

Mrs P. Malhotra

**SYNTHESIS, TAUTOMERISM AND EVALUATION OF
CHROMOGENIC CALIX[N]ARENES FOR IONIC AND
MOLECULAR RECOGNITION**

by

MEENAKSHI NANDA

Department of Chemistry

Submitted

in fulfilment of the requirement of the degree of

Doctor of Philosophy

to the



Indian Institute of Technology, Delhi

August , 2001

CERTIFICATE

This is to certify that the thesis entitled "*Synthesis, Tautomerism and Evaluation of Chromogenic Calix[n]arenes for Ionic and Molecular Recognition*" being submitted by **Ms. Meenakshi Nanda** to the Department of Chemistry, Indian Institute of Technology, Delhi, for the award of the degree of **Doctor of Philosophy** is a record of bonafide research work carried out by her.

Meenakshi Nanda has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis which to my knowledge has reached the requisite standard.

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


(H.M. Chawla)
Thesis Supervisor

Professor,
Department of Chemistry
Indian Institute of Technology,
New Delhi – 110016, India.

ACKNOWLEDGEMENTS

It gives me an immense pleasure and great opportunity to express my profound sense of gratitude and indebtedness to Professor H.M. Chawla, for his painstaking guidance, invaluable suggestions and constant encouragement throughout the execution of research work embodied in this thesis.

I wish to express my sincere thanks to the Head of the Department, Department of Chemistry, Indian Institute of Technology, New Delhi for providing facilities available in the Department.

I also express my sense of thankfulness to Dr. N. Pant and Dr. R. Varadarajan for fruitful discussions and encouragement.

I am extremely thankful to my research colleagues Anuradha, Vandna, Lukesh and Satish for their help and cooperation. I am also thankful to my friends and seniors, Dr. Ipsita, Dr. Shailja, Dr. P. Wadhwani, Dr. Abhishek Upadhyay, Dr. N. Venkatesan, Dr.(Mrs.) Meena and Dr. K. Srinivas for freely sharing their experiences in research.

I am extremely thankful to my dear friend Himanshu who has not only been a sincere advisor but has kept my spirits high during ups and downs of circumstances during the tenure of my research.

My humble regards to my parents and my brother who have had the rough end of bargain but never complained. Their constant encouragement and help in every possible way has made it possible to pursue and complete my research work.

I wish to record my appreciation and warm feelings of gratitude to my loving husband and father-in-law to enable me to conclude my research work embodied in this thesis.

I thankfully acknowledge the award of a research fellowship from Council of Scientific and Industrial Research, New Delhi during the tenure of my research work. Last but not the least I express my sense of gratitude to the supporting staff of the Department for timely help and to Mrs. Seema Arora and Ms. Biji for typing and word-processing of this manuscript.

Meenakshi Nanda
MEENAKSHI NANDA

ABSTRACT

The thesis titled *Synthesis, Tautomerism and Evaluation of Chromogenic Calix[n]arenes for Ionic and Molecular Recognition* concerns with some aspects of chemistry of recently rediscovered calix[n]arenes. These molecules possess a cavity in their molecular architecture due to the presence of distinct hydrophobic and hydrophilic sites to constitute what are popularly known as their upper and the lower rims respectively. Calixarenes are amenable to chemical modifications to provide a variety of molecular receptors with tunable selectivity and specificity. The research work embodied in the thesis has been divided into five chapters.

Chapter I gives an overview of research work reported in the literature on chemistry of calix[n]arenes during the last ten years with special emphasis on their applications in diverse fields. **Chapter II** describes the experiments conducted to synthesize and characterize novel chromogenic calix[n]arenes while **Chapter III** describes a study on their tautomerism. The synthesis of azo calix[n]arenes has been achieved by the azo coupling of hydroxy calix[n]arenes with diazotized aromatic amines, amino acids and esters. The synthesized compounds have been characterized and their conformations established by spectroscopic (IR, NMR, UV, FAB mass) analysis and chemical derivatization as well as by visualization and analysis through CPK models.

