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-Alb-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 Alb-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 -Alb-Xxx- segments, where Xxx = Alb, L-Ala, Gly, D-Ala. It was anticipated that the −Alb-Gly- and −Alb-D-Ala- containing peptides would also provide models for equilibration between well folded, helical and hairpin structures [1-7] (Figure 3).

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

(1) Boc-Leu-Phe-Val-Alb-L-Ala-Leu-Phe-Val-OMe
(2) Boc-Leu-Phe-Val-Alb-D-Ala-Leu-Phe-Val-OMe
(3) Boc-Leu-Phe-Val-Alb-Gly-Leu-Phe-Val-OMe
(4) Boc-Leu-Phe-Val-Alb-D-Ala-NHMe
(5) Boc-Alb-D-Ala-NHMe
(6) Boc-Alb-D-Ala-Leu-NHMe
(7) Boc-Phe-Val-Alb-D-Ala-Leu-Phe-NHMe
(8) Boc-Alb-NHMe
(9) Boc-Alb-L-Ala-Leu-NHMe
(10) Boc-Alb-L-Ala-Leu-Phe-NHMe

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.

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 Cα--CO bond of Val (8) (ψ = -57.3º). 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 Boc-Val-Alb-D-Ala-Leu-NHMe and Boc-Val-Alb-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 1H NMR spectroscopy and mass spectrometer.
The target octapeptides have not yet been completed (Figure 4).

Unlike protein amino acids, the designed peptide sequence has been synthesized complete non-protein amino acid which is one of $\alpha$-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 $\alpha$-Val at position 2. The fortunate formation of single crystal permitted a structure determination which established the configuration at $\alpha$-Val relative to other amino acids in sequence. The observed structure and relevant parameters in the Figures 5a-5e.

Figure 2: Molecular conformation in crystals of the Boc-Leu-Phe-Val-Aib-$\alpha$-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

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

Figure 5b: Crystal structure of Boc-Val-Aib-Aib-Leu-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/CHCl₃ 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 Ca-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.

References


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