FUNCTIONAL SELF-ASSEMBLING SYSTEMS: SYNTHESIS AND BIOPHYSICAL CHARACTERIZATION

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AUGUST 2022

FUNCTIONAL SELF-ASSEMBLING SYSTEMS: SYNTHESIS AND BIOPHYSICAL CHARACTERIZATION

by

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Submitted

in fulfillment of requirements of degree of Doctor of Philosophy

to the

Indian Institute of Technology Delhi

August 2022

DEDICATED TO MY BELOVED

‘PARENTS AND FAMILY’

CERTIFICATE

This is to certify that the thesis entitled, **" Functional Self-assembling Systems: Synthesis and Biophysical Characterization",** being submitted by **Mr. Govind Prasad Maurya**, to the Indian Institute of Technology Delhi, for the award of degree of '**Doctor of philosophy in Chemistry**', is a record of bonafide research work carried out by him. **Govind Prasad Maurya** has worked under my guidance and supervision and has fulfilled all the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results embodied in this thesis have not been submitted in part or in full, to any other University or Institute for award of any degree or diploma.

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ACKNOWLEDGEMENTS

First and foremost, it's my great pleasure to pay my deepest gratitude and respect to my supervisor, **Dr. V. Haridas**, **Professor**, Department of Chemistry, IIT Delhi, who has been of constant support to me throughout my research work. It was a great opportunity to work under his supervision. Without his assistance and dedicated involvement in every step throughout the process, this would have never been accomplished. I would like to thank you very much for your support, constant encouragement, sincere guidance and valuable suggestions over past 6 years of our research and non-research discussions.

I extend my sincere thanks to various Heads of the Department of Chemistry, Prof. Ravi Shankar, Prof. Ashok K. Ganguli, Prof. Anil J. Elias and Prof. N.D Kurur for providing all the necessary facilities required for my research. I was privileged to have such an eclectic assembly of SRC members, **Prof. N.G. Ramesh**, **Prof. Nalin Pant** and **Prof. Bishwajit Kundu**. I am grateful to all of them for their encouragement and perspicacious analyses of my results.

I would also like to show my gratitude to **Prof. Chai Lin Kao**, KMU, Taiwan for providing me great opportunity to work under his supervision for 4 month Internship.

I gratefully acknowledge the financial support from University grants commission (UGC), India in the form of research fellowship. I would like to express my gratitude towards almighty for giving me the strength, courage and perseverance.

I would like to thank my lab mates Dr. Parveen Kumar PP, Dr. Ishanki Bhardwaj, Dr. M. B. Bijesh, Dr. Appa Rao Sapala, Dr. Sakshi Sharma, Dr. Sameer Dhwan, Rachit Sapra, Hanuman Singh, Ankit, Sagar, Surya, Souvik, Divya and Neeraj for their support. I also would like to acknowledge all the non-teaching staffs of chemistry department, Mr. Keshav, Mr. J. P. Sharma,

Mr. Narugopal Kuily, Mrs. Shubhra Gupta, and Mr. Kuldeep, for their support for data acquirement. I thank Mrs. Dimple Hindwani, Mr. Vinod, Mr. Ashish, and Mrs. Namita for their help in administrative work. I also thank the Central Research Facility (CRF) and Nanoscale Research Facility (NRF) of IIT Delhi, for the analysis of the SEM, HR-TEM, AFM, NMR and Confocal Microscopic imaging.

I am extremely grateful to my beloved parents (**Mr. Shalik Ram Maurya** and **Mrs. Lalpari Maurya**) for their unconditional love and support throughout my research work. I thank my ever loving and caring **brother** (**Durga P. Maurya**) for their support and encouragement to pursue my interests. I offer special thanks to my wife **Meenu Maurya**, who always motivated me to achieve my goals. I offer my gratitude towards my mother's lovable and support. Finally, I would like to thank my dearest friends Chandan, Kasim, Akhilesh, and Kaushal Kishor.

