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Conformationally Constrained Aliphatic−Aromatic Amino-Acid-Conjugated Hybrid Foldamers with Periodic β-Turn Motifs

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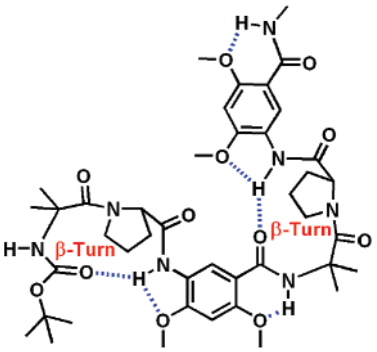

In this note, we describe the design, synthesis, and structural studies of novel hybrid foldamers derived from Aib-Pro-Adb building blocks that display repeat β-turn structure motif. The foldamer having a conformationally constrained aliphatic−aromatic amino acid conjugate adopts a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by the individual amino acids with which it is made of. Conformational investigations by single-crystal X-ray and solution-state NMR studies were undertaken to investigate the conformational preference of these foldamers with a hetero-backbone. Our findings suggest that constrained aliphatic−aromatic amino acid conjugates would offer new avenues for the de novo design of hybrid foldamers with distinctive structural architectures.

Conformationally ordered synthetic oligomers, also called foldamers,[1,2] show considerable promise for the creation of unnatural oligomers that mimic the structural features of biopolymers. The conformational rigidity coupled with their modifiable shape and size shows potential of developing novel protein mimics that might be difficult to design based on small-molecule scaffolds.[3] Investigations by various groups have led to the generation of a multitude of such synthetic oligomers with diverse backbone structural architectures and functions.[4]

In an effort to expand the conformational space available for foldamer design, synthetic oligomers made of building blocks of independent conformational preferences were recently developed. A noteworthy example is the possibility of formation of special helix types in hybrid peptides derived from alternately changing aliphatic amino acid residues.[5,6] We have recently demonstrated that synthetic oligomers containing unconventional foldamer building blocks could mimic protein secondary structures.[7] Herein, isotactic acrylamide tetramers have been shown to adopt protein β-sheet-like structures, formed by extensive intermolecular hydrogen bonding interactions of the individual strands. With an objective of expanding the conformational space available for foldamer design, we recently set

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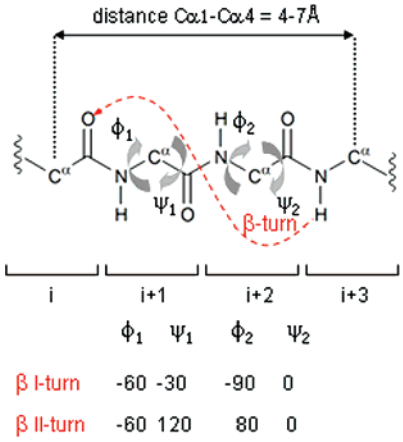

FIGURE 1. Schematic representation of the intramolecular hydrogen bonding interaction that stabilizes β-turns ($i \leftarrow i + 3$). The ideal values for the torsion angles ϕ and ψ (highlighted in bold gray arrows) for the most common types of β-turns (βI and βII) are indicated.

out to generate novel hybrid foldamers composed of conformationally restricted α-amino acid/aromatic amino acid conjugates as building blocks.[8,9] By suitable choice of the amino acid constituents, it was possible to obtain a foldamer exhibiting doubly bent conformation that stabilizes a polymeric array of water clusters.[8] Using the same strategy, but with different amino acid constituents, we could also obtain a foldamer displaying periodic γ-turn motifs, stabilized by extensive intramolecular hydrogen bonding interactions.[9]

