Design and Synthesis of a Diamino Diacid-based Short Cyclic Peptide with Tunable Self-Assembly

Devki Nandan and Dr. Ramesh Ramapanicker

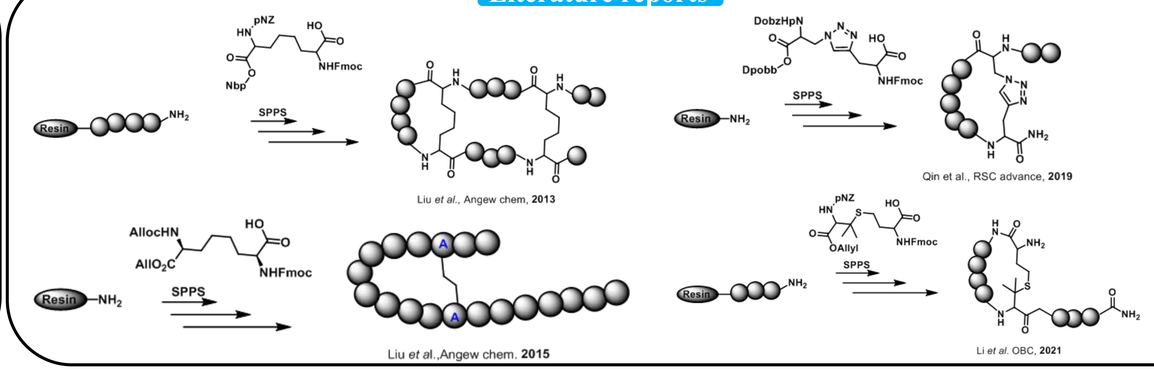
Department of Chemistry, Indian Institute of Technology Kanpur, Uttar Pradesh, India.

https://doi.org/10.17952/37EPS.2024.P1295

Introduction

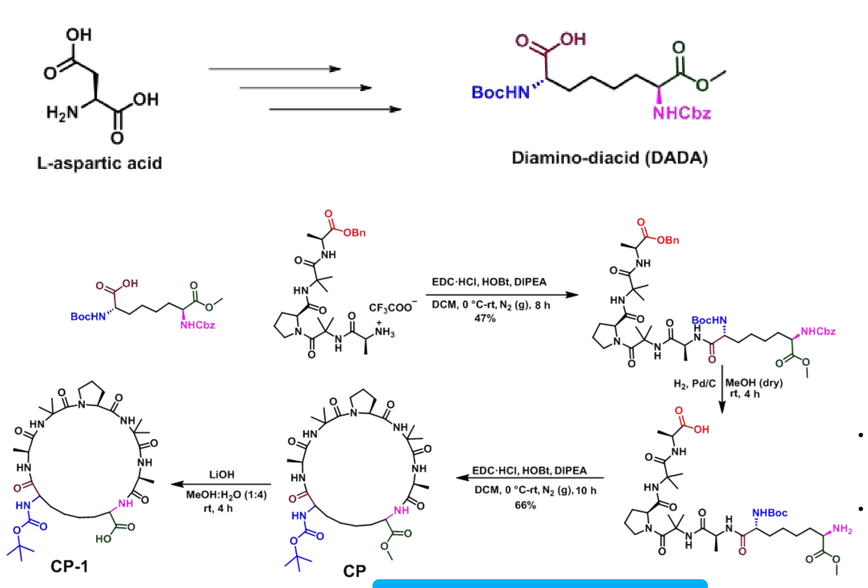
- Cyclic peptide nanostructures are thought to be potential candidates for biomedical applications because of their biocompatibility. The diamino diacid residues are formed from two α-amino acid units, which are coupled with a linker. They have been used as external templates for synthesizing short cyclic peptides (CP).
- We have used a diamino diacid for the preparation of a cyclic heptapetide with an aliphatic chain connecting the two terminal α-amino acid units.
- The properties of this cyclic peptide were compared with that of the corresponding linear peptide (LP). It was found that the CP showed concentration dependent self-assembly resulting in the formation of different nanostructures at different concentrations.
- These self-assembled nanostructures were characterized using FESEM, AFM, DLS, and FTIR. The study showed that the self-assembling behaviors of the cyclic and linear peptides are significantly different. Both the CP and the LP have very low critical aggregation concentrations (CAC), which were measured using fluorescence and DLS. The conformations of the CP and LP were analyzed at different concentrations using CD spectroscopy and marked differences were observed in their native conformations at different concentrations and solvents.

