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Research Article

Design of Peptide Models for β-Hairpins and Equilibrating Helix-Hairpin Structures

Introduction

It is well established that synthetic peptides containing a centrally positioned Type-I or Type-II β-turn can form well folded peptide hairpins (1). Earlier studies from this laboratory have established that D-Pro-Xxx segments nucleate β-hairpin structures, with formation of a central Type-II β-turn (2). The octapeptide (Boc-Leu-Phe-Val-Aib-D-Ala-Leu-Phe- Val-OMe) is a rare example of a synthetic peptide hairpin, containing a central Type-I β-turn. Hairpins with Type-I turns are considerably more twisted than their Type-II counterparts. The Aib-Xxx segment has also been shown to adopt a Type-I β-turn structure, resulting in incorporation into the centre of a long synthetic, helical peptide (3) (Figures 1,2).

This observation prompted further studies on the context dependent conformational preferences of -Aib-Xxx- segments, where Xxx = Aib, L-Ala, Gly, D-Ala. It was anticipated that the –Aib-Gly- and –Aib-D-Ala- containing peptides would also provide models for equilibration between well folded, helical and hairpin structures [1-7] (Figure 3).

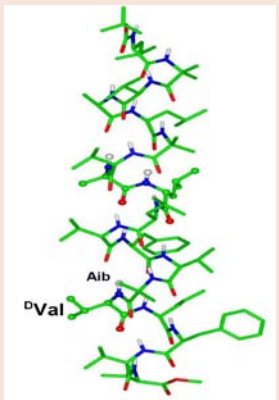


Figure 1: The 19-residue peptide that contains three D residues, αR of Boc-LUVALUV-DA-DL-LVFV-U-DV-LFVV-OMe.

The following sequences Boc-Leu-Phe-Val-**Aib-Xxx**-Leu-Phe-Val-OMe have been chosen for further study.

(1) Boc-Leu-Phe-Val-**Aib-Aib**-Leu-Phe-Val-OMe

(2) Boc-Leu-Phe-Val-**Aib-^{D}Ala**-Leu-Phe-Val-OMe

(3) Boc-Leu-Phe-Val-**Aib-^{L}Ala**-Leu-Phe-Val-OMe

(4) Boc-Leu-Phe-Val-**Aib-Gly**-Leu-Phe-Val-OMe

In addition smaller fragments are also being investigated to probe structure formation in the presence of a smaller number of internal (cross-strand) hydrogen bonds.

(5) Boc-**Aib-D-Ala**-NHMe

(6) Boc-Val-**Aib-D-Ala**-Leu-NHMe

(7) Boc-Phe-Val-**Aib-D-Ala**-Leu-Phe-NHMe

(8) Boc-**Aib-Aib**-NHMe

(9) Boc-Val-**Aib-Aib**-Leu-NHMe

(10) Boc-Phe-Val-**Aib-Aib**-Leu-Phe-NHMe

In the crystalline β-hairpin structure of the octapeptide shown in Figure 2, of the four anticipated cross-strand hydrogen bonds in an idealized β-hairpin, the terminal interaction Leu (1) NH--OC Val (8) is disrupted by a large re-orientation about the C^{α}--CO bond of Val (8) (ψ = -57.3°). Such fraying at hairpin termini is not uncommon.

The target peptides are being synthesized by solution phase procedures and characterized by NMR Spectroscopy. In addition, single crystals have been obtained for peptide sequence that **Boc-Val-Aib-^{D}Ala-Leu-NHMe** and **Boc-Val-Aib-Aib-Leu-NHMe** and related peptides highly important in vaccine development [8-13].

Experimental section

Peptides synthesis has been undertaken by standard solution phase chemistry. A representative scheme is shown in Figure 4. The following sequences have been synthesized and purified by medium pressure liquid chromatography (MPLC), homogeneity established by HPLC and characterized by ^{1}H NMR spectroscopy and mass spectrometer.

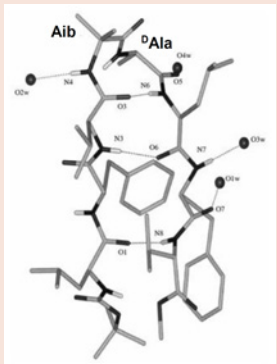


Figure 2: Molecular conformation in crystals of the Boc-Leu-Phe-Val-Aib-^{D}Ala-Leu-Phe-Val-OMe (4).

