INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: **Effect of the Position of Geminal Di-Substitution of γ Amino Acid Residues on their Conformational Preference**

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SHORT ABSTRACT

This thesis investigated the role germinal di-substitution at various backbone positions ofthe gamma amino acid residue on their conformational preferences. The thesis consists of 5 chapters. The first chapter describes the gamma amino acids and their conformations reported in the literature. Chapters 2-5 describe the investigations carried out in this thesis, which includes the incorporation of gamma amino acid residues ($\gamma^{2,2}$,$\gamma^{3,3}$ and $\gamma^{4,4}$) in the peptides. Chapter 2, describes the structures and assemblies in the solid and solution state of different derivatives of gamma amino acid residue. The structures and assemblies in the solid state are reported to be different for the three amino acid residues. The position of the backbone di-substitution is shown to drive the assembly in the solid state but not in solution. In the Chapter 3, three gamma amino acidresidues were incorporated in all □ amino acid containing model helical peptide sequences (tri, hexa and nona petides) and compared their relative helical propensity. The C12 helical conformation diminished as: $\gamma^{4,4}$ $\gamma^{3,3}$ $\gamma^{2,2}$. Helices with a central □ amino acid residue was shown to adopt mixed 10/12 helices of both handedness (left and right) in both solid and in solution state. Nona peptides containing $\gamma^{3,3}$ and $\gamma^{2,2}$ amino acid residues adopted an unusual ambidextrous helical conformation in the solid and in solution state. The ambidextrous conformation was stabilized by a water mediated hydrogen bonding. Ambidexterity was not observed in the nona-peptide containing $\gamma^{4,4}$ amino acid residues, likely due to the absence of the key water molecule in the structures. Chapter 4 describes the propensity of these three amino acid residues in being able to nucleate an isolated expanded C12 B-turn motif. Chapter 5 studies the ability of these amino acid residues in nucleating □ hairpin conformation. Both C12 □-turn and □-hairpin conformation was favoured by $\gamma^{3,3}$ and $\gamma^{4,4}$ favoured, whereas $\gamma^{2,2}$ failed to nucleate either of them due to unfavourable steric contacts. This thesis reported conformational preference of the three differently di-substituted amino acid residues, in the solution and in solid states by primarily using NMR, CD and X ray crystallography. In collaboration with the computational lab, ab initio calculations have also been done to understand the energetics of conformational preference. The conclusions are very well supported by experiments and computations. The thesis showed how a position of di-substitution (in the γ amino acid backbone) determines its conformational preference by fine-tuning the energetics. The results are useful for peptidomimetics and rational design of peptides with various architectures.