It has been observed that while some azo calixarenes exist in their azo form, others exist as their quinone-hydrazone tautomeric analogues. The calix-quinone hydrazone form seems to be stabilized by non covalent interactions and hydrogen bonds. Tautomerization of one form of azo calix[n]arenes to the other has been determined to be dependant upon pH, solvent, substitution pattern, conformation and size of calix[n]arenes under study. Details of

experiments conducted to determine tautomerization constants have been provided in **Chapter III** along with plausible explanation for the observations on synthesized new azo calix[n]arenes.

Chapter IV of the thesis explores the evaluation of synthesized calix[n]arenes as plausible ionophores through UV-visible spectral investigations. Mole ratio plots and application of Hildebrand Benesi equation have been used for determining the stoichiometry of the complexes formed. It has been determined that 5-(2' - carboxyphenylazo)-25,26,27,28-tetrahydroxycalix[4]arene in its cone conformation interacts strongly with copper (II) and 1, 3-alternate conformation of azo pyridylcalix[4]arene is highly selective towards caesium ion.

Since calix[4]arenes possess a cavity in their molecular architecture encompassed by hydrophobic and hydrophilic upper and lower rims, they can recognize ionic and molecular species either through the complementarity of size and shape of the cavity or through self organization to provide voids to accommodate suitable guest molecules. In order to obtain suitably functionalized calix[n]arenes for self organization, several calix[n]arenes containing long hydrocarbon chains at the lower and the upper rim were envisaged as they can entwine to produce aggregates of varying shapes and sizes. Efforts were made to arrive at long hydrocarbon chain containing calix[n]arenes through Friedel-Crafts alkylation and acylation. Results of our preliminary investigations reported in **Chapter V** reveal that Friedel-Crafts acylation of calix[n]arenes is successful only when the reaction is carried out in the presence of nitrobenzene as the solvent. While acylation of calix[n]arenes at the lower rim has been observed to be generally useful with short chain alkyl halides complications are encountered while using long chain alkyl halides. Plausible explanation for the observations has been provided in the thesis.

TABLE OF CONTENTS

<i>Title</i>	<i>Page No.</i>
Certificate	i
Acknowledgement	ii
Abstract of the Thesis	iv
List of Figures and Schemes	vi
Notes	xii
 <i>Chapter I</i>	
Calixarene Based Molecular Receptors For Ionic And Molecular Recognition	1
 <i>Chapter II</i>	
Synthesis Of Some New Chromogenic Calix[n]arenes	74
 <i>Chapter III</i>	
Azo Hydroxy - Quinone Hydrazone Tautomerism In Azo Calixarenes	134
 <i>Chapter IV</i>	
Evaluation Of Chromogenic Calix[n]arene Receptors For Recognition of Metal Ions	176
 <i>Chapter V</i>	
Preliminary Observations On Attempted Synthesis Of Calixarene based Surfactants	207
 Brief bio-data of the Author	248
List of Publications	249

