Synthesis and Evaluation of New Molecular Receptors for Molecular Recognition

by

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Submitted

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to the

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Spectroscopy of Organic Compounds

DEDICATED

TO

MY PARENTS

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis and Evaluation of New Molecular Receptors for Molecular Recognition"** being submitted by **Ms. Ananya Chakrabarti** to the Indian Institute of Technology, Delhi, for the award of degree of **Doctor of Philosophy** is a record of bonafide research work carried out by her. **Ms. Ananya Chakrabarti** has worked under our guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to our knowledge has reached the requisite standard.

The results contained in this thesis are original and have not been submitted, in part or full, to any other University or Institute for the award of any other degree or diploma.

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ABSTRACT

The thesis entitled "**SYNTHESIS AND EVALUATION OF NEW MOLECULAR RECEPTORS FOR MOLECULAR RECOGNITION**" concerns with the synthesis, characterization and evaluation of the recognition properties of novel macrocyclic compounds based on tetrathiacalix[4]arene and cyclotriveratrylene frameworks. The synthesis of the molecular receptors was achieved through modification, optimization and innovation of procedures available in the literature. The structural and conformational characterization of synthesized compounds has been accomplished by spectroscopic techniques (IR, NMR, X-ray, FAB-MS and UV-visible spectroscopy). Molecular recognition attributes have been examined by using UV-visible and NMR spectroscopic methods. The research work embodied in this thesis has been divided into five chapters.

Molecular recognition involves the selection and binding of substrate(s) by a molecular receptor through weak intermolecular interactions. The design of new molecular receptors usually involves a combination of binding and orientation of molecule to be recognized with complementary sites in the molecular receptor besides comprehension and modulation of weak attractive forces responsible for the recognition phenomena at molecular level.

The fundamental and applied studies on synthetic receptors have led to a better understanding of design and development of molecular carriers and molecular devices for performing specific functions. **CHAPTER I** of the thesis highlights some of the general aspects of molecular recognition. An attempt has been made to compile and present examples from thiacalix[n]arene and cyclotriveratrylene based receptors.

CHAPTER II of the thesis embodies the synthesis of sixteen new macrocyclic compounds by the incorporation of arylazo- and heteroaryl azo- units (phenylazo-, thiazoleazo-, pyridylazo- and β-naphthylazo- groups) on the tetrathiacalix[4]arene molecular architecture at their upper rim through diazotization and coupling reactions. Since comparatively fewer reports are available on upper rim substitution of tetrathiacalix[4]arenes as compared to lower rim derivatized tetrathiacalix[4]arenes, the above procedure provides a feasible route to upper rim functionalized tetrathiacalix[4]arenes. The synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, FAB-MS spectroscopic and X-ray crystallographic analysis (for two of the synthesized compounds).

CHAPTER III describes the preliminary experiments conducted towards determination of primary recognition attributes of the synthesized molecular receptors in Chapter II for a variety of cation and neutral guest molecules. Some of the synthesized chromoionophores elicit significant visual and spectral changes upon interaction with specific metal ions, while others are useful for recognition of aliphatic amines.

Quantitative UV-visible spectral measurements (UV-visible titration experiments as well as Job's continuous variation experiments) have been employed to unravel the nature and the stoichiometry of the target-molecular receptor interaction.

CHAPTER IV describes our efforts in obtaining the various conformers of the tetrathiacalix[4]arene esters in the presence of different bases using different solvents followed by their aminolysis with several aminoalkanes and diaminoalkanes to yield conformationally diverse tetrathiacalix[4]arene amidocrowns and tetrathiacalix[4]arene amides. The new compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, FAB-

MS spectroscopic analysis and X-ray crystallographic analysis. Mechanisms for the aminolysis of the *partial cone* conformer of the tetrathiacalix[4]arene tetraester with aminoalkanes and diaminoalkanes have been proposed.