Figure 3: Helix to hairpin transition peptide sequence of Boc-Leu-Phe-Val-Aib-Aib-Leu-Phe-Val-OMe.

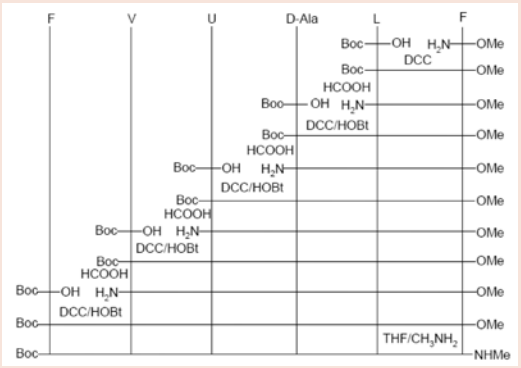


Figure 4: Synthetic scheme for solution phase peptide synthesis.

(a) Boc-Val-**Aib**-**D**-**Ala**-Leu-NHMe

(b) Boc-Val-**Aib**-**Aib**-Leu-NHMe

(c) Boc-Phe-Val-**Aib**-**D**-**Ala**-Leu-Phe-NHMe

(d) Boc-**Aib**-**D**-**Ala**-NHMe

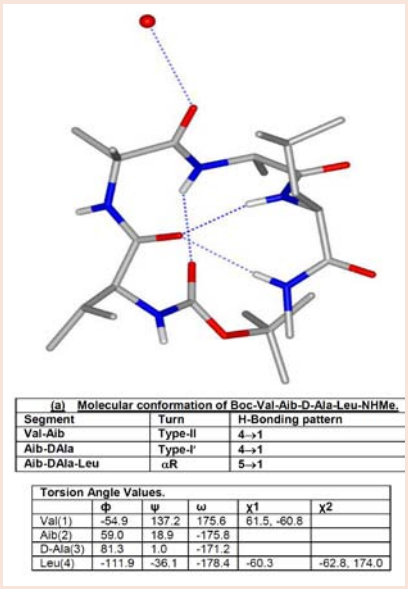
(e) Boc-**Aib**-**Aib**-NHMe

(f) Boc-Phe-Val-**Aib**-**Aib**-Leu-Phe-NHMe

The target octapeptides have not yet been completed (Figure 4).

An anticipated diastereomeric hexapeptide Boc-Phe-^{D}Val-Aib-^{D}Ala-Leu-Phe-NHMe during the synthesis of the hexapeptide (7) 2 + 4 strategy was followed, involving activation of the C-terminus carboxylated of the Phe-Val dipeptide resulting in racemization, yielding isolable amounts of diastereomeric peptide containing ^{D}Val at position 2. The fortunate formation of single crystal permitted a structure determination which established the configuration at ^{D}Val relative to other amino acids in sequence. The observed structure and relevant parameters in the Figures 5a-5e.

Unlike protein amino acids, the designed peptide sequence has been synthesized complete non-protein amino acid which is one of



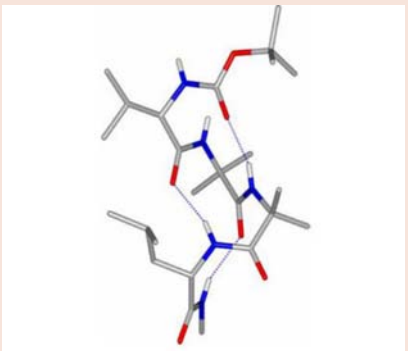
(a) Molecular conformation of Boc-Val-Aib-D-Ala-Leu-NHMe.

Segment	Turn	H-Bonding pattern
Val-Aib	Type-II	4→1
Aib-DAla	Type-I'	4→1
Aib-DAla-Leu	αR	5→1

Torsion Angle Values.

	Φ	ψ	ω	χ1	χ2
Val(1)	-54.9	137.2	175.6	61.5, -60.8	
Aib(2)	59.0	18.9	-175.6		
D-Ala(3)	81.3	1.0	-171.2		
Leu(4)	-111.9	-36.1	-178.4	-60.3	-62.8, 174.0

Figure 5a: Crystal structure of Boc-Val-Aib-D-Ala-Leu-NHMe.



