

**STUDIES ON SYNTHESIS  
AND  
REACTIONS OF CALIX[n]ARENES**

**By**

**LUKESH BAJAJ**

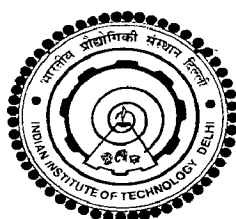
**Department of Chemistry**

**Submitted**

*in fulfilment of the requirement of the degree of*

**Doctor of Philosophy**

**to the**



**Indian Institute of Technology, Delhi  
February, 2004**

## CERTIFICATE

This is to certify that the thesis entitled, “*STUDIES ON SYNTHESIS AND REACTIONS OF CALIX[n]ARENES*”, being submitted by Mr. Lukesh Bajaj 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 him.

Lukesh Bajaj 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

Head and Professor,  
Department of Chemistry,  
Indian Institute of Technology,  
New Delhi-110016, India.

## ACKNOWLEDGEMENTS

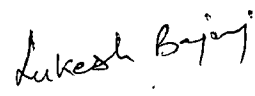
*It gives me an immense pleasure and great opportunity to express my profound sense of gratitude and indebtedness to Professor and Head H. M. Chawla, for his painstaking guidance, invaluable suggestions and constant encouragement throughout the execution of research work embodied in this thesis. I would also like to thank him for making all facilities available for my research work.*

*I would also like to thank Dr. R. Varadarajan for his valuable support and guidance.*

*A mention of my colleagues, whose support egged me on, is a must. Of note among them are Tania and Satish – their help during writing of the thesis was immense. My seniors, Venkatesh, Anuradha and Meenakshi – who set an example of ability and intelligence before us -- deserve special mention. I would also like to thank my lab mates Vandna, Bindu, Ananya, Sahu, Rahul, Suneel, Anjali, Sarika, Namrata, Arpita and Kamini for their constant help and support. I am also extremely grateful for the help rendered to me by Dr. Ranjana Saxena and Personal Secretary to Prof. Chawla, Ms. Seema Arora.*

*I thank Department of Biotechnology, Govt. of India and Indian Institute of Technology, Delhi for research fellowships.*

*Last, but not the least, I would like to take this opportunity to offer my sincere regards to all members of my family for their invaluable support and constant encouragement that made it possible for me to pursue and complete my research work.*

  
LUKESH BAJAJ

## ABSTRACT

The thesis titled, “**STUDIES ON SYNTHESIS AND REACTIONS OF CALIX[n]ARENES**”, presents the research work carried out on the synthesis, characterization and applications of some novel calix[n]arene derivatives. The research work has been divided into six chapters.

Calixarenes represent phenolic macrocyclic metacyclophanes that possess a flexible hydrophobic pocket encompassed by hydrophobic and hydrophilic ends (termed upper and lower rim) in their molecular architecture. They can serve as useful building blocks for designing novel derivatives/conjugates that can provide molecular assemblies and aggregates to induce molecular recognition behavior. **Chapter-I** of the thesis presents an overview of the literature published during the past ten years in the field with special emphasis on their synthesis, conformational analysis, organizational behaviour and self-assembly of calixarenes.

**Chapter II** deals with the synthesis of various chromoionophores and their spectral characterization (IR, NMR, UV and FAB mass spectral analysis). Conformational analyses of the synthesized azocalixarenes have been accomplished by  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectroscopy. The synthesis of these chromoionophores has been achieved by combining the chromogenity and thiophilicity concepts reported earlier from our laboratory.

**Chapter III** describes the synthesis of various acyl, bromo and Mannich base derivatives of calix[4]arenes followed by their further functionalization. For instance, the acyl calixarene derivatives have been converted to their respective hydrazones and oximes, the bromo derivatives to their cyano analogues while the Mannich reaction products have been converted to the corresponding (thiophenyl)methyl and cyano methyl derivatives.

The cyano derivatives have also been converted to the corresponding tetrazoles by treatment with sodium azide. The characterization of synthesized compounds has been achieved by IR, UV, NMR and single crystal X-ray diffraction analysis.