Within the context of seeking foldamers that form ordered structures, both in solution and in the solid state, this note describes the design, synthesis, and conformational studies of a novel hybrid foldamer **4b**, derived from regularly repeating α-aminoisobutyric acid (Aib), proline (Pro), and 3-amino-4,6-dimethoxy benzoic acid (Adb)[2i] residues as subunits (Aib-Pro-Adb motif), which forms periodic β-turn motifs as evidenced from various structural studies (vide infra). It is noteworthy that, among the various secondary structures found in peptides and proteins, reverse turns (γ- and β-turns) have achieved a privileged status for considerable mimicking studies. A turn is defined as a site where the peptide chain reverses its overall direction.[10,11] The terms γ- and β-turn describe turns of three or four consecutive residues, respectively. These turns may or may not be stabilized by intramolecular hydrogen bonding interactions. In β-turns, the C═O of the first residue (i) may be hydrogen bonded to the NH (amide) of the fourth residue (i + 3), forming a 10-membered ring hydrogen bonded structure (Figure 1). The term "open" β-turn is used for situations where no "intraturn" hydrogen bond network is present. Further classification into specific γ-turn or β-turn classes is based upon the geometry of the peptide backbone, as described by the ϕ and ψ Ramachandran angles in residues i + 1 and i + 2 (β-turn).[10] Among various turn conformations, β-turns have achieved considerable attention particularly due to the fact that a multitude of biological receptors recognize peptides in such

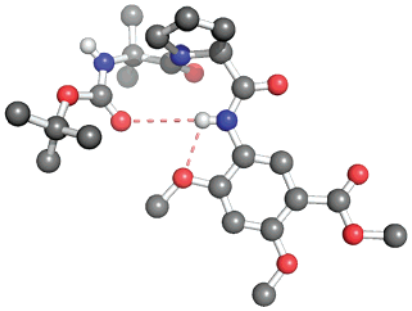

FIGURE 2. Single-crystal X-ray structure (ball and stick representation) of the Boc-Aib-Pro-Adb-OMe foldamer **3a**. H-bonding interactions are highlighted in salmon colored dashes. In addition to the N−H···O═C β-turn interaction, S(5) type interaction[15] is also visible. Hydrogens, other than at the hydrogen bonding sites, have been deleted for clarity.

conformations.[12] β-Turns comprise a rather diverse group of structures with the distance from the Cα of the first residue to the Cα of the fourth residue in the range of 4−7 Å. The O_1···H_4−N hydrogen bonding interaction is not an essential structural feature but is often an indication of a β-turn structure, as shown by X-ray crystallography and NMR spectroscopy.[10]

Design Principles. We designed the Aib-Pro-Adb motif-based foldamer building block **3** (Scheme 1) anticipating that the corresponding oligomers would adopt a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by the conformationally constrained individual amino acid residues: Aib, Pro, and Adb (the conformationally restricted sp^3 backbone bonds in **4** are highlighted in blue bold bonds). Central to the design strategy is stabilizing and restoring the 10-membered cyclic hydrogen bond between residue i and i + 3 defining a β-bend ribbon spiral motif, a characteristic feature found in peptides with −(Aib-Pro)− sequence.[13]

In a sequential peptide, the alternation of a Pro (proline) residue that disrupts the conventional H-bonding schemes found in helices and a helix-forming residues such as Aib (α-amino isobutyric acid) may give rise to a novel helical structure, called the β-bend ribbon spiral.[13] This structure may be viewed as a subtype of the 3_{10}-helix, having somewhat the same helical fold of the peptide chain with intramolecular N−H···O═C H-bonds of the β-bend type,[14] and is characterized by two sets of (ϕ,ψ) angles: $\phi_i = -54°$, $\psi_i = -40°$; $\phi_{i+1} = -78°$, $\psi_{i+1} = -10°$ associated with the Aib-Pro motif. The complete structural

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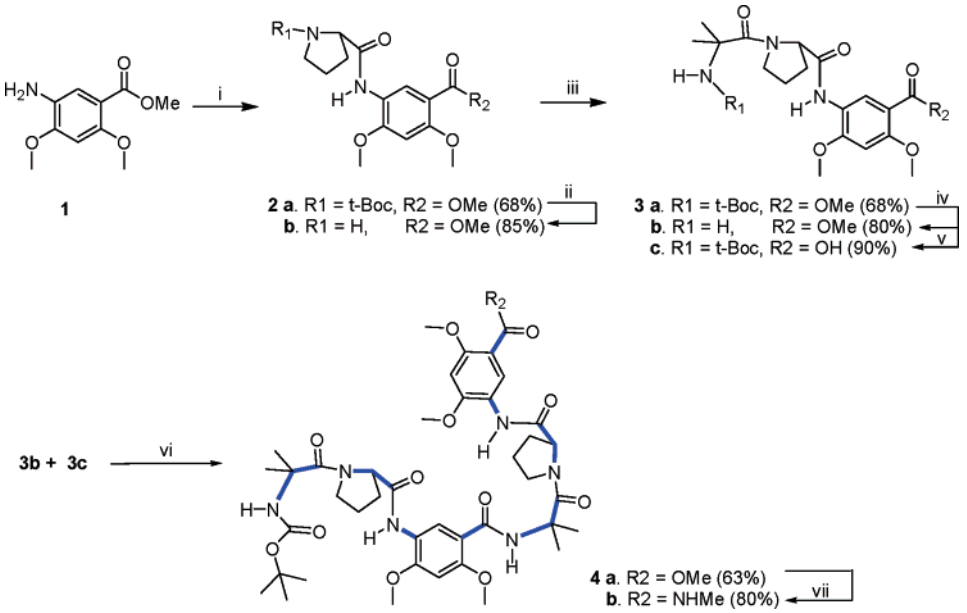
SCHEME 1 [a]



