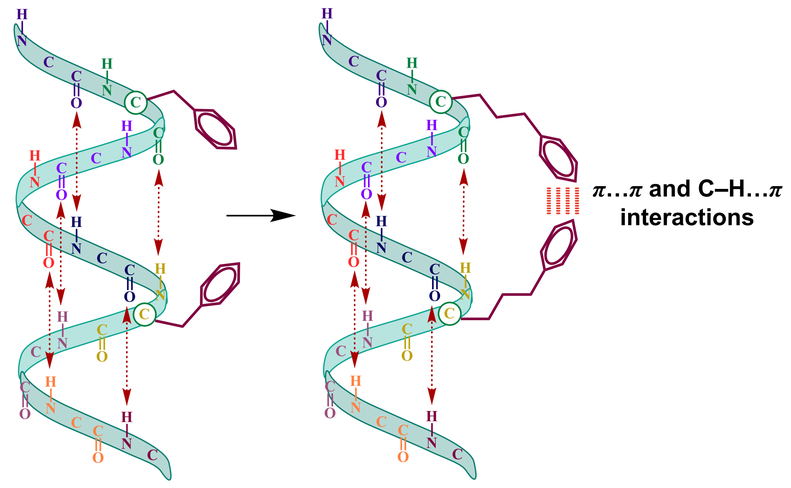
Stabilization of Helical Structures in Oligopeptides through Modification of Phenylalanine Residues

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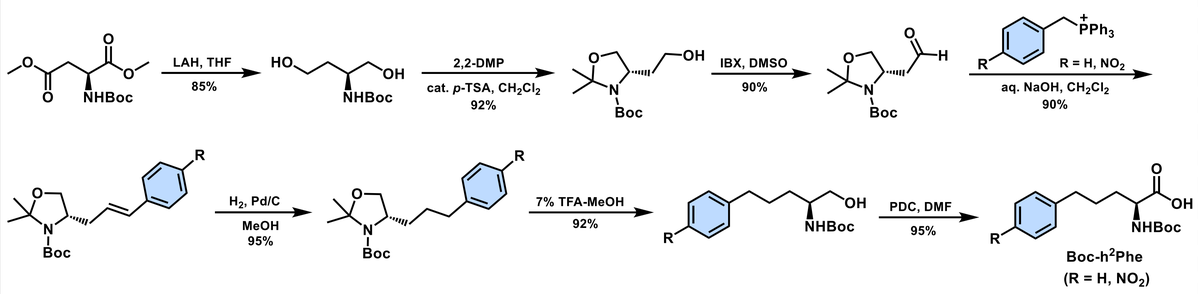


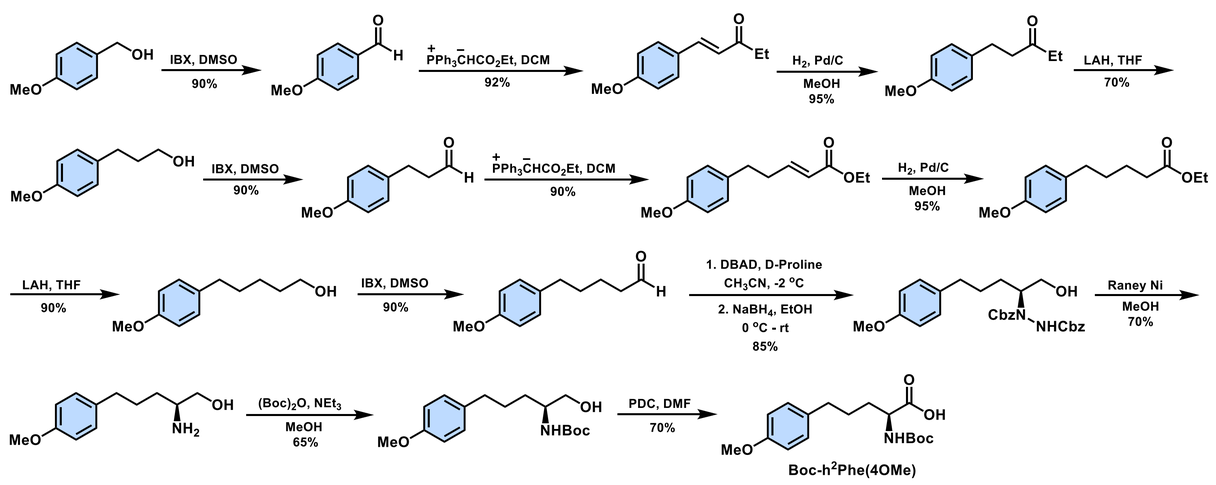
Introduction

- Non-covalent interactions between aromatic side chains of amino acids play a crucial role in directing peptide folding and stabilizing secondary structures in oligopeptides.
- In helical peptides, canonical phenylalanine (Phe) residues placed at the *i* and *i*+4 positions are too distant to have effective, stabilizing intramolecular aromatic interactions.
- Modification of Phe side-chains can tune both the spatial and electronic properties of aromatic residues, thereby influencing aromatic interactions and peptide folding.
- This study explores a library of Phe-modified oligopeptides to elucidate how aromatic side-chain engineering promotes intramolecular aromatic interactions and stabilizes helical conformations.

