkyl nitro groups,[10] we subjected **P4** to various organic transformations (Scheme 3).The nitro group in **P4** was transformed to corresponding peptide carboxylic acid (**P6**) using simple oxidation mediated by the mixture of $NaNO_2$ and acetic acid in DMSO.[19] Further, the nitro group of **P4** was reduced to corresponding amine using catalytic

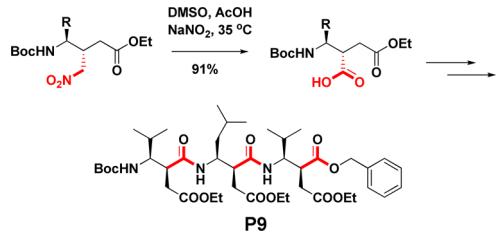
Scheme 3. Organic Transformations of Hybrid Peptide P4 to P6, P7, and P8



hydrogenation[20] in the presence of 20% Pd/C under hydrogen atmosphere and the free amine was subsequently protected with Cbz-group (**P7**). The 1,3-dipolar cycloaddition product **P8** from **P4** was achieved by the treatment of phenylacetylene in the presence of phenyl isocyanate and triethylamine under mild conditions.[21] All hybrid peptide derivatives were isolated in good yields after purification and characterized (see the Supporting Information). These results suggested that the nitro group on peptides can be transformed into various functional derivatives.

The transformation of β-nitromethyl to the corresponding carboxylic acid was further explored in simple amino acids to derive new 2,3-disubstituted β-amino acids (Scheme 4).[19] The

Scheme 4. Transformation of β-Nitromethyl γ-Amino Esters into 2,3-Disubstituted β-Amino Acids and Sequence of $\beta^{2,3}$-Peptide P9



2,3-disubstituted β-amino acids were isolated in excellent yields and directly subjected to the synthesis of β-peptide **P9**. The peptide was synthesized in the solution phase, and pure peptide was subjected to crystallization. The single-crystal conformation of **P9** is shown in Figure 3. Instructively, the 2,3-disubstituted β-

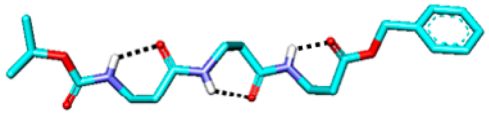


Figure 3. X-ray structure of β-peptide **P9** C_6-helix (side chains omitted for clarity).

peptide adopted a helical screwtype conformation with 6-memberd H-bonds. Even though extensive theoretical calculations suggested stable C_6-helical conformation in β-peptides,[22] they are scarcely studied in single crystals. However, C_6-helical conformations of β-peptides have been reported using cyclic β-amino acids in solution.[23] The torsion angles and H-bond parameters of **P9** are tabulated in the Supporting Information. It is worth mentioning that β-nitromethyl γ-amino acids can be transformed into novel 2,3-disubstituted β-amino acids.

In conclusion, we have presented the synthesis, conformational analysis, and chemical diversity of novel β-nitromethane-substituted γ-amino acid homo-oligomers and α,γ-hybrid peptides. In addition, β-nitromethyl-substituted γ-amino acids were used to construct 2,3-disubstituted β-peptide foldamers. Both $\gamma^{3,4}$ and $\alpha,\gamma^{3,4}$-hybrid peptides showed characteristic C_{14}- and C_{12}-helical conformations, respectively. Additionally, the 2,3-disubstiuted β-peptide derived from the nitro amino acids showed a notable C_6-helix signature. Overall, the single-crystal conformations of the $\gamma^{3,4}$-peptides, the self-organized helical pore from the $\alpha,\gamma^{3,4}$-hybrid 12-helix, and the transformation of alkyl nitro group into a variety of functional groups reported here can be utilized further for the construction of functional foldamers and peptidomimetics.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02263.

Experimental procedures, ^{1}H and ^{13}C NMR, mass spectra, and CCDC numbers (PDF)

Crystallographic data for **P1**−**P5** and **P9** (CIF)

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Notes

The authors declare no competing financial interest.

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