Pentapeptide Nanoreactor as a Platform for Halogenations, Diels–Alder Reaction, and Morita–Baylis–Hillman Reaction

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Supporting Information

ABSTRACT: A pentapeptide nanoreactor has been designed and synthesized as a platform to carry out the traditional organic reactions such as bromination, iodination, cycloaddition, and condensation reactions. The pentapeptide Boc−Phe−Phe−Aib−Phe−OMe with a supramolecular helical structure and π-rich channel provides nanococonfinements and thus facilitates the organic reactions. Bromination and iodination of aniline take place without any halogen carrier (Lewis acid) in the pentapeptide platform. Iodination produced p-iodoaniline only. The Diels–Alder reaction between furan and maleic anhydride increased 2-fold in the presence of the pentapeptide platform and the Morita–Baylis–Hillman reaction of benzaldehyde and ethyl acrylate in methanol enhanced 1.5-fold.

INTRODUCTION

Nature shows excellent selectivity and efficiency within definite compartments. Even microorganisms produce thousands of complicated chemicals with extreme selectivity and almost zero chemical waste.¹ Hence, the fabrication of biomimetic supramolecular structures to facilitate organic syntheses in a confinement is highly important for chemical research and industry.²−⁵ Nanoreactors are devices having nanometer-size inner channel dimensions and which follow the main features of microreactors such as high surface-area-to-volume ratio. Hence, the outcome of a nanoreactor is higher in comparison to that of a conventional reaction pot.⁶ The mixing times (about several milliseconds) in nanoreactors are smaller than those in conventional syntheses, and also, due to the nanoconfinement, the diffusion times are very small. Thus, the effect of mass transport on the speed of the reaction becomes reduced significantly and catalyzes reactions with high selectivity.⁷ The very small reaction volume in nanoreactors is also an advantage for technical safety of toxic, explosive, and hazardous materials.⁸ It has been reported that the traditional organic reactions such as fluorination,⁹ chlorination,¹⁰ nitration,¹¹ hydrogenation,¹² and oxidation¹³ can be performed better in small confinements. Many chemical conversions including additions,¹⁴ eliminations,¹⁵ nucleophilic substitutions,¹⁶ electrophilic substitutions,¹⁷ and cycloadditions,¹⁸ have been carried out with improved results in reactors. Although nanostructure reactors have been reported to optimize many reactions, most of them have been used as catalyst,¹⁹ but they have not yet received the attention they deserve for performing classical reactions. We are looking for a nanoreactor that will act as a platform to facilitate the organic reactions, like a microreactor that does not have catalytic activity in the reaction process.²⁰ Ryadnov has reported a self-assembled peptide polynanoreactor having dendrimer architecture.²¹ Thus, we have opted a supramolecular peptide-based nanostructure²² as a platform to carry out the traditional organic reactions like halogenations, cycloaddition, and condensation.

Herein, we have synthesized a pentapeptide, Boc−Phe−Phe−Aib−Phe−OMe (1), containing L-phenylalanine and a central α-aminoisobutyric acid (Aib) residue. X-ray crystallography reveals that the pentapeptide adopts a 3₁₀-helical structure with multiple i + 3 → i hydrogen bonding interactions. The presence of Aib(3) residue at the central position might be beneficial in inducing the helical structure. At higher-order packing, the peptide forms a supramolecular helix-like structure with π-rich channels by intermolecular hydrogen bonding as well. These π-rich channels have been used as a potential platform to carry out the traditional organic reactions. In the pentapeptide platform, bromination and iodination of aniline take place without any halogen carrier (Lewis acid). Moreover, the iodination reaction selectively synthesized p-iodoaniline. The Diels–Alder reaction between furan and maleic anhydride increases 2-fold in the presence of the supramolecular nanoreactor in chloroform solution, and the Morita–Baylis–Hillman (MBH) reaction of benzaldehyde and ethyl acrylate in methanol enhanced 1.5-fold.
**RESULTS AND DISCUSSION**

For pentapeptide 1 (Scheme 1), the design principle explored was how to use a conformationally rigid helicogenic Aib to develop a robust peptide helix. The incorporation of four phenylalanine moieties helps in creating a supramolecular channel with a rich π atmosphere that could be utilized for some chemical transformations. Pentapeptide Boc–Phe–Aib–Phe–Ome 1 and Its Folding into a Helix and Self-Assembly to a Supramolecular Nanoreactor was synthesized by conventional solution-phase methodology using N,N′-dicyclohexylcarbodimide (DCC) and N-hydroxybenzotriazole (HOBT) as coupling reagents. The synthesized peptide and the intermediates were purified by column chromatography and characterized by 1H NMR, 13C NMR, circular dichroism (CD), Fourier transform infrared (FT-IR), and mass spectrometry analyses.