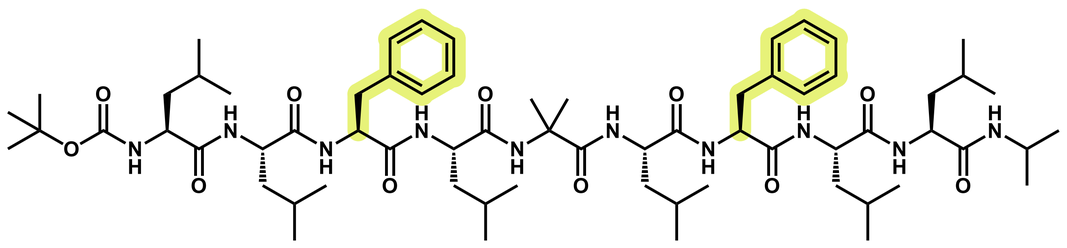


Synthetic Scheme of Modified Phenylalanine Residues

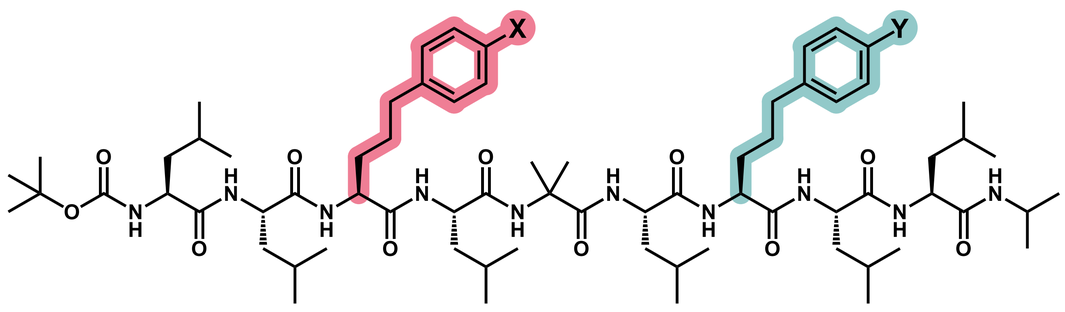




Design of Peptides Containing Modified Phe Residues



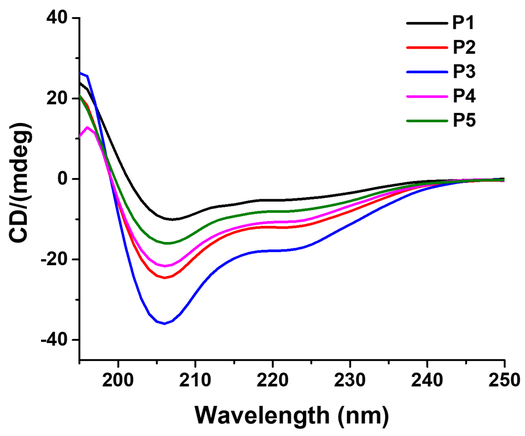
Boc-Leu-Leu-Phe-Leu-Aib-Leu-Phe-Leu-Leu-NH*i*Pr
P1



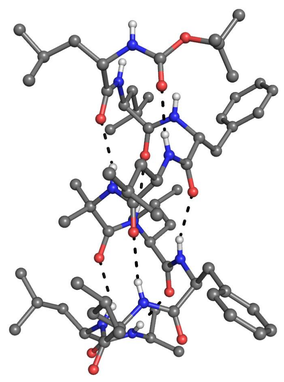
Boc-Leu-Leu-Phe*-Leu-Aib-Leu-Phe*-Leu-Leu-NH*i*Pr
Phe* = Modified Phe

P2 : X = Y = H
P3 : X = NO_2 ; Y = H
P4 : X = NO_2 ; Y = OMe
P5 : X = OMe ; Y = H

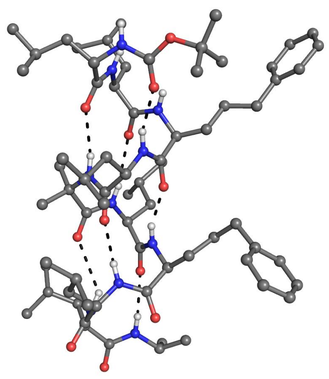
Conformational Analysis of Designed Peptides



