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A hybrid foldamer with unique architecture from conformationally constrained aliphatic–aromatic amino acid conjugate

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Abstract—In this paper, we describe the design and synthesis of a novel hybrid foldamer, derived from a conformationally constrained aliphatic–aromatic amino acid conjugate that adopts a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by the individual amino acids from which the foldamer is composed. Conformational investigations confirmed the prevalence of a unique doubly bent conformation for the foldamer, in both solid and solution states, as evidenced from single crystal X-ray and 2D NOESY studies, respectively. The findings suggest that constrained aliphatic–aromatic amino acid conjugates offer new avenues for the de novo design of hybrid foldamers with distinctive structural architectures. Furthermore, the de novo design strategy disclosed herein has the potential for significantly augmenting the 'tool-box' of the modern day peptidomimetic chemist, as well as providing a novel approach to the field of rational design.

1. Introduction

Foldamers[1] as a class of conformationally ordered synthetic oligomers have been ushered into prominence primarily due to their enormous potential for the creation of unnatural oligomers that adopt discrete tertiary structures, just as biopolymers. The compact conformational features and their adjustable lengths mean that these synthetic oligomers may provide excellent starting points for the elaboration of protein mimics that might be difficult to design based on small-molecule scaffolds. Extensive investigations by several groups have resulted in the generation of a myriad of such synthetic oligomers with diverse backbone structures, conformations,[2] and functions.[3] Of late, increasing attention is being devoted to the design and development of hybrid foldamers with a view to expanding the conformational space available for foldamer design.[4–6] Of particular interest are α,β-hybrid peptides, reported by Gellman's group,[4] composed of alternately changing α- and β-amino acid constituents. NMR studies provided convincing hints for the formation of special helix types in this novel foldamer class.

2. Design principles

In an effort to augment the repertoire of conformational space available for foldamer design, we set out to generate novel foldamers, which contain conformationally constrained α-amino acid–aromatic amino acid-conjugated building blocks as subunits. In this article, we describe the design, synthesis, and conformational studies of a novel hybrid foldamer **3**, derived from regularly repeating α-aminoisobutyric acid (Aib) and 3-amino-4,6-dimethoxybenzoic acid (Adb) residues (Aib-Adb motif). We designed the Aib-Adb motif-based foldamer **3** anticipating that the corresponding oligomers would adopt a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by both Aib and Adb residues (highlighted in blue and red bold bonds in **3**, Scheme 1). The achiral Aib residue is known to play a key role[7] in the conformational restriction of polypeptides due to its overwhelmingly constrained phi ($\phi\pm60°$) and psi ($\psi\pm30°$), while the backbone-rigidified aromatic amino acid residue Adb[8] is known to induce a crescent conformation in its oligomers via localized five- and six-membered ring hydrogen bonding interactions. Thus, we reasoned that hetero-oligomers made of Aib-Adb repeat motif should also display conformational rigidity. Structural studies (vide infra) indeed showed that the Aib-Adb dimer **3** folds into a well-defined, compact, three-dimensional structure, as evidenced from single crystal X-ray and 2D NOESY studies.

Keywords: Foldamer; Amino acids; Peptidomimetics; Conformation.
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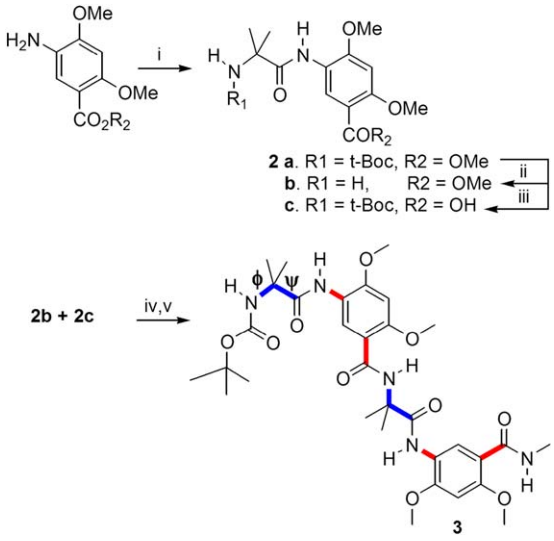
Most astonishingly, the crystal structure analysis revealed a fascinating arrangement of water clusters, in the crystal lattice, held by the backbone amide groups of the foldamer with a peculiar architecture. It is noteworthy that the understanding of three-dimensional structures of water clusters has profound implications in several areas ranging from water-mediated molecular self-assembly[9] to protein structure and function.[10] Furthermore, exploration of conformationally ordered synthetic oligomers that interact with water molecules may enable better understanding of the much debated issue of water interaction with Anti Freeze Proteins (AFPs) and Anti Freeze Glyco Proteins (AFGPs).[11]