(b) Molecular conformation of Boc-Val-Aib-Aib-Leu-NHMe

Segment	β-turn	H-Bonding pattern
Val-Aib	Type-I	4→1
Aib-Aib	Type-I	4→1
Aib-Leu	Type-I	4→1

Torsion Angle Values

	ϕ	ψ	ω	χ^1	χ^2
Val(1)	-52.0	-39.3	-173.9	-60.3, 174.8	
Aib(2)	-53.1	-33.6	-175.5		
Aib(3)	-56.2	-27.6	-178.6		
Leu(4)	-69.0	-21.5	-177.4	-61.1	-63.6, 171.7

Figure 5b: Crystal structure of Boc-Val-Aib-Aib-Leu-NHMe.

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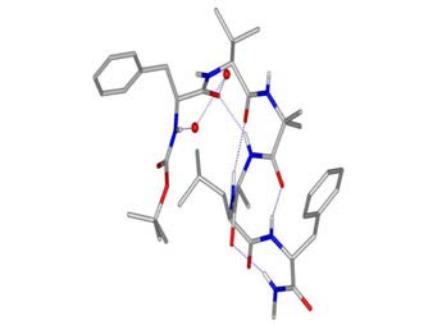

(c) Molecular conformation of Boc-Phe-Val-Aib-D-Ala-Leu-Phe-NHMe

Segment	β-turn	H-Bonding pattern
Phe-Val	Type-II	4→1
Val-Aib	Type-III	4→1
Aib– DAla	Type-III	4→1
DAla-Leu	Type-III	4→1

Torsion Angle Values

	Φ	Ψ	ω	χ1	χ2
Phe(1)	-112.4	147.6	171.8	-53.9	-34.4, 145.4
Val(2)	65.2	-124.2	-177.1	58.5, -178.4	
Aib(3)	-54.6	-25.6	179.2		
D-Ala(4)	-53.7	-30.7	179.2		
Leu(5)	-66.1	-12.9	174.7	-68.7	-62.3, 173.6
Phe(6)	-93.5	2.1	176.7	-69.3	-7.7, 173.7

Figure 5c: Crystal structure of Boc-Phe-Val-Aib-D-Ala-Leu-Phe-NHMe.

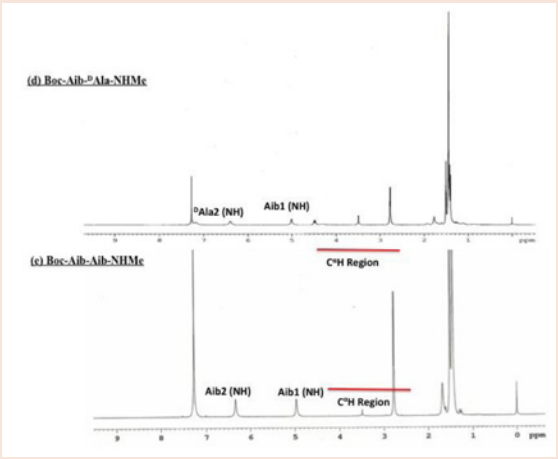

Figure 5d,e: (d) Boc-Aib-D-Ala-NHMe, (e) Boc-Aib-Aib-NHMe.

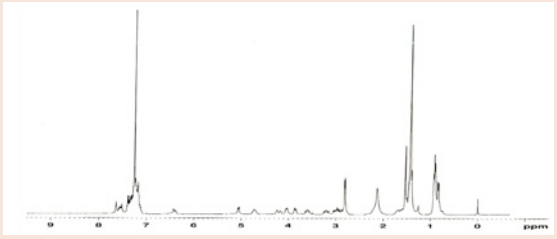

Figure 5f: Boc-Phe-Val-Aib-Aib-Leu-Phe-NHMe.

the non-coding amino acid in protein synthesis. Moreover this amino acid well known to be nucleating α-helix in designed peptides. The assigned proton NMR spectra have been shown above. The crystal grew by MeOH/$CHCl_3$ solvent system at room temperature by slow evaporation method (Figure 5f).

The characteristic 1D proton NMR spectra were shown. Approximately, Proton 1D spectrum can be assigned the backbone of the Cα-H protons, amide groups of N-H protons and side chain of aromatics so. But interest motivated towards crystallization of the peptides. The crystal set up is carried by different kind of solvent medium but the crystal growth not obtained yet. The above said peptides no interaction biding with metal ions due to hydrophobic interactions.

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