August 2022 **Govind Prasad Maurya**

ABSTRACT

The thesis entitled **"Functional Self-assembling Systems: Synthesis and Biophysical Characterization"** deals with the design and synthesis of peptide-based molecules and their self-assembling properties. We have demonstrated the self-assembly of various peptide-based molecules and their self-assembly upon addition of cations and anions along with their conformational changes. The self-assembly of various designer peptides and their effect on liquid crystals were also studied. The research work presented in this thesis is divided into five chapters.

Chapter I

Chapter I deals with selected exaples of self-assembling peptides. The focus has been majorly on small peptide, cyclic peptde, peptide-polymers, amphiphilic, and aromatic-based peptides. A special emphasis is given to cation and anion induced self-assembling peptidtic systems.

Chapter II

Chapter II presents the design, synthesis and self-assembly of Zn-finger resembling cystine-cored trizole containing pseudopeptides. The pseudopeptides exhibited conformational transition to β-sheet upon binding with Cu^{2+}, resulting in the disruption of vesicles.

Chapter III

Chapter III deals with the design and synthesis of hydrophobically driven chiral functional assembly of diacetylene-cored pseudopeptides. The designer pseudopeptides self-assembled, as a result of tuning solvent environment, causing associations through hydrophobic forces resulting in chiral assembling system with Aggregation Induced Emission (AIE) property. The self-assembling dialkynes with supramolecular chirality and AIE property induce chirality to the non-chiral LC matrix with high helical twisting power.

Chapter IV

Chapter IV presents the investigation on the self-assembly of aromatic cored bis-urea systems. The phenylalanine adjacent to urea peptides showed supramolecular helical organization. Anion binds to these self-assembled urea-peptides causing the inversion of helicity. The amino acid dependence on the helicity was also investigated.

Chapter V

Chapter V describes the design, synthesis and self-assembly of a series of fluorescent disulfide-cored molecules. These disulfide containing molecules associate to heterodimers and shows intermolecular fluorescence resonance energy transfer (FRET). The microscopic analysis of designer fluorescent molecules shows vesicular morphology in acetonitrile. These molecules forms heterodimers that further self-assemble to vesicles. In addition, these disulfide cored fluorescent molecules serve as sensor for nitroaromatics (NACs).

सारांश

"**उपादेय स्व-संयोजित सिस्टम्स: संश्लेषण और जैवभौतिक निरूपण**" नामक थीसिस पेप्टाइड-आधारित अणुओं के डिजाइन और संश्लेषण और उनके स्वयं-संयोजन गुणों से संबंधित है। हमने विभिन्न पेप्टाइड-आधारित अणुओं के स्व-संयोजन का प्रदर्शन किया है और उनके गठनात्मक परिवर्तनों के साथ-साथ धनायनों और आयनों को जोड़ने पर उनकी स्व-संयोजन का प्रदर्शन किया है। स्व-संयोजन विभिन्न डिजाइनर पेप्टाइड्स और लिक्विड क्रिस्टल पर उनके प्रभाव का भी अध्ययन किया गया। इस शोध प्रबंध में प्रस्तुत शोध कार्य को पाँच अध्यायों में विभाजित किया गया है।

अध्याय 1

अध्याय 1 स्व-संयोजन पेप्टाइड्स के चयनित उदाहरणों से संबंधित है। मुख्य रूप से छोटे पेप्टाइड, चक्रीय पेप्टाइड, पेप्टाइड-पॉलिमर, एम्फीफिलिक और सुगंधित-आधारित पेप्टाइड्स पर ध्यान केंद्रित किया गया है। धनायन और ऋणायन प्रेरित स्व-संयोजन पेप्टिडटिक प्रणालियों पर विशेष बल दिया जाता है।

अध्याय 2

अध्याय 2, Zn-Finger के डिजाइन, संश्लेषण और स्व-संयोजन को प्रस्तुत करता है जो सिस्टीन-कोर वाले ट्राइज़ोल से मिलता-जुलता है जिसमें स्यूडोपेप्टाइड होते हैं। स्यूडोपेप्टाइड्स ने Cu^{2+} के साथ बंधने पर β-शीट में गठनात्मक संक्रमण प्रदर्शित किया, जिसके परिणामस्वरूप पुटिकाओं का विघटन हुआ।

