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Can a consecutive double turn conformation be considered as a peptide based molecular scaffold for supramolecular helix in the solid state?

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Abstract—Helices and sheets are ubiquitous in nature. However, there are also some examples of self-assembling molecules forming supramolecular helices and sheets in unnatural systems. Unlike supramolecular sheets there are a very few examples of peptide sub-units that can be used to construct supramolecular helical architectures using the backbone hydrogen bonding functionalities of peptides. In this report we describe the design and synthesis of two single turn/bend forming peptides (Boc-Phe-Aib-Ile-OMe **1** and Boc-Ala-Leu-Aib-OMe **2**) (Aib: α-aminoisobutyric acid) and a series of double-turn forming peptides (Boc-Phe-Aib-Ile-Aib-OMe **3**, Boc-Leu-Aib-Gly-Aib-OMe **4** and Boc-γ-Abu-Aib-Leu-Aib-OMe **5**) (γ-Abu: γ-aminobutyric acid). It has been found that, in crystals, on self-assembly, single turn/bend forming peptides form either a supramolecular sheet (peptide **1**) or a supramolecular helix (peptide **2**), unlike self-associating double turn forming peptides, which have only the option of forming supramolecular helical assemblages.

1. Introduction

The challenge in molecular self-assembly is to design molecular building blocks that are predisposed to give definite supramolecular structures using non-covalent interactions. Supramolecular helices and sheets are the most common and indispensable form of structures in biological systems. Helicity exists in numerous biological and chemical systems. In proteins, the α-helical structure is a very common motif. In DNA-double helices,[1] collagen triple helix[2] and even in the coat protein complex of Tobacco Mosaic Virus (TMV),[3] helicity is a common observable feature. Surprisingly, a considerable amount of helicity is also present in some misfolded, neurodegenerative disease-causing protein aggregates popularly known as amyloid plaques.[4] Unnatural supramolecular helical structures can be constructed using conformational restriction of macromolecules,[5] intra or intermolecular hydrogen bonds[6] or by metal ion chelation.[7] The most common and well-studied example of supramolecular single-, double- and triple-stranded helical conformations are metal chelated, self-assembled, oligonuclear coordination compounds,[7] the helicates.[8] Different approaches to construct supramolecular helices without metal ions and stabilized only by intermolecular and intramolecular hydrogen bonding have also been pursued.[6,9] Recently pyrene-4, 5-dione derivatives have been used to design supramolecular helical structures.[10] Peptide derivatives[11] and even chiral amino acids like the chiral 2,6-pyridinedicarboxamide containing the podand L-histidyl moieties and the corresponding D-derivative[12a] and ferrocene bearing the podand chiral dipeptide moieties (-L-Ala-L-Pro-OEt) and the corresponding D-derivative[12b] have been used to form supramolecular helical assemblages. Parthasarathi and his colleagues have synthesized and characterized a series of tripeptides which form extended helical structures with intervening water molecules between two consecutive peptide molecules and they demonstrated the hydrated helix pattern in crystals.[13] Our group is involved in constructing supramolecular peptide helices utilizing the backbone hydrogen bonding functionalities of the peptide molecules.[14] From our previous report, it has been observed that the short synthetic terminally blocked peptides with single turn/bend conformations can form either supramolecular sheets[15] or supramolecular helices.[14a] However, the peptide molecules with a double turn structure, self-assemble to form

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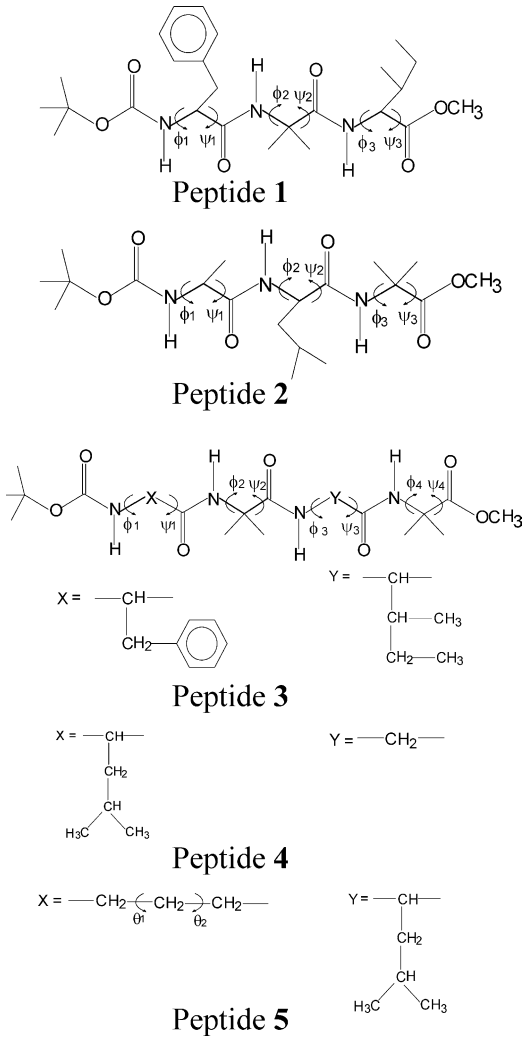