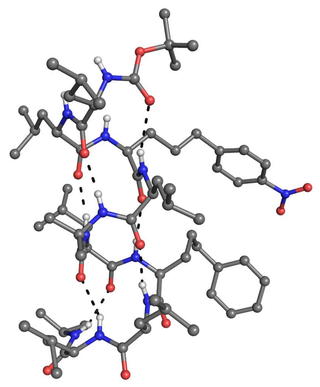
CD spectra of 1 mM peptides P1-P5 in MeOH



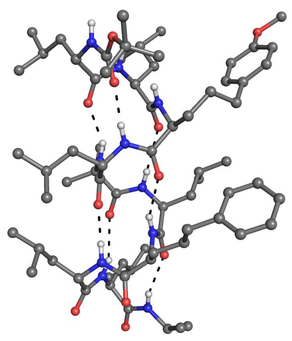
P1



P2 (X and Y = H)

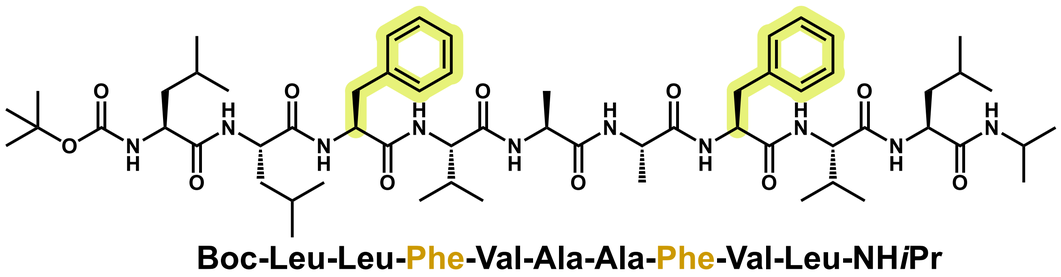


P3 (X = NO_2 ; Y = H)

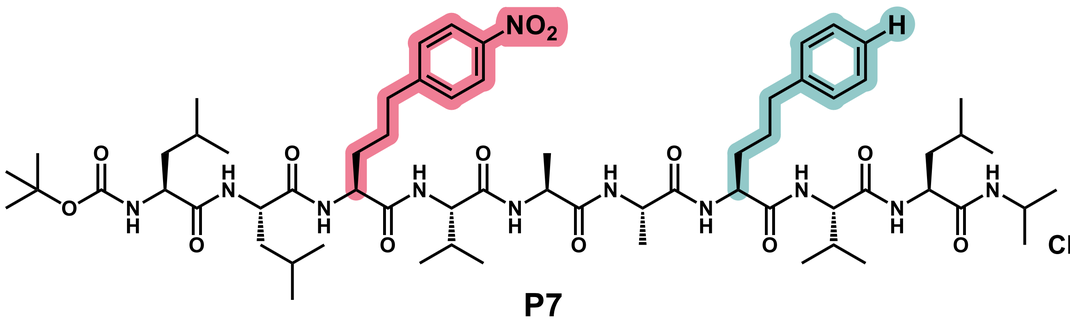


P5 (X = OMe ; Y = H)

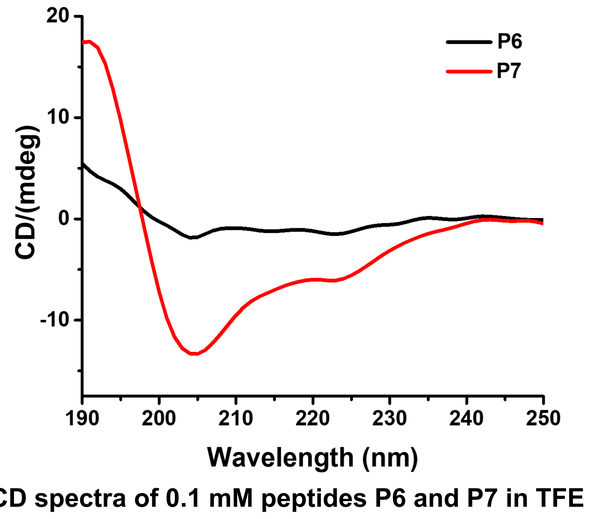
Modified Phe Residues as Non-Covalent Staples



Boc-Leu-Leu-Phe-Val-Ala-Ala-Phe-Val-Leu-NH*i*Pr
P6



P7



CD spectra of 0.1 mM peptides P6 and P7 in TFE

Summary

- Side-chain homologation of Phe residues at the i^{th} and i+4th position enables favourable intramolecular aromatic interactions that promote helix formation.
- Non-covalent stapling through modified Phe residues demonstrates an effective method to stabilize helical conformations in peptides with low intrinsic helical propensity.

Acknowledgement

- Department of Chemistry, IIT Kanpur

References

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- Ramapanicker *et al*., *Pept. Sci.* **2026**, *118*, e70032.