अध्याय 3

अध्याय 3, डायसेटिलीन-कोरेड स्यूडोपेप्टाइड्स के हाइड्रोफोबिक रूप से संचालित काइरल फंक्शनल असेंबली के डिजाइन और संश्लेषण से संबंधित है। डिज़ाइनर स्यूडोपेप्टाइड्स स्व-इकट्ठे, ट्यूनिंग सॉल्वेंट

पर्यावरण के परिणामस्वरूप, हाइड्रोफोबिक बलों के माध्यम से संघों का कारण बनता है जिसके परिणामस्वरूप एकत्रीकरण प्रेरित उत्सर्जन (एआईई) संपत्ति के साथ काइरल संयोजित सिस्टम होता है। सुपरमॉलेक्यूलर कायरैलिटी और एआईई प्रॉपर्टी के साथ स्व-संयोजित डायलकेनेस उच्च पेचदार घुमा शक्ति के साथ गैर-काइरल एलसी मैट्रिक्स के लिए कायरैलिटी को प्रेरित करता है।

अध्याय 4

अध्याय 4 सुगंधित कोर्ड बिस-यूरिया प्रणालियों के स्व-संयोजन पर जांच प्रस्तुत करता है। यूरिया पेप्टाइड्स से सटे फेनिलएलनिन ने सुपरमॉलेक्यूलर हेलिकल संगठन दिखाया। आयन इन स्व-इकट्ठे यूरिया-पेप्टाइड्स को बांधता है जिससे हेलिकल संगठन का उलटा होता है। हेलिकल संगठन पर अमीनो एसिड निर्भरता की भी जांच की गई।

अध्याय 5

अध्याय 5 फ्लोरोसेंट डाइसल्फ़ाइड कोर्ड अणुओं की एक श्रृंखला के डिजाइन, संश्लेषण और स्व-संयोजन का वर्णन करता है। ये डाइसल्फ़ाइड युक्त अणु हेटेरोडिमर्स से जुड़ते हैं और इंटरमॉलिक्युलर फ्लोरेसेंस रेजोनेंस एनर्जी ट्रांसफर (FRET) को दर्शाते हैं। डिजाइनर फ्लोरोसेंट अणुओं का सूक्ष्म विश्लेषण वेसिकुलर आकारिकी को दर्शाता है। ये अणु हेटेरोडिमर्स बनाते हैं जो आगे पुटिकाओं में स्वयं-इकट्ठे होते हैं। इसके अलावा, ये डाइसल्फ़ाइड कोर्ड फ्लोरोसेंट अणु नाइट्रोएरोमैटिक्स (एनएसी) के लिए सेंसर के रूप में काम करते हैं।

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LIST OF ABBREVIATIONS

%	Percent
δ	Chemical shift
^{o}C	Degree centigrade
ACQ	Aggregation Caused Quenching
ACN	Acetonitrile
AFM	Atomic force microscopy
AIE	Aggregation Induced Emission
aq.	Aqueous
Ar	Aryl
ArH	Aromatic proton
Boc	t-butyloxycarbonyl
br	Broad
CD	Circular dichroism
Conc.	Concentrated
CuAAC	Copper catalyzed azide alkyne cycloaddition

d	Doublet
DCM	Dichloromethane
dd	Double doublet
DCC	N,N'-dicyclohexylcarbodiimide
DIPEA	N,N'-Diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
ESI	Electronspray ionization
EDC.HCl	N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
eq.	Equivalent
FTIR	Fourier-transform infrared
FRET	Fluorescence resonance energy transfer
g	Gram
h	Hour
Hz	Hertz
HRMS	High resolution mass spectrum

HRTEM	High resolution transmission electron microscope
IR	Infrared
LC	Liquid Crystal
LOD	Limit of detection
m	Multiplet
MeOH	Methanol
mM	Micromolar
μm	Micrometer
mg	Milligram
mL	Milliliter
μL	Microliter
min	Minutes
mmol	Millimoles
mol	Mole
Mp	Melting point
m/z	Mass/charge
NHS	N-Hydroxysuccinimide

NMR	Nuclear magnetic resonance
nm	Nanometer
ppm	Parts per million
PDA	Polydiacetylene
q	Quartet
r.t.	Room temperature
s	Singlet
t	Triplet
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
$TBAH_2PO_4$	Tetrabytyl ammonium dihydrogen phosphate
TMEDA	Tetramethylenediamine
TMS	Tetramethylsilane
UV	Ultraviolet
Vis	Visible

NOTES

1. All amino acids were used of L-configuration. Standard single/triple letter codes are used to represent the amino acids.