To determine the conformational features of pentapeptide 1 in solution, nuclear magnetic resonance (NMR) experiments were performed. The concentration-dependent 1H NMR experiment in CDCl3 exhibits no shift of the amide protons with increasing concentration, which indicates the existence of stable supramolecular helices in solution (Figure 1a). On the other hand, small shifts of amide protons with increasing temperature further indicate the stability of the pentapeptide 1 in solution (Supporting Information; Figure S1). Aib(3), Phe(4), and Phe(5) NH protons are intramolecularly hydrogen-bonded as evident from their large chemical shift changes upon heating (Figure 1a). Generally, addition of small amounts of a hydrogen-bond-accepting solvent like DMSO-d6 in CDCl3 solution of peptide brings about monotonic downfield shifts of exposed NH groups, leaving solvent-shielded NH groups almost unaffected. The effects of adding DMSO-d6 to CDCl3 solution of peptide 1 indicate that Phe(1) and Phe(2) NHs are solvent-exposed as it is evident from their significant chemical shift changes (Δδ = 0.56, 0.25 respectively) upon addition of DMSO-d6 in CDCl3 solutions (Figure 1b). Aib(3), Phe(4), and Phe(5) NHs exhibit very little chemical shift changes (Δδ: 0.1, 0.012, and 0.002, respectively) even at higher percentages of DMSO-d6 which indicates that these NHs are involved in intramolecular hydrogen bondings (Supporting Information; Figure S2). Table S1, Supporting Information, shows Δδ values of all NHs for peptide 1. We conclude that peptide 1 forms an intramolecularly hydrogen-bonded helical structure in CDCl3 solution. Circular dichroism (CD) is an excellent method to determine the backbone structural preferences of peptides. CD spectrum of pentapeptide 1 in chloroform shows negative bands at 208 and 214 nm (Supporting Information; Figure S3). This result further indicates that the peptide 1 forms an intramolecularly hydrogen-bonded stable helical conformation in chloroform solution.

We have investigated the structure of peptide 1 in a solid state by the FT-IR technique. The FT-IR region 3500–3200 cm⁻¹ is important for the N–H stretching vibrations; however, the range 1800–1500 cm⁻¹ is assigned for the stretching band of amide I and the bending peak of amide II. For peptide 1, an intense band at 3319 cm⁻¹ indicates the presence of hydrogen-bonded NH groups (Supporting Information; Figure S4). The amide I and amide II bands appear at 1658 and 1527 cm⁻¹, respectively (Supporting Information; Figure S4). The ester carbonyl appears at 1736 cm⁻¹. This suggests that the peptide 1 adopts a helical backbone conformation and all amide NHs are hydrogen-bonded. To explore the molecular conformation and self-assembly pattern of peptide 1, single-crystal X-ray diffraction was performed. The monoclinic light yellow crystals of 1 were obtained from 1,2-dichlorobenzene solution by slow evaporation. There is one molecule of peptide 1 with two solvent (1,2-dichlorobenzene) molecules in the asymmetric unit (Supporting Information; Figure S5).

The solvent molecules (1,2-dichlorobenzene) are held stabilized by π–π interactions with the peptide molecule (shortest C–C distance 4.0 Å). Most of the φ and ψ values of the residues are in the right-handed helical region of the Ramachandran diagram. Important backbone torsional angles are listed in Table S2; Supporting Information. The peptide 1 adopts a right-handed 3₁₀ helical structure, stabilized by three intramolecular i + 3 → i N–H–O hydrogen bonds between Aib NH and Boc C=O, Phe(4) NH and Phe(1) C=O, and Phe(5) NH and Phe(2) C=O (Figure 2a). The structures obtained from the X-ray diffraction study are consistent with the peptide conformation in solution. The hydrogen bond parameters are listed in Table S3; Supporting Information.
entrapped anilines are stabilized by T-shaped liquid or gas system, there are two main reaction categories: biphasic (gas-rich channel formed by peptide folding. To gain insight into the role of solvents in pentapeptide 1 folding, we also tried crystallization of peptide 1 in a basic solvent such as aniline. Diffraction-quality light yellow crystals of peptide 1 were obtained from aniline by slow evaporation. Again, one molecule of pentapeptide 1 crystallized with two molecules of aniline in the asymmetric unit (Figure 3a). There is no change of the 3_10-helical peptide backbone by changing solvent from 1,2-dichlorobenzene to aniline. One solvent unit is placed in the molecular π-rich channel (Figure 3b) and the second one in the supramolecular channel (Figure 3c). The entrapped anilines are stabilized by T-shaped π−π interactions between Phe(2) and aniline(1) (C-to-centroid distance, 3.51 Å) and NH−π interactions between the aniline molecules (N-to-centroid distance, 3.21 Å).