LIST OF FIGURES AND SCHEMES

<i>Scheme/ Figure</i>	<i>Description</i>	<i>Page</i>
Scheme 1.1	Preparation of <i>p</i> -tert-butylcalix[n]arenes from <i>p</i> -tert-butyl phenol.	3
Scheme 1.2	Convergent, step-wise synthesis of calix[4]arenes (No and Gutsche method).	5
Scheme 1.3	Suggested pathway for the formation of calix[n]arenes.	6
Scheme 1.4	Suggested pathway for the reversion of <i>p</i> -tert-butylcalix[8]arene to <i>p</i> -tert-butylcalix[4]arene.	7
Scheme 1.5(a)	Suggested reaction pathway for electrophile induced fragmentation of linear oligomers	8
Scheme 1.5(b)	Suggested reaction pathways for formation of linear oligomers of <i>p</i> -tert-butylphenol and HCHO with electrophiles	9
Scheme 1.6	Synthesis of calix[4]pyridine derivatives.	10
Scheme 1.7	Synthesis of calix[4]pyrrole derivatives.	11
Scheme 1.8	Plausible synthesis of calix[4]arene derivatives in a specific conformation using benzyl residues as protecting groups.	19
Scheme 1.9	Different substitution routes for the functionalization of calixarenes at the upper rim.	21
Scheme 1.10	Functionalization of cyclodextrins.	27
Scheme 1.11	Wittig olefination of the o-propyltetraformylcalix[4]arene with sugarphosphoranes.	36
Scheme 1.12	Calix[6]arene sulphonate catalysed hydration of N-benzyl-1,4-dihydronicotinamide.	49
Scheme 1.13	Alkaline hydrolysis of substituted benzoates in the presence of calixarenes.	50
Scheme 1.14	Synthesis and ligand exchange of X ₆ Me ₃ Pic ₃ complexes.	56
Scheme 1.15	Synthesis of the novel biomimetic calix[6]arene based zinc complexes.	56
Fig. 1.1	<i>p</i> -Alkylcalix[4]arene	1
Fig. 1.2	Preparation of <i>p</i> -tert-butyl calix[n]arenes.	3
Fig. 1.3	Examples of recently synthesized calix[n][furano[n]pyrroles and	12

	calix[n]thieno[n]pyrroles	
Fig. 1.4	Structural representation of different conformers of <i>p</i>-tert-butylcalix[4]arene.	13
Fig. 1.5	Structural representation of eight possible conformers of <i>p</i>-tert-butylcalix[6]arene.	14
Fig. 1.6	Pleated loop conformation of calix[8]arene.	15
Fig. 1.7	ArCH₂Ar resonances near 20°C and -55°C for <i>p</i>-tert-butylcalix [4-16]arene in CDCl₃.	16
Fig. 1.8	Plot of the ΔG values for <i>p</i>-tert-butylcalix[4-20]arenes in CDCl₃.	17
Fig. 1.9	Two different pathways of conformational interconversion of calixarene.	18
Fig. 1.10	Schematic diagram of an active site showing cavity with three interacting functional groups for molecular recognition.	26
Fig. 1.11	(a) Sizes of different cyclodextrins (b) Space filling model of the complex between α-CD and aromatic molecule.	27
Fig. 1.12	Crystal structure of [HNEt₃]₂[(UO₂)₂(NO₃)(Py)₂(H₄L)]	30
Fig. 1.13	Conformational change of biscalix[5]arene on complexation with C₆₀	37
Fig. 1.14	Longitudinal sections of ion selective electrode	42
Fig. 1.15	Classification of chiral calix[4]arenes.	48
Fig. 1.16	Formation of a complex between <i>p</i>-nitrophenylbenzoate and calix[n]arene during alkaline hydrolysis.	50
Fig. 1.17	Linear correlation between concentration of 71 and picrate exchange between aqueous and organic phase	52
Fig. 1.18	Typical time-dependent FHRS signals of the four conformers of tetranitrotetrapropoxycalix[4]arene.	54
Scheme 2.1	Example of a molecular recognition system that undergoes a change in pH⁵.	75
Scheme 2.2	Example of a molecular recognition system that undergoes a redox change to form a cavity⁶.	75
Scheme 2.3	Example of a molecular recognition system that involves an electrochemical reduction⁷.	76