2. All solvents used in the reaction were distilled or dried from appropriate drying agent prior to use. All reagents were used in the reactions without further purification.

3. Melting points were recorded in a Fisher-Scientific melting point apparatus and were uncorrected.

4. IR spectra were recorded on a Nicolet, Protégé 460 spectrometer as KBr pellets.

5. ^{1}H NMR spectra were recorded on Bruker-DPX (^{1}H NMR, 300, 300 and 500 MHz; ^{13}C NMR, 75, 100 and 125 MHz) spectrometer using tetramethylsilane (^{1}H) as an internal standard. ^{1}H NMR data are reported as s (singlet), d (doublet), br (broad), br d (broad doublet), t (triplet), q (quartet), m (multiplet) and coupling constnats are in Hz.

6. High resolution mass spectra (HRMS) were recorded in Bruker MicrO-TOF-QII model using Electrospray Ionization (ESI) technique.

7. Silica gel G (Merck) Thin Layer Chromatography (TLC) was used for monitored the reactions. Silica gel (100-200 mesh and 60-120) was used for column chromatography prrification, which were generally made from slurry in hexane, hexane/ethyl acetate or chloroform.

8. CD measurements were made using AVIV-420/ Jasco spectropolarimeter. Quartz cell of 0.1 cm was used for the measurements.

9. UV-Vis spectroscopy-The absorption spectra were recorded on a Shimadzu UV-2450 spectrometer.

10. SEM images were recorded using ZEISS EVO Series Scanning Electron Microscope EVO 50 operating at an accelerating voltage of 0.2 − 30 kV. For SEM, a 10 μL aliquot of the sample solution was drop-casted on a glass cover slip, dried and coated with ∼10 nm of gold.

11. HR-TEM images were recorded on a TECHNAI G2 (20S-TWIN) electron microscope operated at an accelerating voltage of 200 kV. Samples were prepared by drop-casting the sample on 200 square mesh carbon-coated copper grids.

12. Atomic force microscope (Bruker Dimension Icon) in tapping mode was used for imaging. The data obtained was analyzed using Nanoscope 5.31r software. About 10μl aliquot of the sample solution was transferred onto freshly cleaved mica and allowed to dry and imaged using AFM.

13. X-ray diffraction study was carried out on a BRUKER AXS SMART-APEX diffractometer with a CCD area detector (Mo Ka = 0.71073Å, monochromator: graphite). Frames were collected at T = 298 by w, f and 2q-rotation at 10 s per frame with SMART. The measured intensities were reduced to F2 and corrected for absorption with SADABS. Structure solution, refinement, and data output were carried out with the SHELXTL program. Non-hydrogen atoms were refined anisotropically. C-H hydrogen atoms were placed in

geometrically calculated positions by using a riding model. Image was created with the diamond program.

14. Confocal microscopy was recorded using FLUOVIEW FV1200 laser scanning confocal microscope. The samples were excited using 405 nm and emission was captured from 450-500 nm. The images captured were processed using Image J software.
15. Fluorescence measurements, were recorded in FluoroMax-4 spectrofluorometer (HORIBA JOBIN YVON Scientific), using a 3 mL quartz cuvette with slit width of 5 nm.
16. The pitch of the induced cholesteric phases has been calculated by measuring the distance between two neighboring extinction dark striations of cholesteric fingerprints as per the earlier reported methods. The ImageJ software has been used for precise measurements of length scales of fingerprints.
17. The helical twisting power (β) was calculated using the formula $\beta w = 100pc'$ where p is the calculated pitch in micron and c is the weight fraction of chiral dopant in **5CB**. In addition, the plot of the inverse helical pitch with the concentrations of chiral dopant give straight line and the slope of this line within the linear region is used to calculate the helical twisting power of the compound as per the previous reports.