Therefore, we have a rigid peptide platform with a π-rich channel, where we can incorporate the reagents like 1,2-dichlorobenzene or aniline. We perform traditional organic reactions in these confinements. For the microreactor system, there are two main reaction categories: biphasic (gas-liquid or gas-solid) and triphasic (gas-liquid-solid) systems. We opt for a biphasic system. Traditionally, gas-liquid mixing is achieved by pumping or purging gas into a solution. Modern approaches use membranes to dissolve a gas in a liquid phase to effect reagent mixing. Here, we have passed reagent vapor through the crystals. First, we have tried bromination of aniline inside the nanoreactor in a solid state. Thus, we kept together bromine and dried peptide crystals from aniline in a sealed container for 2 h and then removed the excess bromine by simple evaporation. It was found that most of the crystals ruptured into small pieces. We have performed mass spectrometry of the resultant material, and the analysis revealed that the bromination reaction has taken place and the major products were monobromoaniline, tribromoaniline, and dibromoaniline (Supporting Information; Figure S6). The mass spectrum of the reaction mixture after bromination also contains peptide 1 and peptide 1 complexes with dibromoaniline. Therefore, due to size exclusion, the products could not accommodate in the supramolecular nanoreactor and hence ruptured the crystals. However, this gives a proof of concept that the supramolecular nanoreactor can act as a platform for the bromination reaction. Then, we tried the iodination reaction. Hence, we kept together iodine (75 mg, 0.3 mmol) and the dried peptide 1 crystals from aniline (10 mg, of which aniline was 1.88 mg, 0.02 mmol, and peptide 1 was 8.12 mg, 0.01 mmol) in a sealed container for 2 h and then removed the excess iodine by aerial evaporation. This time, we found that the crystals are intact but light red in color. Mass spectrometry of the reaction product revealed that the iodination reaction has taken place and the major product is monoiodoaniline (Figure 4). Also, we have found the existence of peptide 1 from aniline.
between 4-iodoaniline and aromatic rings of peptide 1 in two-dimensional NMR experiments (Supporting Information; Figure S7) clearly support the concept.

In view of the fact that the peptide 1 retains its conformation in the solution state as well, we have used this reactor in chloroform solution for the Diels−Alder reaction between furan and maleic anhydride (Figure 5a).29 At the beginning, we observed a significant decrease in the value of diffusion coefficient for the mixture (Supporting Information; Figure S9). This result further confirms the interaction of maleic anhydride with peptide 1. In chloroform, the Diels−Alder reaction between furan and maleic anhydride increases 2-fold in the presence of the nanoreactor 1 (Figure 5a) and the exo-product was found to form exclusively. However, the Diels−Alder reaction between furan and maleic anhydride in the presence of the supramolecular reactor in toluene has been found to be facilitated more as the solid product gets precipitated out of the solution during the course of the reaction (Figure 5b). Finally, we have used the peptide 1 reactor for the Morita−Baylis−Hillman (MBH) reaction between benzaldehyde and ethyl acrylate in methanol in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO).30 The MBH reaction of benzaldehyde and ethyl acrylate in methanol increases 1.5-fold in the presence of the supramolecular nanoreactor 1 (Figure 5c) in 96 h. The experimental details are given in the Supporting Information.