[a] Reagents and conditions: (i) Boc-Pro-OH, IBCF (isobutyl chloroformate), Et_3N, dry DCM, rt, 6 h; (ii) dry HCl (gas), dioxane, rt, 5 min; (iii) **2b**, Boc-Aib-OH, DIPEA, TBTU, dry MeCN, rt, 8 h; (iv) dry HCl (gas), dioxane, rt, 5 min; (v) 2 N LiOH, MeOH, rt, 12 h; (vi) DIPEA, TBTU, dry MeCN, rt, 12 h; (vii) methanolic $MeNH_2$, 50 °C, 70 h, rt. *Note:* To facilitate identification, the conformationally restricted sp^3 backbone bonds in **4** are highlighted in blue bold bonds.

characterization of this peptide conformation, which may be of relevance in the development of model systems for peptaibol antibiotics (e.g., zervamicin)[13] and for the numerous $(Pro-X)_n$ (with X ≠ Pro) segments found in globular and fibrous proteins, was achieved by X-ray diffraction studies of terminally blocked $(L\text{-Pro-Aib})_n$ sequential peptides.[14]

The Aib-Pro-Adb motif-based foldamer **4b** was assembled from Boc-Aib-Pro-Adb-OMe building block **3a** (Scheme 1). The easily crystallizing building block **3a**, readily available by the TBTU-mediated coupling of the dipeptide H-Pro-Adb-OMe **2b** with BOC-Aib-OH, was subjected to segment doubling strategy to afford **4a**, which could be easily amidated to afford the amide analogue **4b**.

The shorter foldamer **3a** could be crystallized readily from an ethyl acetate/petroleum ether (1:1) solvent mixture. Investigation of its crystal structure revealed the existence of the anticipated folded conformation having Aib and Pro residues taking the $i + 1$ and $i + 2$ positions, respectively, of a β-bend ribbon spiral motif (Figure 2), characteristic of $(L\text{-Pro}-Aib)_n$ sequential peptides.[13,14] The intramolecular N−H···O═C hydrogen bonding interaction forming a 10-membered ring hydrogen-bonded network was relatively weaker with D−H···A distance [d(N−H···O)] 3.04 Å and the D−H···A angle [∠(N−H···O)] 173.57°. The phi (ϕ°) and psi (ψ°) dihedral angles from the crystal structure of **3a** were $\phi_1 = -55$, $\psi_1 = -36$; $\phi_2 = -75$, $\psi_2 = -11$, which are in excellent agreement with the observed phi and psi dihedral angles observed in $(L\text{-Pro-Aib})_n$ sequential peptides ($\phi_1 = -54$, $\psi_1 = -40°$; $\phi_2 = -78°$, $\psi_2 = -10°$) characterized by the β-bend ribbon spiral motif.[13,14] This also means that incorporation of Adb residue (itself a constrained amino acid) close to the L-Pro-Aib site does not disrupt the β-bend ribbon spiral motif. It is noteworthy that incorporation of constrained amino acids into peptide sequences often causes dramatic conformational flipping.[15]

Investigation of the crystal structure further revealed that the amide NH of Aib that does not participate in intramolecular hydrogen bonding interaction participates in intermolecular interaction with the proline C═O of another molecule forming a self-assembled extended chain structure (Supporting Information).