Scheme 1. Synthesis of **3**: Reagents and conditions: (i) Boc-Aib-OH, DIPEA, TBTU, MeCN, rt, 6 h; (ii) dry HCl (gas), dioxane, rt, 5 min; (iii) 2 N LiOH, MeOH, rt, 12 h; (iv) DIPEA, TBTU, MeCN, rt, 8 h; (v) methanolic $MeNH_2$, 48 h, rt. *Note*: for aiding quick identification, the conformational restriction imposed by both Aib and Adb residues in **3** is highlighted in blue and red bold bonds, respectively.

3. Results and discussion

The Aib-Adb motif-based foldamer **3** was assembled from Boc-Aib-Adb-OMe building block **2a**, which in turn was synthesized by coupling the protected amino acids Aib and Adb using TBTU as a coupling agent (Scheme 1). However, attempts to synthesize higher oligomers using this 'segment doubling strategy' were unsuccessful, due to the formation of intractable mixture of products under various conditions.

The foldamer **3** crystallized from acetonitrile/water (90:10) in triclinic space group *P*-1. The unit cell contained two foldamers and 14 water molecules (Fig. 1).

Investigation of the crystal structure revealed that the intrinsically constrained Aib residues imposed a significant twist on the foldamer backbone, as expected, with ϕ and ψ torsion angles close to 60 and 30°, respectively, forcing the foldamer backbone to adopt a doubly bent conformation. It is interesting to compare the conformational propensities of the homo-oligomers made of the individual amino acids (Aib and Adb) and their hybrid oligomer **3**. Whereas the homo-oligomers of Aib and Adb have been reported to adopt 3_{10}-helical[12] and crescent architectures,[8] respectively, the hybrid foldamer

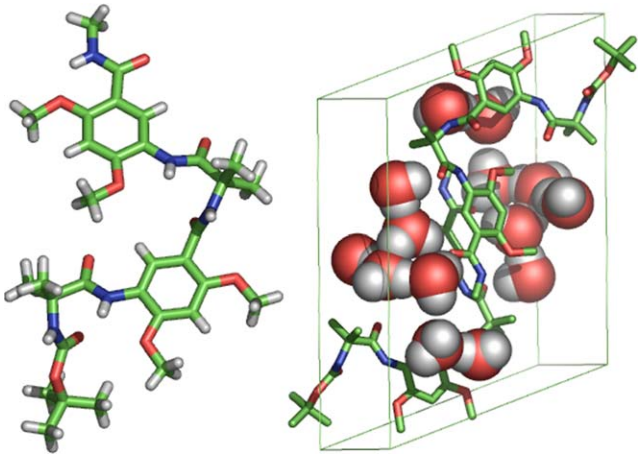


Figure 1. Crystal structure of the Aib-Adb motif-based foldamer **3**. Water molecules in the unit cell are represented in spheres, for aiding quick identification. Color coding: C green, H gray, N blue, O red.

3, containing alternately changing Aib and Adb residues, shows an entirely different structural architecture, a fact that clearly attests the importance of hybrid foldamer strategy[4] for augmenting the conformational space available for novel foldamer design.

Investigation of the crystal structure of **3** revealed the presence of water molecules embedded in the crystal lattice. A detailed analysis of the arrangement of water molecules revealed highly interesting features (Fig. 2).

There are mainly two types of water molecules discernible in the crystal lattice: the first type (colored red) forms a polymeric chain of water clusters and the second type (colored orange) bridges adjacent foldamer molecules as well as connects the foldamer to the water clusters, eventually forming a complex three-dimensional hydrogen bonded network. All the backbone carbonyl oxygens of the foldamer are involved in strong hydrogen bonding interactions with water molecules (O···O<3.0 Å).[13] However, only the Aib amide NHs (N3*H* and N5*H*) partake in interactions with water molecules, leaving the Adb amide NHs (N2*H* and N4*H*) and the methyl amide NH (N1*H*) to be satisfied with S(5)- and S(6)-type[14] hydrogen bonding interactions, respectively.