## CONCLUSIONS

In summary, we have synthesized a pentapeptide Boc−Phe−Phe−Aib−Phe−Phe−OMe 1 with l-phenylalanine and a central α-aminoisobutyric acid (Aib). The pentapeptide adopts a robust 310-helical structure. The Aib residue at the central position helps to induce the overall helical structure. At higher-order packing, the pentapeptide 1 forms a supramolecular helical structure by intermolecular hydrogen bonding as well as π−π stacking interactions. Conformational analysis by various NMR experiments further confirms the presence of the robust helical structure in the solution state as well. The pentapeptide 1 is able to accommodate reagents in its molecular and supramolecular channels. These π-rich channels have been used as a potential platform for the organic reactions. The halogenations of aniline take place without any halogen carrier (Lewis acid), and the Diels−Alder reaction between furan and maleic anhydride increases 2-fold in nanoreactor 1. The MBH reaction of benzaldehyde and ethyl acrylate increases 1.5-fold in pentapeptide nanoreactor 1. Overall, these studies offer new opportunities to carry out traditional organic transformations in nanoconfinements.

## EXPERIMENTAL SECTION

### General

All amino acids were purchased from Sigma Chemicals. N-Hydroxybenzotriazole (HOBt) and N,N′-dicyclohexylcarbodiimide (DCC) were purchased from SRL.

### Peptide Synthesis

All of the peptides (3, 6, and 1) were synthesized (Scheme S1) by conventional solution-phase methods using a racemization-free fragment condensation strategy. The Boc group was used for N-terminal protection, and the C-terminus was protected as a methyl ester. Deprotectons of methyl ester were performed using the saponification method. Couplings were mediated by N,N′-dicyclohexylcarbodiimide/N-hydroxybenzotriazole (DCC/HOBt). The intermediates were characterized by 500 MHz Bruker AVANCE and 400 MHz JEOL 1H NMR and 13C NMR spectrometers. The final compound was fully characterized by 400 MHz 1H NMR spectroscopy, 13C NMR spectroscopy (100 MHz), FT-IR spectroscopy, and single-crystal X-ray diffraction analysis.

**Boc−Phe−OH (2)**.22 A solution of l-phenylalanine (3.30 g, 20 mmol) in a mixture of dioxane (40 mL), water (20 mL), and 1 M NaOH (20 mL) was stirred and cooled in an ice-water bath. Di-tertbutylpyrocateonate (4.8 g, 22 mmol) was added, and stirring was continued at room temperature for 6 h. Then, the solution was concentrated in vacuum to about 20−
30 mL, cooled in an ice-water bath, covered with a layer of ethyl acetate (about 50 mL), and acidified with a dilute solution of KHSO₄ to pH 2–3 (Congo red). The aqueous phase was extracted with ethyl acetate, and this operation was done repeatedly. The ethyl acetate extracts were pooled, washed with water, dried over anhydrous Na₂SO₄, and evaporated in a vacuum. The pure material was obtained as a viscous liquid. Yield 4.87 g (18.35 mmol, 91.78%).

1H NMR (DMSO-d₆, 500 MHz, δ ppm): 12.75 [1H, bs, COOH], 7.28–7.09 [8H, m, ArH], 7.11–7.09 [1H, d, J = 10, Phe NH], 4.09–4.01 [1H, m, Phe C²H], 3.02–2.87 [2H, m, Phe C²H], 1.36 [9H, s, BOC] (Figure S16). 13C NMR (DMSO-d₆, 125 MHz, δ ppm): 171.3, 170.7, 155.3, 136.5, 129.2, 127.1, 80.2, 55.7, 1.39 [9H, s, BOC] (Figure S18). 13C NMR (CDCl₃, 125 MHz, δ ppm): 173.6, 155.4, 138.0, 129.0, 128.0, 126.3, 80.2, 55.1, 36.4, 20.7 (Figure S17).

Boc–Phe–Phe–Aib–OMe (3). To 2.58 g (4.4 mmol) of Compound 3, 5 mL of trifluoroacetic acid (TFA) was added, and the removal of BOC group was monitored by thin layer chromatography (TLC). After 6 h, TFA was removed under vacuum and the residue was neutralized by Et₃N.

1H NMR (CDCl₃, 500 MHz, δ ppm): 7.28–7.19 [8H, m, NH & ArH], 6.99–6.97 [2H, m, ArH], 6.31 [1H, b, ArH], 4.95 [1H, b, ArH], 4.79–4.77 [1H, b, Phe C²H], 4.33 [1H, b, Phe C²H], 3.67 [3H, s, OMe], 3.06–3.03 [4H, m, Phe C²H], 1.39 [9H, s, BOC] (Figure S18). 13C NMR (CDCl₃, 125 MHz, δ ppm): 171.3, 170.7, 155.3, 126.3, 125.5, 129.0, 128.7, 128.6, 127.1, 80.2, 55.1, 36.4 (1H, m, Phe C²H), 1.39 [9H, s, BOC] (Figure S18). JₙH2N–Phe–Phe–OMe (4). To 1.70 g (4 mmol) of compound 3, 5 mL of trifluoroacetic acid (TFA) was added, and the removal of BOC group was monitored by thin layer chromatography (TLC). After 6 h, TFA was removed under vacuum and the residue was neutralized by Et₃N.