Scheme 2.4	Example of a molecular recognition system that can undergo a photochemical transformations of azo benzene ⁸ .	76
Scheme 2.5	Synthesis of (14a), (14b).	79
Scheme 2.6	Synthesis of dinitrocalix[4]crowns.	80
Scheme 2.7	Synthesis of (25). Reagents and conditions (i) $\text{Ti}(\text{CF}_3\text{CO}_2)_3$, TFA in dark at room temperature (ii) 2,4-Dinitrophenylhydrazine. H_2SO_4 , EtOH, CHCl_3 2h at room temperature.	83
Scheme 2.8	Synthesis of (27). Reagents (iv) $\text{H}_2/\text{Pd}(\text{C})$, ethanol, (v) TPP, ethanol, NaOAc.	83
Scheme 2.9	Coupling reaction between tetrazonium salts and calix[n]arenes.	84
Scheme 2.10	Schematic representation of the autoaccelerative azocoupling of tetrahydroxycalix[4]arene with aryl diazonium salts.	86
Scheme 2.11	Synthesis of 2-carboxyphenylazocalix[n]arenes.	88
Scheme 2.12	Derivatization of synthesized new chromogenic calixarenes (39-44).	95
Scheme 2.13(a,b)	Synthesis of {(4''-nitrophenyl)-2'-carboxyphenylazo} calix[n]arenes (n = 4, 8).	99
Scheme 2.14	Synthesis of azopyridylcalix[n]arene.	102
Scheme 2.15	Chemical derivatization of azopyridylcalix[n]arenes	107
Fig. 2.1	Selective complexation of molecular guest by a topologically complementary organic host molecule.	74
Fig. 2.2(a)	^1H -NMR spectrum of 5-(2'-carboxyphenylazo)-25,26,27,28-tetrahydroxy calix[4]arene (39) in CDCl_3 .	91
Fig. 2.2(b)	^{13}C -NMR spectrum of 5-(2'-carboxyphenylazo)-25,26,27,28-tetrahydroxy calix[4]arene (39) in $\text{DMSO } d_6$.	91
Fig. 2.3	FAB mass spectrum of 5-(2'-carboxyphenylazo)-25,26,27,28-tetrahydroxycalix[4]arene (39).	93
Fig. 2.4	^1H -NMR spectra of 4'-nitrophenyl-2-amino benzoate (45) in CDCl_3 .	100
Fig. 2.5	^1H -NMR of 5,11,17,23-tetrakis(4'-azopyridyl)-25,26,27,28-tetrahydroxy calix[4]arene (48) in $\text{DMSO } d_6$.	103
Fig. 2.6	CPK model of 1,3-alternate conformation of 5,11,17,23-tetrakis	104

	(4'-azopyridyl)-25,26,27,28-tetrahydroxycalix[4]arene (48).	
Fig. 2.7	FAB mass spectrum of 5,11,17,23-tetrakis(4'-azopyridyl)-5,26,27,28-tetrahydroxy calix[4]arene (48).	106
Scheme 3.1	Tautomeric structures (a) via discrete cationic or anionic intermediates (b) via. simultaneous loss and gain of different protons.	139
Fig. 3.1	Double Helical structure of DNA.	135
Fig. 3.2	Biosynthesis of porphyrins from glycine and succinyl-CoA.	136
Fig. 3.3	Pathway for synthesis of black pigment melanin and pigments of reddish hair and feathers.	137
Fig. 3.4	Azo-quinone-hydrazone tautomeric equilibrium in the case of 1-phenylazo-2-naphthol (5).	141
Fig. 3.5	Absorption spectra of dye 8 in 50 vol% ethanol-water solution at 20°C. pH values: 1, 2.5; 2, 3.2; 3, 3.7; 4, 4.0; 5, 5.2; 6, 6.0-12.0.	144
Fig. 3.6	Relationship between content of hydrazone form and pH value for (8) in a binary mixture of acetone and water (1:1).	146
Fig. 3.7	Relationship between ratio of contents of hydrazone form and azo form (K_T) and pH value for (8) in a binary mixture of acetone and water (1:1).	146
Fig. 3.8	Spectra of 12b in ethanol-water. Curve numbers (1-5) correspond to $x_2 = 0, 0.088; 0.175; 0.320$ and 0.734 to 1.00 .	150
Fig. 3.9	Semilog plots of K_T at 25°C vs mol fraction of alcohol in a binary mixture of solvents open data points correspond to $[dye] = 2.5 \times 10^{-5}M$; while closed data points correspond to $[dye] = 2.5 \times 10^{-6}M$.	150
Fig. 3.10	Absorption spectra of 13a in different volume ratios of ethanol/water.	151
Fig. 3.11	Variation of energy of absorption with solvents dipolarity at 5 eV.	152
Fig. 3.12	Spectral variation of 24 as a function of pH in THF/H ₂ O (1:1) (1) pH 7.09, (2) pH 8.0, (3) pH 9.0, (4) pH 9.25, (5) pH 9.7, (6) pH 10.0, (7) pH 10.25, (8) 10.5.	156
Fig. 3.13	Spectral variation of 25 as a function of pH in THF-H ₂ O (1:1) (1)	157