Literature reports



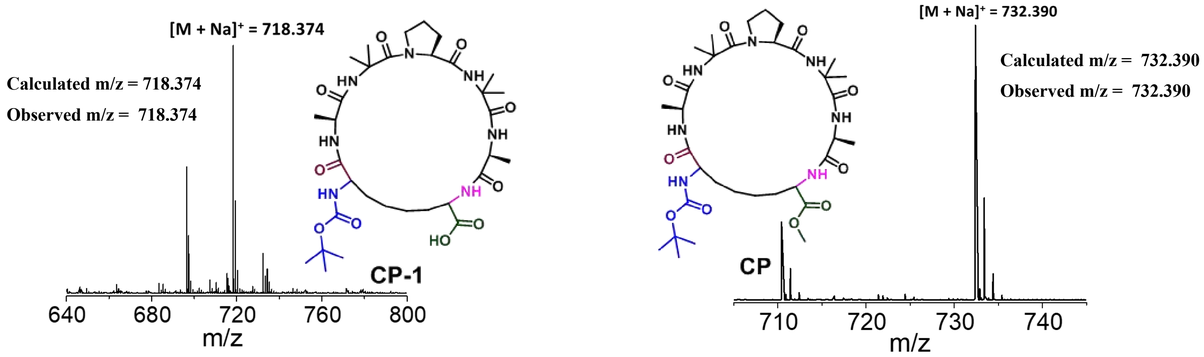
Results and discussion

Design and synthesis of diamino diacid (DADA) and cyclic peptide (CP)

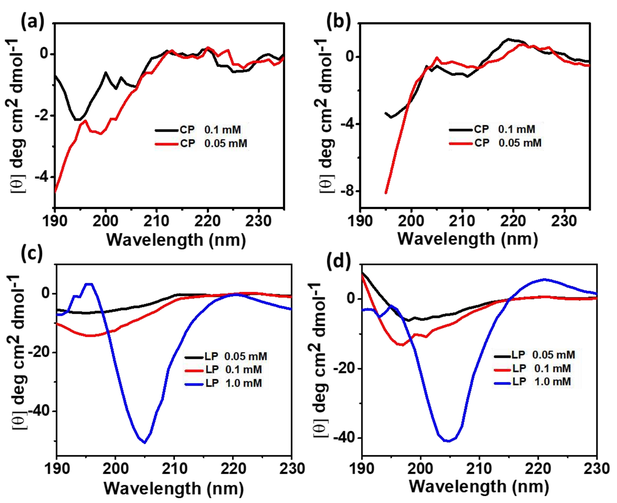


- Synthesis of DADA is 19 steps reaction involved with asymmetric α-amination of extended garner aldehyde.
- Proline containing peptide provides conformational flexibility for close proximity to N and C-terminal side of peptide