1H NMR (DMSO-d₆, 400 MHz, δ ppm): 8.29–8.27 [1H, d, NH], 7.30–7.14 [10H, m, ArH], 4.66–4.60 [1H, m, Phe C²H], 3.67 [3H, s, OMe], 3.47–3.44 [1H, m, Phe C²H], 3.04–3.00 [2H, m, Phe C²H], 2.97–2.91 [1H, m, Phe C²H], 2.62–2.58 [1H, m, Phe C²H], 1.80–1.60 [2H, NH₂] (Figure S20).

Boc–Phe–Phe–OH (5). To 3.41 g (8 mmol) of compound 3, 25 mL of MeOH and 15 mL of 2 M NaOH were added and stirred, and the progress of saponification was monitored by thin layer chromatography (TLC). After 10 h, methanol was removed under vacuum and the residue was dissolved in 50 mL of water and washed with diethyl ether (2 × 50 mL). Then, the pH of the aqueous layer was adjusted to 2 using 1 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in a vacuum to yield 3 as a white solid. Yield 1.69 g (3.4 mmol, 85%).

Boc–Phe–Phe–Aib–Phe–OMe (7). To 2.05 g (4 mmol) of compound 6, 15 mL of MeOH and 10 mL of 2 M NaOH were added and stirred, and the progress of saponification was monitored by thin layer chromatography (TLC). After 10 h, methanol was removed under vacuum and the residue was dissolved in 50 mL of water and washed with diethyl ether (2 × 50 mL). Then, the pH of the aqueous layer was adjusted to 2 using 1 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in a vacuum to obtain compound 7 as a white solid. Yield 1.69 g (3.4 mmol, 85%).

Boc–Phe–Phe–Phe–OMe (6). Compound 5 (2.48 g, 6 mmol) was dissolved in 30 mL of dry DCM in an ice-water bath. H–Aib–OMe (1.84 g, 12 mmol) was isolated from the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate, and solvent evaporation. It was then added to the reaction mixture, followed immediately by 1.24 g (6 mmol) of DCC and 0.81 g (6 mmol) of HOBT. The reaction mixture was allowed to come to room temperature and stirred for 48 h. DCM was evaporated, the residue was taken in ethyl acetate (50 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate, and evaporated under vacuum to yield peptide 6 as a white solid. The product was purified by silica gel (100–200 mesh) using n-hexane–ethyl acetate (3:1) as eluent. Yield: 2.25 g (4.4 mmol, 73.33%).
bs, Aib C^H], 1.25 [9H, s, BOC] (Figure S25). $^{13}$C NMR (CDCl$_3$, 100 MHz, $\delta$ ppm): 174.0, 172.6, 172.1, 171.6, 171.2, 156.3, 138.0, 137.2, 135.6, 135.8, 129.3, 129.2, 129.2, 129.1, 128.9, 128.7, 128.7, 128.4, 128.3, 127.5, 127.5, 126.6, 126.4, 81.2, 60.4, 57.2, 54.9, 53.7, 52.2, 37.5, 37.2, 36.8, 36.3, 28.2, 28.0, 26.1, 23.7 (Figure S26). HRMS (ESI-TOF) (m/z): [M + H]$^+$ Calcd for C$_{46}$H$_{55}$N$_5$O$_8$ 806.5350; Found 806.5396 (Figure S26). Elemental analysis calculations for C$_{46}$H$_{55}$N$_5$O$_8$: C 68.55, H 6.88, N 8.69; found C 68.58, H 6.91, N 8.72.

4-Iodoaniline. Dried peptide 1 crystals from aniline (10 mg, of which aniline was 1.88 mg, 0.02 mmol) and peptide 1 was 8.12 mg, 0.01 mmol) and iodine (75 mg, 0.3 mmol) were kept together in a sealed container for 2 h, and then the excess iodine was removed by aerial evaporation. The product was purified by column chromatography using silica gel (100–200 mesh size) as the stationary phase and the $n$-hexane–ethyl acetate mixture as eluent. Isolated yield: 2.90 mg (0.0132 mmol, 66%).