Preliminary UV-visible spectral investigations have been conducted to evaluate the recognition characteristics of synthesized chromoionophores towards transition metal ions and results have been described in **Chapter IV**. Some of the synthesized chromoionophores have been found to selectively recognize Hg(II) and Pd(II) ions. The interaction of palladium complex of the 5,11,17,23-tetrakis-(2-hexadecylthiophenylazo)-25,26,27,28-tetrahydroxy calix[4]arene ( $2c_3$ ) with aliphatic amines has also been reported in this chapter.

**Chapter V** describes an economic procedure for the synthesis of different esters of *p-tert*-butylcalix[n]arenes and development of their analytical profiles through HPLC analyses. While synthesized products obtained have been spectroscopically characterized, their HPLC profiles have been documented in this chapter. Preliminary results on the study of reactions at the methylene bridge of tetramethoxy *p-tert*-butylcalix[4]arene using strong bases like *n*-BuLi or LDA in THF have been incorporated in **Chapter VI**.

## 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 Perkin Elmer's(Lambda-3B) spectrophotometer.
3. IR spectra were recorded in KBr discs on a [5-DX] Nicolet FT-IR spectrophotometer.
4.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$  on Bruker Spectrospin-300MHz FT-NMR spectrometers using TMS as internal standard and values reported are on  $\delta$  scale. The abbreviation such as s, bs, d, t, q, bm and m indicate singlet, broad singlet, doublet, triplet, quartet, broad multiplet 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*-Nitro benzyl 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.
9. All analytical HPLC assays were carried on Waters 2487 instrument with a Dual  $\lambda$  Absorbance Detector. The samples were dissolved in HPLC grade THF.

10. The solvents used were 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.
11. For the sake of convenience, the names of calixarenes used in this thesis have been shortened. For example, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene has been usually referred as *p-tert*-butylcalix[4]arene or even parent calix[4]arene while 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-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*-calix[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-hexahydroxy calix[6]arene and 49,50,51,52,53,54,55,56-octahydroxycalix[8]arene have been shortened to tetrahydroxycalix[4]arene, hexahydroxycalix[6]arene and octahydroxycalix[8]arene and even further shortened to calix[4]arene, calix[6]arene and calix[8]arene.
12. Abbreviations used in this thesis are:
- THF – Tetrahydrofuran;
  - DMF – N,N'-Dimethylformamide;
  - CDCl<sub>3</sub>- Deuterated chloroform;
  - CD<sub>3</sub>OD- Deuterated methanol;
  - D<sub>2</sub>O – Deuterated water;
  - DMSO-d<sub>6</sub> – Deuterated Dimethyl sulfoxide.

## CONTENTS

<b>Title</b>	<b>Page No.</b>
<b>Certificate</b>	<b>i</b>
<b>Acknowledgements</b>	<b>ii</b>
<b>Abstract of the Thesis</b>	<b>iii</b>
<b>List of Figures and Schemes</b>	<b>v</b>
<b>Notes</b>	<b>xiii</b>
<b>Chapter I</b>	
<b>Synthesis, spectral properties and molecular assemblage of functionalized calix[n]arenes</b>	<b>1</b>
<b>Chapter II</b>	
<b>Synthesis of Some New Chromogenic Calixarenes</b>	<b>56</b>
<b>Chapter III</b>	
<b>Studies in Some Reactions of Calix[n]arenes</b>	<b>101</b>
<b>Chapter IV</b>	
<b>Studies on interaction of chromogenic calixarenes with transition metal ions</b>	<b>153</b>
<b>Chapter V</b>	
<b>Immobilization of calix[n]arenes through derivatization and their analysis through High Performance Liquid Chromatography</b>	<b>193</b>
<b>Chapter VI</b>	
<b>Preliminary Studies on Functionalization of Methylene Bridges in Calix[4]arene</b>	<b>240</b>
<b>Brief Bio-Data of the Author</b>	<b>264</b>
<b>List of Publications</b>	<b>265</b>