	pH 7.1, (2) pH 8, (3) pH 9.25, (4) pH 9.75, (5) pH 10.25.	
Fig. 3.14	Spectral variation of 26 as a function of pH in THF-H ₂ O (1:1, v/v).	160
Fig. 3.15	Spectral variation of 27 as a function of pH in THF-H ₂ O (1:1, v/v).	160
Fig. 3.16	Variation in the calixarene quinone hydrazone content of (a) 24 (b) 25 with pH.	164
Fig. 3.17	Plot of K_T vs mole fraction of water in DMF and DMSO (x_2).	166
Fig. 3.18	Spectra of 26 in different solvents.	167
Fig. 4.1	Influence of alkali metal ions on the absorption spectra of 6b in 99% ethanol [metal salt/ 6b] =30, 6b=5x10 ⁻⁵ mol dm ⁻³	182
Fig. 4.2	Spectral changes upon addition of Ca(SCN) ₂ .4H ₂ O to a solution of 7b in 99% ethanol, 7b=1.5x10 ⁻⁵ mol dm ⁻³ .	182
Fig. 4.3	UV absorption spectra of 8a (3.0x10 ⁻⁵ M. CHCl ₃) upon extraction with aqueous metal chloride solution [Ca ²⁺]=0.05M.[Sr ²⁺]=[Ba ²⁺] = [Na ⁺]=0.1M.	183
Fig. 4.4	UV-vis absorption spectra of (a) 10a (b) 10a.Pb ²⁺ , (c) 10b (d) 10b.Pb in CH ₂ Cl ₂	185
Fig. 4.5	Schematic representation of redox switch	186
Fig. 4.6(a)	UV-vis absorption spectrum of 14 (curve 1) in methanol and its change upon the addition of Cu(II) (curve 2), Ni(II) (curve 3), Cr(III) (curve 4) solutions in methanol.	188
Fig. 4.6(b)	Plot of (absorbance) ⁻¹ with addition of various metal ions.	189
Fig. 4.7	Mole ratio plot for the formation of 14-Cu ²⁺ complex	190
Fig. 4.8	Job's plot for the formation of 14-Cu ²⁺ complex	191
Fig. 4.9	Change in absorption spectrum of 15 upon addition of Cs ₂ CO ₃ (1) 0 (2) 10 ⁻⁶ (3) 10 ⁻⁵ (4) 10 ⁻⁴ (5) 10 ⁻³ (6) 2x10 ⁻³ (7) 3x10 ⁻³ (8) 4x10 ⁻³ (9) 5x10 ⁻³ (10) 6x10 ⁻³ (11) 10 ⁻² mol dm ⁻³ to a 99% methanol solution of (15) [5x10 ⁻⁶ mol dm ⁻³]	193
Fig. 4.10	Spectral responses [$\Delta\lambda_{\max} = \lambda_{\max}(\text{complex}) - \lambda_{\max}(\text{ligand})$] of 15 in the presence of (10 ⁴ equiv.) or absence of metal ions at 20°C [15]=5x10 ⁻⁶ mol dm ⁻³	194
Fig. 4.11	Variation in absorbance of 15 [5x10 ⁻⁶ mol dm ⁻³ in methanol] at 422nm as a function of metal ion concentration	195
Fig. 4.12	Hildebrand Benesi plot for the formation of 15-Cs ⁺ complex	197