CHAPTER V of the thesis describes our preliminary experiments on the convenient synthesis and isolation of the *crown* and *saddle* conformers of cyclotriveratrylene and their analysis by ^{1}H NMR and Differential Scanning Calorimetry. Easy and direct routes to arrive at crown conformers of phenolic dihydrocyclononenes through selective demethylation of cyclotriveratrylene to yield one, three or six free –OH groups in a CTV molecular bowl have been achieved. The products obtained have been characterized by ^{1}H, ^{13}C NMR, FAB-MS and single crystal X-ray analysis.

Crown conformers of cyclotriveratrylenes have been linked with *p-tert*-butylcalix[6]arenes through different spacer linkers to provide novel molecular receptors. A preliminary investigation on the recognition properties of synthesized molecular receptors reveal that they are useful for the extraction/ encapsulation of organic molecular species.

NOTES

1. All melting points reported in this thesis are uncorrected and have been recorded on an electric melting point apparatus (Toshniwal, India).
2. UV-visible spectra have been recorded on Perkin Elmer's (Lambda-3B) spectrophotometer.
3. FT-IR spectra have been recorded on KBr discs on a [5-DX] Nicolet FT-IR spectrophotometer.
4. ^{1}H-NMR and ^{13}C-NMR spectra have been recorded on a 300MHz Bruker DPX 300 instrument at room temperature in deuterated solvents ($CDCl_3$, CD_3OD, CD_3SOCD_3 using tetramethylsilane (TMS) as an internal standard with the values of chemical shifts reported on δ scale. The abbreviations *s*, *bs*, *d*, *t*, *q* and *m* indicate singlet, broad singlet, doublet, triplet, quartet and multiplet respectively.
5. FAB-mass spectra of the synthesized compounds have been recorded on a JEOL SX 102/DA-6000 Mass Spectrometer at Central Drug Research Institute, Lucknow using *m*-Nitrobenzylalcohol as the matrix and Argon/ Xenon (6kV, 10mA) as the FAB gas.
6. Elemental Analysis has been carried on a Perkin Elmer's 240C-CHN Analyzer.
7. Thermal analyses (DSC) of the compounds have been carried out using Perkin Elmer V.04 Differential Scanning Calorimeter.
8. X-ray crystallographic data have been recorded on a CCD area detector diffractometer on a fine focus sealed tube (MoK_α = 0.71073 Å). All the crystal structures have been solved using direct methods (SHELXS-97) and refined on *F*2 (SHELXL-97).

9. The completion of the reactions have been monitored by *Thin Layer Chromatography* performed on silica gel (Silica gel-G; Merck) coated glass plates using iodine for visualizing the spots.
10. Purification of the synthesized compounds has been carried out by column chromatography over silica gel (60-120 mesh; Merck) or by flash chromatography (230-400 mesh).
11. The solvents used have been purified and dried before use by procedures described in "Purification of Laboratory Chemicals" by W. L. F. Amarego and D. D. Perrin, *Bath Press and Bath*, Britain.
12. For the sake of convenience, the names of tetrathiacalix[4]arenes, cyclotriveratrylenes and calixarenes used in this thesis have been shortened. For example, 5,11,17,23-tetra-*p-tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiacalix[4]arene has been commonly referred to as *p-tert*-butyltetrathiacalix[4]arene or even parent thiacalix[4]arene.

    2,3,7,8,12,13-hexamethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene has been referred to as cyclotriveratrylene or CTV.

    5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexahydroxycalix[6]arene has been referred to as *p-tert*-butylcalix[6]arene.
13. Abbreviations used in this thesis are:

    THF – Tetrahydrofuran;

    DMF – N,N'-Dimethylformamide;

    $CDCl_3$- Deuterated chloroform;

    CD_3OD- Deuterated methanol;

    D_2O – Deuterated water;

    DMSO-d_6 – Deuterated Dimethyl sulfoxide.

TABLE OF CONTENTS