

The investigations described in this thesis attempt to synthesise, characterise and elucidate three dimensional structures of a few model peptides containing a non-coding unsubstituted  $\beta$ -amino-acid:  $\beta$ -Ala residue(s). The wide existence in nature may indicate its specific biological role which may be modulated by neighbouring residues or chemical entities. The extra tetrahedral carbon atom, introduces an additional torsion angle *i.e.* ' $\mu$ ' which seems to direct and dictate the overall folding behaviours of the model  $\beta$ -Ala peptides. The investigation presented in this thesis allowed us to draw following major conclusions.

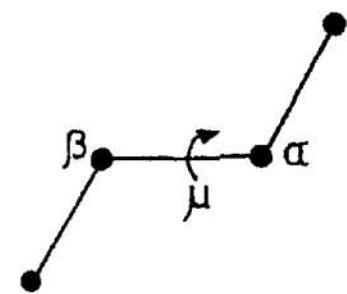
1. The conformational analysis of the model systems *i.e.* Boc- $\beta$ -Ala-NHCH<sub>3</sub> and Boc- $\beta$ -Ala-Pda reveals that simple neighbouring substituents in the vicinity of the  $\beta$ -Ala residue may be an excellent probe for the incorporation of parallel and antiparallel *novel*  $\beta$ -sheet-like features in the host without any major deviations in the hydrogen bond geometry. An all-*anti* conformation in Boc- $\beta$ -Ala-NHCH<sub>3</sub> ( $\phi = -145.5^\circ$ ,  $\mu = 171.6^\circ$  and  $\psi = 154.5^\circ$ ) vs an extended *skew*, *trans* and *skew* conformations ( $\phi = -115.3^\circ$ ,  $\mu = 173.1^\circ$  and  $\psi = 121.6^\circ$ ) in Boc- $\beta$ -Ala-Pda provide precedence for such conclusions. However, the *parallel* orientations of the potential hydrogen-bond donors and acceptors groups result in unique sheet-like supramolecular structures and such scaffolds may be *strategically* positioned on the constituent molecules in order to engineer the structures in solid state.
2. A comparative X-ray diffraction studies of Boc- $\beta$ -Ala-Acc<sup>6</sup>-OCH<sub>3</sub> and Boc- $\beta$ -Ala-Aib-OCH<sub>3</sub> provide the first example of the characterisation of a *novel*  $\beta$ -turn like motif, which can be stabilised by non-conventional weak C-H...O type intramolecular hydrogen bonding interactions in linear  $\beta$ -Ala peptide(s). The proposed geometric criteria fully satisfy the definition of a non-conventional C-H...O hydrogen bonding interactions. Further from the studies it was also concluded that the  $\beta$ -Ala residue can be well accommodated at the left-corner of the  $\beta$ -turn structures without any significant deviation. The conclusion is of particular interest since the earlier investigations suggested that to incorporate a  $\beta$ -Ala residue in a  $\beta$ -turn structure there should be a preceding  $\beta$ -bend at the N-terminus. The co-existence of a folded and a fully

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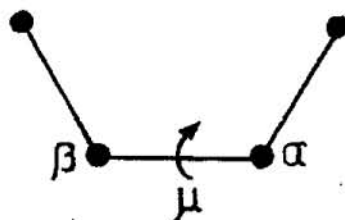
extended backbone conformation in Boc- $\beta$ -Ala-Aib-OCH<sub>3</sub> provide strong experimental support which established that both conformations are energetically accessible to the  $\beta$ -Ala residue. It indicates that the energy barrier for transition between two preferred conformational states, *i.e.* *folded* and *extended* may be significantly lower than can be overcome by a variety of structural and environmental factors. Such distinctive diversity of the conformational flexible  $\beta$ -Ala residue expected to be exploited not only in biomimetic chemistry but also in crystal engineering and in the development of novel-scaffolds.

3. The crystal structure of Boc-Pip- $\beta$ -Ala-NHCH<sub>3</sub> provides to the best of our knowledge, of the existence of a locally folded conformation of the  $\beta$ -Ala moiety in a terminally protected linear model peptide. The observed fully-extended conformation of the  $\beta$ -Ala residue in Boc-Pro- $\beta$ -Ala-NHCH<sub>3</sub> inclined us to conclude that such dramatic conformational alterations can be induced by constrained neighbouring chiral residue having distinct chemical and stereochemical characteristics. The observed uncommon type *a* urethane moiety also inclined us to conclude that the C-H...O interactions in peptides are indeed energetically favourable and may give rise to unusual structural features.
4. Another interesting conclusion which could be drawn from the crystal molecular structure of Boc- $\beta$ -Ala-Aib- $\beta$ -Ala-NHCH<sub>3</sub> is the existence of two distinctly different conformational features of the flexible  $\beta$ -Ala residue, positioned on either side of a C <sup>$\alpha$</sup> -tetrasubstituted Aib residue. The unusual folding propensities of the *two methylene units* of the C-terminus  $\beta$ -Ala residue further signify the potential role of the C-H...O interactions in stabilising unique conformational features may be specific to  $\beta$ -peptides in general.
5. An overview of the results associated with the conformational preferences of the  $\beta$ -Ala peptides tends to establish that their exist overwhelming preferences for a folded *gauche* ( $\mu \sim \pm 65^\circ \pm 10^\circ$ ) and an extended *trans* conformations ( $\mu \sim$

$\pm 165^\circ \pm 10^\circ$ ) across  $\beta$ -Ala residue in both cyclic as well as acyclic peptides as depicted below.



(Extended *trans*)



(Folded *gauche*)

Finally we substantiated the conclusion that “in addition to conformational restrictions of the stereochemical constrained residues, the complex chemical and stereochemical nature of the hydrophobic moieties, environmental effects, dipole moments *etc.* may collectively modulate the subtle *folding-unfolding* characteristics of the  $\beta$ -Ala residues.