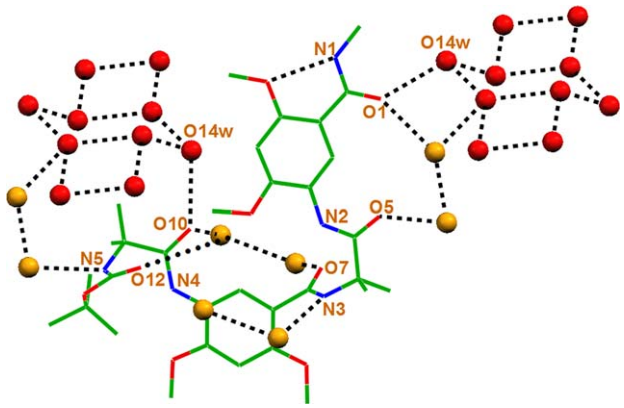


Figure 2. Crystal structure of Aib-Adb motif-based foldamer **3** showing interaction of the foldamer backbone with water molecules.

The water molecules, in pairs (colored orange), that bridge the backbone carbonyls of the adjacent residues donate two hydrogen bonds to the backbone carbonyl oxygens of the foldamer forming 12-membered ring hydrogen bonded network. Further, these *water pairs* accept hydrogen bonds (one each) from the Aib NHs of the adjacent foldamers. The backbone carbonyls O1 and O10 keep the parallel running water chains in place by hydrogen bonding with the water molecule ($O14_W$) that is part of the centrosymmetric six-membered water cluster. Interestingly, the same water molecule ($O14_W$) helps in building the hydrogen bonded three-dimensional network by donating a hydrogen bond to the carbonyl oxygens (O1 and O10) of another foldamer.

The infinite chain of water clusters has alternate four- and six-membered rings (oxygen atoms) sharing one edge. The oxygen atoms of the water molecules in four-membered rings assume square planar structure and the six-membered rings display a centrosymmetric chair conformation. The infinite chains of water clusters are held together by strong O_w–H$\cdots O_w$ hydrogen bonding interactions ($O_w\cdots O_w$=2.73–2.85 Å).[13] The supramolecular chains of water clusters are aligned parallel to each other (Fig. 3).

The folded structure is organized by the backbone H-bonds in solution state, as evidenced from the FTIR spectroscopy, a sensitive tool that is easily applicable for the detection of vibrational modes influenced by the presence of the H-bonds. In the N–H stretch region of **3**, the free N–H vibration, presumably due to the N-terminal Boc amide NH, appears as a weak signal at 3419 cm^{-1}, while intramolecular H-bonded N–H stretches give rise to a broad band in the region 3388 cm^{-1}. Another important source of information in IR spectra is the amide carbonyl region (1600–1700 cm^{-1}). The band at 1647 cm^{-1} can be ascribed to the H-bonded carbonyl in the backbone. Weaker H-bonds result in a slightly increased frequency. The band at 1683 cm^{-1} could be assigned to the N-terminal Boc carbonyl that is not taking part in intramolecular H-bonding.

Solution-state NMR studies (500 MHz) of the foldamer **3** in $CDCl_3$ strongly suggested the prevalence of a doubly bent conformation in solution state, similar to the one observed in the solid state, although the existence of water clusters in solution state could not be verified. One of the most characteristic NOE interactions that can be anticipated for a doubly bent conformation for **3**, as observed in the solid state, would be the NH versus NH dipolar couplings of the amide NHs of the adjacent Aib-Adb residues. Analysis of the 2D NOESY data (500 MHz, $CDCl_3$) indeed revealed the existence of NH versus NH dipolar couplings of the adjacent Aib-Adb residues (NH1/NH2 and NH3/NH4) as anticipated (Fig. 4). Furthermore, the characteristic NOE interactions between amide N*H* and the adjacent *O*-aryloxymethyls in **3** (NH2/OMe1, NH3/OMe2, NH4/OMe3, and NH5/OMe4) also strongly suggest their *syn* orientation, thereby making space for the S(5) and S(6)[14] type hydrogen bonded arrangement, a common feature in *O*-alkoxy arylamides.[8]