Fig. 4.13	(a) ^1H-NMR of (15) (b) (15)-Cs⁺ complex	198
Scheme 5.1	A self-organized two dimensional monolayer with subsequent self assembly and cleavage.	213
Scheme 5.2	Self-replication by condensation product of 3-amino-benzamidines and 2-formylphenoxyacetic acids.	214
Scheme 5.3	Lower rim functionalization (etherification)	227
Scheme 5.4	Lower rim functionalization (esterification)	230
Fig. 5.1	Self assembly of tobacco mosaic virus (TMV) from a single strand of viral RNA and 2130 protein subunits.	208
Fig. 5.2	Various organized molecular assemblies.	211
Fig. 5.3	Dynamic equilibrium between surfactant monomer assemblies and aggregates.	211
Fig. 5.4	Hartley's model of spherical micelle.	212
Fig. 5.5	Diagram showing the spherical bilayer structure of a cell.	212
Fig. 5.6	Calixaryl ureas form a dimeric capsule in the presence of an appropriate guest.	217
Fig. 5.7	Monolayers at air water interface.	219
Fig. 5.8	^1H-NMR of 5,11,17,23-tetramyristoyl-25,26,27,28-tetrahydroxy calix[4]arene (28)	226

NOTES

1. All melting points reported in this thesis are uncorrected and were taken on an electric melting point apparatus (Toshniwal, India).
2. UV spectra were taken on Hitachi 330 and Perkin Elmer's (Lambda-3B) spectrophotometers.
3. IR spectra were recorded in KBr discs on a [5-DX] Nicolet FT-IR and Nicolet protégé 460 ESP spectrophotometers.
4. ^1H -NMR and ^{13}C -NMR spectra were recorded in CDCl_3 and DMSO-d_6 on Jeol [JNM-FX-100] (IIT Delhi) and Bruker Spectrospin-300MHz FT-NMR spectrometers using TMS as internal standard and values reported are on δ scale. The abbreviation such as s, bs, d, t, q and m indicate singlet, broad singlet, doublet, triplet, quartet and multiplet respectively.
5. FAB-mass spectra of some of the synthesized compounds were recorded on a JEOL SX 103/DA-6000 Mass Spectrometer available at Central Drug Research Institute, Lucknow. *m*-Nitrobenzyl alcohol was used as the matrix.
6. Elemental Analysis was carried on Perkin Elmer's 240C-CHN Analyzer.
7. The completion of the reaction and the purity of the synthesized compounds were checked by TLC performed on silica gel coated glass plates using iodine for visualizing the spots.
8. Purification of several of the synthesized compounds was carried out by column chromatography over silica gel (60-120 mesh) obtained from Qualigens Fine Chemicals Limited, Mumbai.

The solvents used were purified and dried before use by procedures described in "Purification of Laboratory Chemicals" by W.L.F. Armarego and D.D. Perrin. Bath Press and Bath, Britain.

For the sake of convenience, the names of calixarenes used in this thesis have been shortened. For example, 5, 11, 17, 23-tetra-*tert*-butylcalix[4]arene or even parent calix[4]arene while 5, 11, 17, 23, 29, 35-hexa-*tert*-butyl-49, 50, 51, 52, 53, 54-hexahydroxycalix[6]arene and 5, 11, 17, 23, 29, 35, 41, 47-octa-*tert*-butyl-49, 50, 51, 52, 53, 54, 55, 56-octahydroxycalix[8]arene are referred as *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene respectively. Similarly names of 25, 26, 27, 28-tetrahydroxycalix[4]arene, 37, 38, 39, 40, 41, 42-hexahydroxycalix[6]arene and 49,50,51,52,53,5,55,56-octahydroxycalix[8]arene have been shortened to tetrahydroxycalix[4]arene, hexahydroxycalix[6]arene and octahydroxycalix[8]arene respectively and even further shortened to calix[4]arene, calix[6]arene and calix[8]arene respectively.

Abbreviations used in this thesis are:

DMSO for Dimethylsulphoxide;

THF for Tetrahydrofuran;

DMF for N, N-Dimethylformamide

DMSO-d₆ for Hexadeuterated Dimethylsulphoxide;

CDCl₃ for Deuterated chloroform;

D₂O for Deuterated water;