Characterization of CP

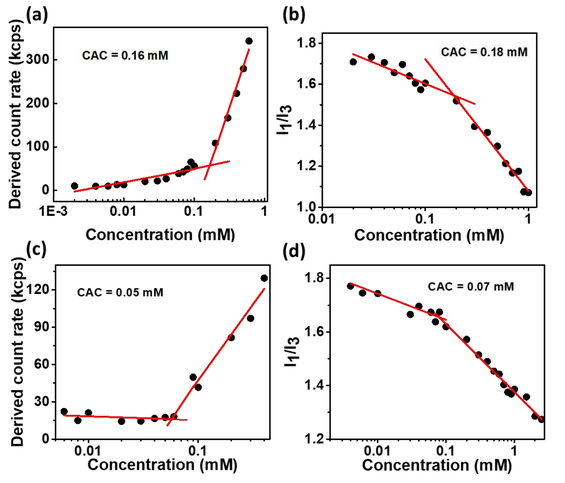


CD analysis of CP and LP



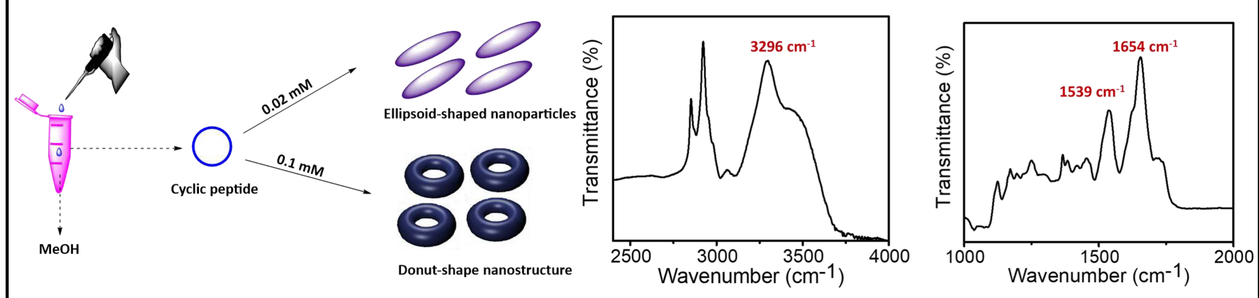
CD spectra of (a) CP in trifluoroethanol with two different concentrations and (b) CP in methanol at two different concentrations. (c) LP in trifluoroethanol and (d) in methanol at three different concentrations

Determination of CAC for CP-1 and LP-1



Aggregation behavior of CP and LP (a) determination of critical aggregation concentration of CP-1 using fluorescence intensity measurement of pyrene and (b) by dynamic light scattering (DLS). (c) determination of critical aggregation concentration of LP-1using fluorescence intensity measurement of pyrene and (d) by dynamic light scattering.

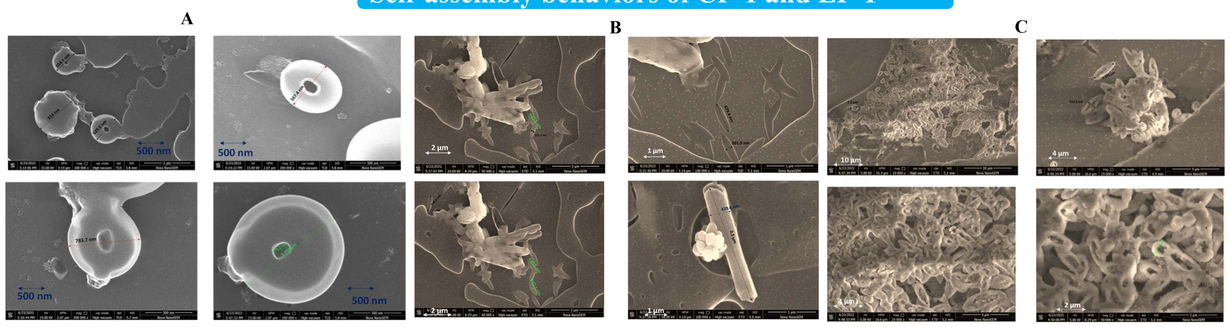
Morphology study



Pictorial representation of cyclic peptide self-assembly at different concentrations.

FT-IR spectra of CP-1 indicating anti-parallel beta sheet is driving force for self-assembly.