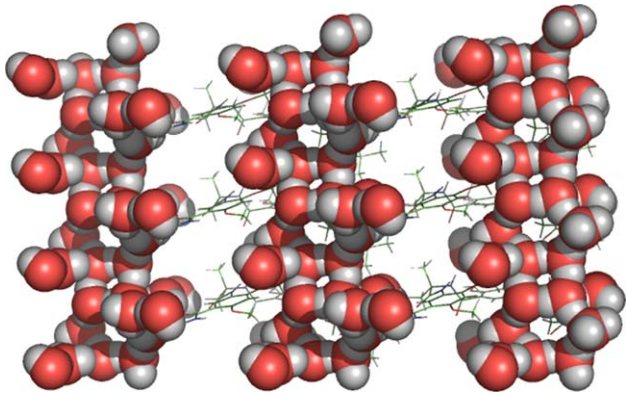


Figure 3. A view of the arrangement of polymeric chain of water clusters in the crystal lattice of **3**. For clarity, the polymeric chains of water clusters are represented in spheres and the foldamers in lines. Color coding: C green, H gray, N blue, O red.

4. Summary

In summary, we have designed and synthesized a novel constrained aliphatic–aromatic conjugated hybrid foldamer that adopts a well-defined, compact, three-dimensional architecture,[16] governed by a combined conformational restriction imposed by the individual amino acids from which it is composed. Conformational investigations confirmed the prevalence of a unique doubly bent conformation for **3**, in both solid and solution states, as evidenced from single crystal X-ray and 2D NOESY studies, respectively. The findings suggest that constrained aliphatic–aromatic amino acid conjugates offer new avenues for the de novo design of foldamers with distinctive structural architectures. The most striking feature of the present de novo designed foldamer is its remarkable ability to stabilize supramolecular polymeric chain of water clusters held together by strong hydrogen bonding interactions. We are currently probing the possibility of water cluster formation in related foldamers, as well as investigating the influence of substitution pattern in the aromatic nuclei on the structural architecture of the corresponding hybrid foldamer.

5. Experimental

5.1. General

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Acetonitrile was dried by distilling over calcium hydride and kept it over 4 Å molecular sieves, prior to use. Chromatography was done on pre-coated silica gel plates (kieselgel $60F_{254}$, Merck). Column chromatographic purifications were done with 100–200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ on Ac 200 MHz or DRX-500 MHz Bruker NMR spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities are reported as singlet (s), doublet (d), quartet (q), broad (br), broad singlet (br s) and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd, Germany). IR spectra were recorded in Nujol or $CHCl_3$ using a Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B 540. MALDI-TOF mass spectra were obtained from Voyager-PE, Voyager DEPRO, and Voyager-DE STR Models. Single crystal