All efforts to crystallize the Aib-Pro-Adb motif-based hexapeptide foldamer **4b** did not succeed. However, it was possible to investigate the essential structural features by solution-state NMR studies (Figure 3). Due to solubility reasons, the solution-state conformational studies were carried out in $CDCl_3$, in which the foldamer was readily soluble. It is noteworthy that the occurrence of periodic β-turn motifs in **4b** is strongly supported by 2D NOESY NMR studies in solution (500 MHz, $CDCl_3$). One of the most characteristic NOE interactions that can be anticipated for a repeat turn conformation, as observed in the solid-state structure of the shorter analogue **3a**, would be the requirement of repeat dipolar couplings between the aryl-N*H* and δ-C*H* of adjacent proline in **4b** since they are in spatial proximity. Analysis of the 2D NOESY data indeed revealed the existence of sequential dipolar couplings between proline δ-C*H* and aryl-N*H* of the adjacent residues in **4b** (NH2/δ1 and NH4/δ2).

Furthermore, the turn conformation also would require the spatial proximity of aryl-N*H* and α-C*H* of adjacent proline, which is also readily borne out in the 2D NOESY data (NH2/α1 and NH4/ α2). The characteristic NOE interactions between aryl-N*H* and the adjacent *O*-aryloxymethyls in **4b** (OMe1/NH2; OMe2/NH3; and OMe3/NH4) strongly suggest their *syn* orientation, thereby making space for the S(5) type hydrogen bonded arrangement,[16] a prerequisite for the bifurcated hydrogen bonding in such systems.[2g,i] Nevertheless, the present study does not rule out the possibility of rotamer formation/local dynamics

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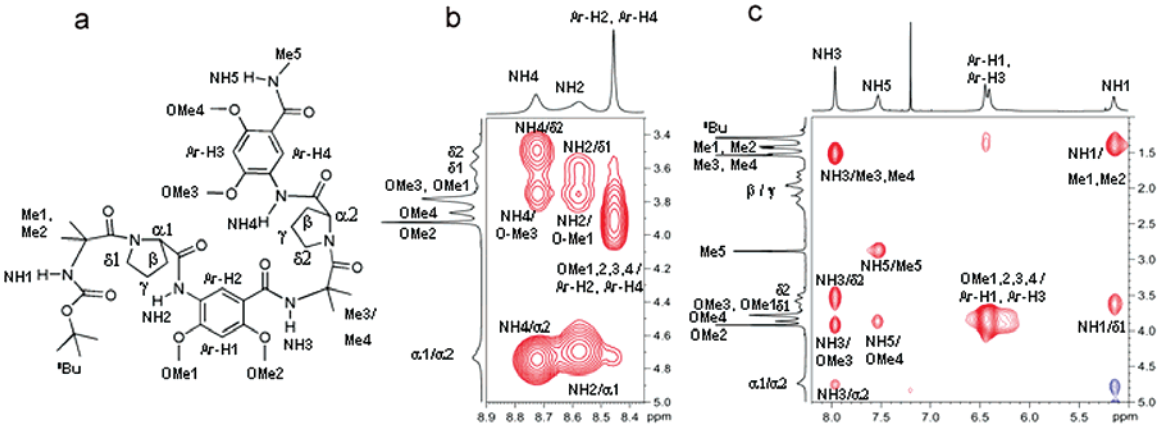

FIGURE 3. (a) Molecular structure of **4b** with selectively numbered protons: (b, c) partial 2D NOESY spectra of **4b** (500 MHz, $CDCl_3$) showing characteristic nOes.

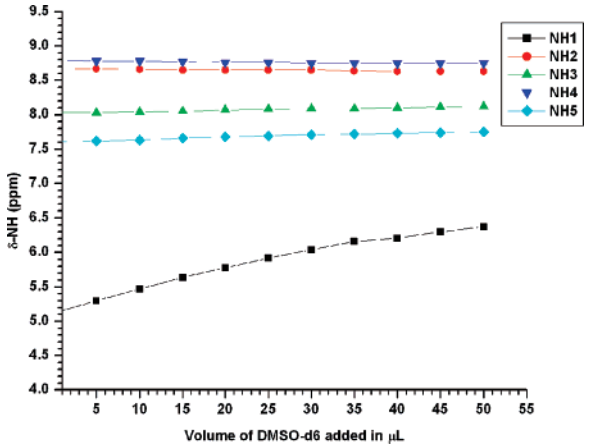

FIGURE 4. [D_6]DMSO titration graph of the hexapeptide foldamer **4b**. The initial concentration of the sample in $CDCl_3$ was 19.5 mM, and the total amount of [D_6]DMSO used was 7.7% of the total volume.

under the conditions of this NMR study since some of the signals are broadened.