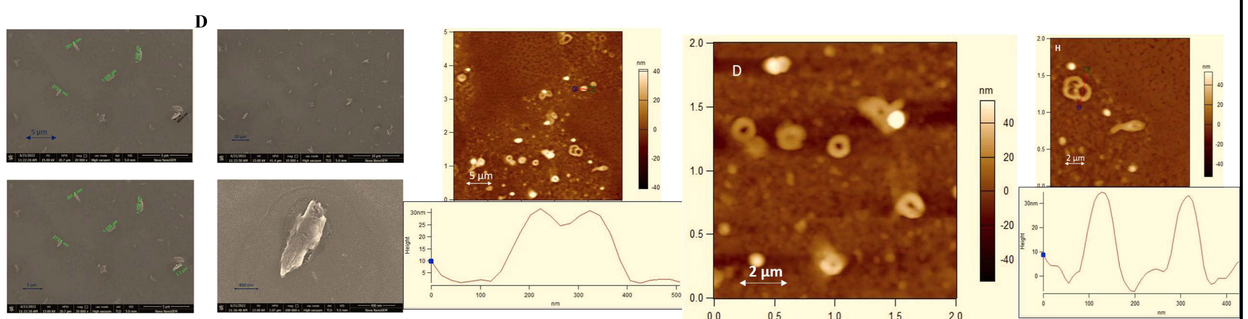
Self-assembly behaviors of CP-1 and LP-1



A. At 0.1 mM concentration its aggregates into donut shape nanostructure.

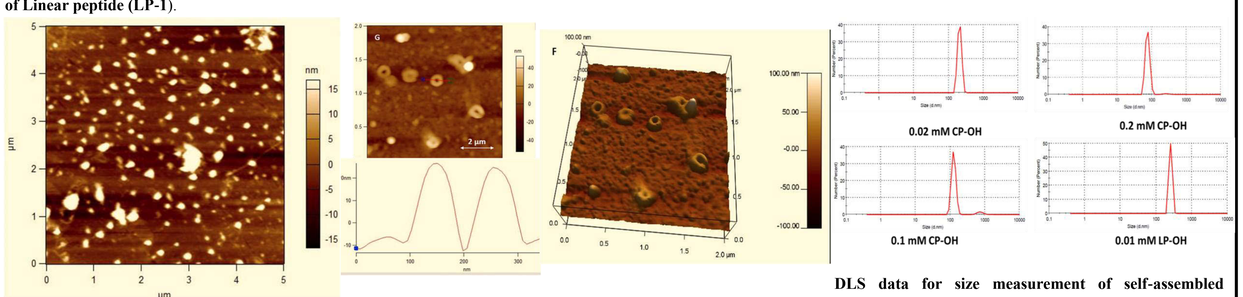
B. At 0.02 mM concentration its aggregates into spindle shape nanostructure.

C. At 0.2 mM concentration CP-1 self-assembled into spindle shape nanostructure with broken surface.



D. Irregular morphology with undefined structures of Linear peptide (LP-1).

AFM image of CP-1 at 0.02 mM



AFM image of LP-1 at 0.02 mM

DLS data for size measurement of self-assembled nanostructures at different concentrations of CP-1 and

References

Ramapanicker, *et al*., *Tetrahedron*, **2014**, **70**, 9554–9563

Advanced imaging center and MSE (IITK) for the AFM and FESEM facility, Dr. A. Thakur for the DLS facility.

Conclusions

- A short cyclic peptide was synthesized using diamino diacid (DADA) as a external templet.
- The CAC value was found to be quite low for both linear and cyclic peptides.
- CD analysis confirmed that CP in methanol exist in β-sheet conformation which is likely a driving force for self-assembly whereas linear peptide was found in α and β-turn conformations.
- In comparison of self-assembly behavior of CP-1 and LP-1. The well ordered self-assembled nanostructures were observed for Cyclic peptide but in linear peptide there is no