$^1$H NMR (CDCl$_3$, 400 MHz, $\delta$ ppm): 7.39–7.42 [2H, m, ArH], 6.46–6.49 [2H, m, ArH], 3.71 [2H, b, NH$_2$] (Figure S27). $^{13}$C NMR (CDCl$_3$, 100 MHz, $\delta$ ppm): 146.03, 137.9, 117.6, 79.4 (Figure S28).

Diels–Alder Reaction. A mixture of 10 mg (0.1 mmol) of maleic anhydride and 5 mg (0.006 mmol) of peptide 1 was dissolved in 0.6 mL of CDCl$_3$ in an NMR tube, i.e., maleic anhydride, 166.67 mM and peptide 1, 10 mM. To this solution, 11 $\mu$L (0.15 mmol) of furan was added, and the sealed NMR tube was subjected to the Diels–Alder reaction at 40 °C in a water bath. A second set of the same reaction was run in the identical condition in the absence of peptide catalyst (control). Both the reactions were monitored by NMR spectroscopy at different time intervals. After 24 h, products of the reaction tubes were extracted and purified by column chromatography using silica gel (mesh size 100–200) as the stationary phase and the $n$-hexane–ethyl acetate mixture as eluent. Isolated yields: 10.6 mg, 0.064 mmol, 64% (in presence of peptide 1) and 5.4 mg, 0.0325 mmol, 32.5% (in the absence of peptide 1).

When the same reactions were carried out in toluene, we observed more than 3 times increase in the reaction in the presence of peptide 1 after 8 h. Isolated yields: 9.8 mg, 0.059 mmol, 59% (in presence of peptide 1, Figure S10) and 3.2 mg, 0.0193 mmol, 19.3% (in the absence of peptide 1, Figure S11).

Morita–Baylis–Hillman Reaction. A mixture of $51 \mu$L (0.5 mmol) of benzaldehyde, 0.2 mL (1.88 mmol) of ethyl acrylate, 56 mg (0.5 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO), and 20 mg (0.024 mmol) of peptide 1 was dissolved in 1 mL of methanol in a $5 \mu$L reaction vial, and the Morita–Baylis–Hillman (MBH) reaction was carried out by normal stirring at room temperature (20 °C). A second set of the same reaction was run in the identical conditions in the absence of peptide 1 (control). Both the reactions were monitored by NMR spectroscopy at different time intervals by dissolving $30 \mu$L of the reaction mixture in 0.5 mL of CDCl$_3$. After 5 days, products of the reaction vials were extracted and purified by column chromatography using silica gel (mesh size 100–200) as the stationary phase and the $n$-hexane–ethyl acetate mixture as eluent. Isolated yields: 78.1 mg, 0.379 mmol, 75.8% (in the presence of peptide 1, Figure S12) and 61.8 mg, 0.3 mmol, 60% (in the absence of peptide 1, Figure S12).

NMR Experiments. All NMR studies were carried out on Bruker AVANCE 500 MHz and JEOL 400 MHz spectrometers at 298 K. Compound concentrations were in the range 1–10 mM in CDCl$_3$ and (CD$_3$)$_2$SO.

FT-IR Spectroscopy. Solid-state FT-IR spectrum was obtained with a PerkinElmer Spectrum RXI spectrophotometer with the KBr disk technique.

Single-Crystal X-ray Diffraction Study. Intensity data of the reported peptide was collected with Mo Kα radiation using a Bruker APEX-2 CCD diffractometer. Data was processed using the Bruker SAINT package, and the structure solution and refinement procedures were performed using SHELXL97.

Circular Dichroism (CD) Spectroscopy. The conformational preference of the reported peptide in chloroform was detected by CD spectroscopy. The peptide was dissolved in chloroform, taken in a cell of path length 1.0 mm, and measured in a JASCO J-815-150S instrument at a temperature of 25 °C.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01393.

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Author Contributions

M.D. has synthesized and analyzed the compounds. S.S. and D.P. have performed the experimental works. D.H. has done the analysis and wrote the manuscript.

Notes

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

We gratefully acknowledge the financial support from IISER Kolkata, India. M.D. and D.P. thank CSIR, India, for fellowships. S.S. acknowledges the IISER Kolkata, India, for research fellowship. We thank Prof. Rangeet Bhattacharyya, IISER Kolkata, for his help in DOSY and 2D NMR experiments.

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