To confirm that intramolecular hydrogen bonds are clearly prevalent in solution, we also performed [D_6]DMSO titration studies of **4b**. The chemical shift changes of all the amide protons are presented in Figure 4. Except for the N-terminal Aib-NH, all other NHs appear in the downfield region and show little shift when solutions of **4b** are titrated gradually with [D_6]-DMSO ($\Delta\delta < 0.15$ ppm), suggesting their strong involvement in intramolecular hydrogen bonding interactions. In contrast, the chemical shift of the N-terminal Aib amide NH proton undergoes significant chemical shift changes ($\Delta\delta = 1.26$ ppm), on incremental addition of [D_6]DMSO, suggesting its involvement in intermolecular hydrogen bonding.

In summary, we have developed novel hybrid foldamers containing constrained amino acids of independent conformational preferences as subunits. Conformational investigations suggest the prevalence of repeat β-turn conformation for these oligomers, in both solid and solution-state, as evidenced from single-crystal X-ray and NMR studies, respectively. The findings suggest that constrained aliphatic−aromatic amino acid conjugates would offer new avenues for the de novo design of foldamers with distinctive structural architectures, entirely different from their homo-analogues. We are currently investigating the influence of substitution pattern in the aromatic nuclei on the overall structural architecture of the corresponding hybrid foldamers containing −(Aib-Pro)− sequences.

Experimental Section

Representative Procedure: {2-[2-{5-{2-[2-{2,4-Dimethoxy-5-methylcarbamoylphenylcarbamoyl}-pyrrolidin-1-yl]-1,1dimethyl-2-oxoethylcarbamoyl}-2,4-dimethoxyphenylcarbamoyl}-pyrrolidine-1-yl]-1,1-dimethyl-2-oxoethyl}carbamic acid *tert*-butyl ester 4b: To an ice-cold stirred solution of the acid **3c** (0.4 g, 0.83 mmol, 1 equiv) and amine **3b** (0.35 g, 0.83 mmol, 1 equiv) in dry acetonitrile (10 mL) was added DIPEA (0.37 mL, 2.08 mmol, 2.5 equiv) followed by TBTU (0.37 g, 1.16 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 product which on column chromatography (5% methanol/ethyl acetate, R_f 0.2) afforded **4a** (0.45 g, 63%), which was directly used for the next amidation reaction, without further purification. The ester **4a** (0.45 g, 0.52 mmol) was taken in saturated methanolic methylamine solution (15 mL) and stirred at room temperature for 2 days. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (8% methanol/ethyl acetate, R_f 0.4) to yield pure **4b** (0.4 g, 80%): $[\alpha]^{26}_D$ −25.6 ($CHCl_3$); mp >248 °C; IR (Nujol) ν (cm^{-1}) 3018, 1645, 1614, 1400, 1215, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.62 (br s, 1H), 8.49 (s, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.60 (s, 1H), 6.50 (br s, 1H), 6.45 (br s, 1H), 5.28 (br s, 1H), 4.90−4.60 (m, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.82 (s, 6H), 3.75−3.45 (m, 4H), 2.92 (d, 3H), 2.25−1.70 (m, 8H), 1.57 (s, 6H), 1.45 (s, 6H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.8, 169.6, 166.2, 164.1, 156.1, 154.9, 128.6, 127.4, 120.8, 113.9, 113.1, 95.8, 80.1, 62.9, 57.0, 48.3, 28.2, 26.7, 26.1, 25.4; MALDI-TOF *m*/*z* 876.36 (M + Na). Anal. Calcd for $C_{42}H_{59}N_7O_{12}$: C, 59.08; H, 6.91; N, 11.48. Found: C, 58.95; H, 6.87; N, 11.39.

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Supporting Information Available: Full experimental procedures, ^{1}H, ^{13}C, and ESI mass spectra of all new compounds (PDF), and crystal data of **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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