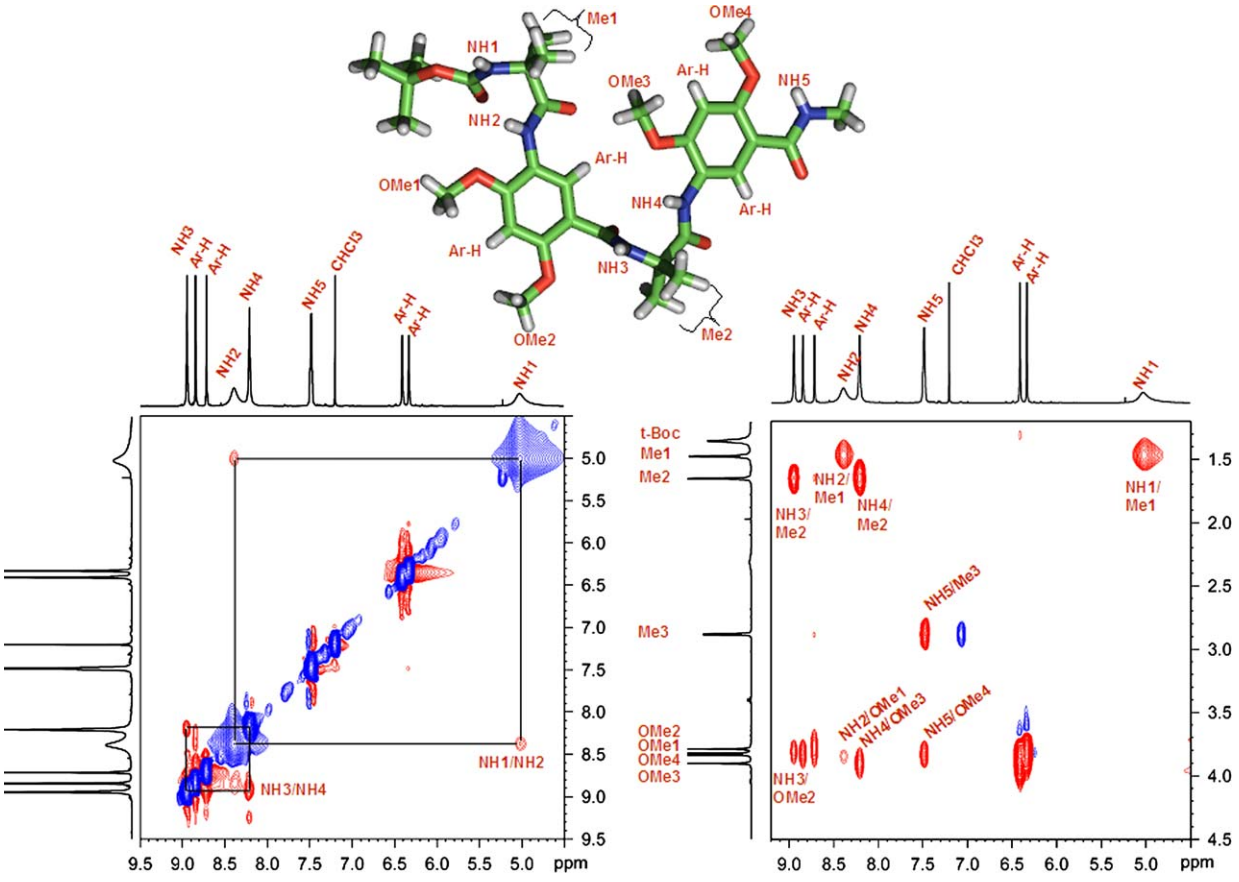


Figure 4. Partial 2D NOESY spectra of **3** (500 MHz, $CDCl_3$) showing characteristic NH1/NH2 and NH3/NH4 interactions (see also Supplementary data). For aiding interpretation of the 2D data, crystal structure of **3**[15] with selected labeled atoms is also shown.

X-ray data were collected on a *Bruker SMART APEX* CCD Area diffractometer with graphite monochromatized (Mo K_α=0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

5.1.1. 5-(2-*tert*-Butoxycarbonylamino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid methyl ester 2a. To an ice-cold stirred solution of the acid Boc-Aib-OH (5.70 g, 28.0 mmol, 1 equiv) and the aromatic amine **1** (5.33 g, 25.3 mmol, 0.9 equiv) in dry acetonitrile (30 mL) was added DIPEA (7.53 mL, 42.1 mmol, 1.5 equiv) followed by TBTU (12.61 g, 39.3 mmol, 1.4 equiv). The resulting mixture was stirred for 6 h at room temperature. The solvent was stripped off under reduced pressure and the residue was diluted with dichloromethane and washed sequentially with potassium hydrogen sulfate solution, saturated sodium bicarbonate, and water. Drying and concentration of the DCM extract under reduced pressure gave the crude product, which on column chromatography (50% EtOAc/Hexane) afforded the desired pure product **2a** (8 g, 72%). Mp 145 °C; IR ($CHCl_3$) ν (cm^{-1}): 3020, 1712, 1531, 1463, 1215, 754; ^1H NMR (500 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.58 (br s, 1H), 6.44 (s, 1H), 5.02 (br s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 1.52 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 165.5, 157.8, 154.5, 152.6, 123.1, 120.4, 111.3, 95.5, 57.6, 56.4, 55.8, 51.5, 28.1, 25.7; MALDI-TOF Mass: 435.34 (M+K). Anal. Calcd for $C_{19}H_{28}N_2O_7$: C, 57.57; H, 7.07; N, 7.07. Found: C, 57.37; H, 7.03; N, 6.99.

5.1.2. 5-(2-Amino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid methyl ester hydrochloride 2b. To an ice-cold stirred solution of the compound **2a** (0.5 g, 1.3 mmol) in dry dioxane (10 ml) was bubbled dry HCl gas for 5 min. Then dry ether (15 mL) was added to the reaction mixture, when the amine hydrochloride (**2b**) precipitated out as a white solid (0.37 g, 87%). The solid was filtered, washed with dry ether, dried, and used for the next reaction, without further purification.