Figure 1. Schematic presentation of peptides **1**–**5**.

supramolecular helices in crystals.[14b–d] Therefore, it is necessary to define the role of a consecutive β-turn structure in the formation of supramolecular helical architecture. In this context we have designed and synthesized a series of single and double turn/ bend forming peptides (Fig. 1). All our previously reported peptides[14,15] and the peptides described in the present work are listed in Table 1. In this paper, we address the question of whether self-assembling double-turn forming peptides can only form supramolecular helical structures or whether other supramolecular architectures are possible.

2. Results and discussion

Peptides (peptides **1**, **2**, **3**, **4** and **5**) reported in this study have been synthesized with conformationally constrained, helicogenic Aib (α-aminoisobutyric acid) residue(s) in order to induce the helical nature of the individual peptide backbone.[16] The terminally protected tripeptides Boc-Phe-Aib-Ile-OMe **1** and Boc-Ala-Leu-Aib-OMe **2** (Fig. 1) have been designed and synthesized to obtain single β-turn/bend forming molecular conformations. The tetrapeptides Boc-Phe-Aib-Ile-Aib-OMe **3** and Boc-Leu-Aib-Gly-Aib-OMe **4** and Boc-γ-Abu-Aib-Leu-Aib-OMe **5**, each containing two Aib residues have been synthesized to obtain double bend conformations with two consecutive β-turns or other unusual turn structures. Previous studies from our group have established that the helix-nucleating Aib (α-aminoisobutyric acid) residue needs to be placed adjacent to the flexible N-terminally located γ-Abu (γ-aminobutyric acid residue) to obtain a turn structure.[17] All the reported peptides were studied using X-ray crystallography, NMR and mass spectrometry.

2.1. Single crystal X-ray diffraction study

Tripeptide **1** contains a helicogenic Aib residue at the central region whereas tripeptide **2** possesses the Aib residue at the C-terminus. The molecular conformations of tripeptides **1** and **2** in the crystal state are illustrated in Figure 2. Most of the ϕ and ψ values (except ψ_1 and ψ_3) of the constituent amino acid residues of tripeptide **1** fall within the helical region of the Ramachandran plot (Table 2). Hence the tripeptide **1** backbone, though it fails to form any intramolecular hydrogen bonded β turn conformation, adopts a bend (turn-like) structure (Fig. 2a), which self-assembles through two intermolecular hydrogen bonds (N6–H6···O8, 2.36 Å, 3.02 Å, 135.00° with symmetry element $-x$, $-0.5+y$, $1-z$) along the crystallographic *b* axis to form a monolayer β-sheet structure. These monolayer structures of tripeptide **1** are further self-assembled into higher order supramolecular β-sheet structure along the crystallographic *a* and *c* directions via van der

Table 1. List of single and double turn/bend forming peptides from our group

Sequence	No. of bends/turns in molecular structure	Supramolecular structure	Reference
1. Boc-Leu-Aib-Phe-OMe	One	Helix	14a
2. Boc-Leu-Aib-Phe-Aib-OMe	Two	Helix	14b
3. Boc-Ala-Aib-Leu-Aib-OMe	Two	Helix	14c
4. Boc-β-Ala-Aib-Leu-Aib-OMe	Two	Helix	14d
5. Boc-Aib-Val-Aib-β-Ala-OMe	Two	Helix	14e
6. Boc-Leu-Aib-β-Ala-OMe	One	Sheet	15a
7. Boc-Ala-Aib-Val-OMe	One	Sheet	15b
8. Boc-Ala-Aib-Ile-OMe	One	Sheet	15b
9. Boc-Ala-Gly-Val-OMe	One	Sheet	15b
10. Boc-Phe-Aib-Ile-OMe	One	Sheet	In current study
11. Boc-Ala-Leu-Aib-OMe	One	Helix	In current study
12. Boc-Phe-Aib-Ile-Aib-OMe	Two	Helix	In current study
13. Boc-Leu-Aib-Gly-Aib-OMe	Two	Helix	In current study
14. Boc-γ-Abu-Aib-Leu-Aib-OMe	Two	Helix	In current study