5.1.3. 5-(2-*tert*-Butoxycarbonylamino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid 2c. To a solution of compound **2a** (2.2 g, 5.6 mmol, 1 equiv) in methanol (15 mL) was added 2 M LiOH solution (11.08 mL, 22.2 mmol, 4 equiv). The reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and diluted with distilled water, and acidified with saturated potassium hydrogen sulfate. Then the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic extracts were washed with brine. Drying and concentration of the organic layer, under reduced pressure, yielded the desired product **2c** (2.0 g, 94%), which was used for the next reaction, without further purification.

5.1.4. 1-(5-(1-(2,4-Dimethoxy-5-methylcarbonyl-phenylcarbamoyl)-1-methyl-ethylcarbamoyl)-2,4-dimethoxy-phenylcarbamoyl)-1-methyl-ethyl)-carbamic acid *tert*-butyl ester 3. To an ice-cold stirred solution of the acid **2c** (2.0 g, 5.2 mmol, 1 equiv) and amine **2b** (1.73 g, 5.23 mmol, 1 equiv) in dry acetonitrile (20 mL) was added DIPEA (2.3 mL, 13.0 mmol, 2.5 equiv) followed by TBTU (2.35 g, 7.3 mmol, 1.4 equiv). The resulting reaction mixture was stirred overnight at room temperature. The solvent was stripped off under reduced pressure; the residue was dissolved in dichloromethane (100 mL) and washed sequentially with potassium hydrogen sulfate solution, saturated sodium bicarbonate, and water. Drying and concentration in vacuum yielded the crude ester, which was directly used for the next amidation reaction, without further purification. The crude ester was taken in an RB flask containing saturated methanolic methylamine solution (25 mL) and stirred at room temperature for two days. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5% methanol/ethyl acetate, R_f 0.4) to yield pure **3** (2.0 g, 69%), which could be crystallized from acetonitrile/water (90:10). Mp 212 °C; IR ($CHCl_3$) ν (cm^{-1}): 3419, 3388, 3018, 1683, 1647, 1610, 1517, 1215, 758; ^1H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.89 (s, 1H), 8.76 (s, 1H), 8.44 (br s, 1H), 8.26 (s, 1H), 7.53 (s, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 5.07 (br s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.93 (d, 3H, J=4.8 Hz), 1.70 (s, 6H), 1.52 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 172.1, 165.7, 164.7, 154.6, 152.8, 152.4, 124.6, 124.0, 121.2, 121.1, 114.1, 113.8, 94.9, 94.8, 58.3, 57.5, 56.4, 56.2, 55.9, 28.1, 26.4, 25.5; MALDI-TOF Mass: 681.95 (M+Na). Anal. Calcd for $C_{32}H_{45}N_5O_{10}$: C, 58.27; H, 6.82; N, 10.62. Found: C, 58.15; H, 6.80; N, 10.59.

5.1.5. Crystal data for 3 $C_{32}H_{45}N_5O_{10}\cdot 7H_2O$. M=785.84. Colorless crystal, approximate size 0.56×0.27×0.05 mm, multi scan data acquisition, θ range=2.12–25.00°, triclinic, space group P-1, a=6.893 (15), b=15.55 (3), c=20.21 (4) Å, α=110.27 (5)°, β=93.77 (5)°, γ=93.37 (5)°, V=2019 (8) Å^3, Z=2, ρ_{calcd}=1.292 gcm^{-1}, T=297 (2), μ (Mo K_α)=0.105 mm^{-1}, 7052 reflections measured, 4044 unique [$I>2\sigma(I)$] reflections, 575 refined parameters, R value 0.0551, $wR2$=0.1244 (all data R=0.0916, $wR2$=0.01372). Crystallographic data of **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-289024. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.032.

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14. For an excellent account on the graph set analysis of H-bonded systems, see: Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
15. This figure was generated using PyMOL molecular graphics system. W. L. DeLano, The PyMOL Molecular Graphics System. http://www.pymol.org (accessed 2004).
16. We have recently disclosed the compact, three-dimensional structural architecture of acrylamide oligomers forming protein β-sheet-like architecture, see: Amol, K.; Rajesh, R.; Rajamohanan, P. R.; Sanjayan, G. J. *Chem. Commun.* **2006**, 2756–2758.