## LIST OF FIGURES AND SCHEMES

	Page no.
Scheme 1.1.1. Preparation of <i>p-tert</i> -butylcalix[n]arene from <i>p-tert</i> -butylphenol.....	3
Scheme 1.1.2. Preparation of <i>p-tert</i> -butylcalix[n]arenes.....	6
Scheme 1.1.3. Stepwise synthesis of calix[n]arenes.....	6
Scheme 1.1.4. Condensation using “3+1” and “2+2” fragments to prepare substituted calix[n]arenes.....	8
Scheme 1.1.5a. Suggested reaction pathway for electrophile induced fragmentation of linear oligomers.....	11
Scheme 1.1.5b. Suggested reaction pathways for the formation of linear oligomers of <i>p-tert</i> -butylphenol and HCHO with an electrophile.....	12
Scheme 2.1.1. Schematic representation of the auto accelerative diazocoupling of tetrahydroxycalix[4]arene.....	60
Scheme 2.1.2. Synthesis of <i>p</i> -(2,3-dihydro-1,4-phthalazinedione-5-azo)calix[n]arene (n=4,6,8).....	61
Scheme 2.1.3. Synthesis of <i>p</i> -nitrophenylazo calix[4]arenes (17a-d).....	63
Scheme 2.1.4. Synthetic pathway of azocalix[4]arene amide and ester.....	64
Scheme 2.1.5. Synthesis of indoaniline derivatives of calix[4]arenes.....	65
Scheme 2.3.1 Synthesis of calix[n]arene dyes.....	69
Scheme 3.3.1. Synthesis of various acyl calix[4]arenes and their derivatives.....	115
Scheme 3.3.2. Synthesis of various bromo calix[4]arenes and their derivatives.....	122
Scheme 3.3.3. Synthesis of Mannich base products of calix[4]arenes and their derivatives.....	128

Scheme: 5.3.1. Synthesis of fully functionalized calixarene ester.....	210
Scheme 5.3.2. Synthesis of partially functionalized calixarene esters.....	221
Scheme 6.1.1. Upper rim functionalization of calix[4]arene.....	243
Scheme 6.1.2. Step wise synthesis of calix[4]- and calix[5]arene bearing functionalized arm on the methylene bridge.....	244
Scheme 6.1.3. Modification of the methylene bridge using “2+2” fragment condensation method.....	246
Scheme 6.1.4. Inversion of diastereomeric form of calixarene to another form...	247
Scheme 6.1.5. Ring inversion of <i>cis</i> form to another <i>cis</i> or <i>trans</i> form to another <i>trans</i> form.....	247
Scheme 6.1.6. Bromination reaction at methylene bridge.....	248
Figure 1.1.1. Pathway for the reversion of <i>p-tert</i> -butylcalix[8]arene to <i>p-tert</i> - butylcalix[4]arene.....	10
Figure 1.1.2. Two different modes for inversion of the phenyl units.....	16
Figure 1.1.3. Structural representation of the conformers of calix[4]arene.....	17
Figure 1.1.4. Dynamic stereochemistry of tetraalkoxycalix[4]arene.....	23
Figure 1.1.5. Calix[4]arene 19 in the chair conformation.....	26
Figure. 1.1.6. Eight possible conformations of calix[6]arene.....	28
Figure. 1.1.7. Pleated loop conformation of calix[8]arene.....	29
Figure 1.1.8. Structure of bisazobiphenylcalix[4]arene.....	31
Figure 1.1.9. Inner cavity dimensions of known molecular containers compared with dimensions of different classes of organic substances.....	32
Figure 1.1.10. Unimolecular capsular structure 35 and its complex.....	38

Figure 1.1.11. Assembly of a restrained bis-rosette structure.....	42
Figure 1.1.12. A schematic representation of the restrained bis-rosette with six pendant calix[4]arene groups.....	44
Figure 2.3.1. <sup>1</sup> H NMR spectrum of 23a <sub>2</sub> .....	71
Figure 2.3.2. FAB mass spectrum of 23a <sub>2</sub> .....	71
Figure 2.3.3. <sup>1</sup> H NMR spectrum of 23c <sub>2</sub> .....	72
Figure 2.3.4. <sup>13</sup> C (proton decoupled) NMR spectrum of 23c <sub>2</sub> .....	72
Figure 2.3.5. Two different views A (side view) and B (top view) of ball and stick model of 23b <sub>2</sub> .....	73
Figure 2.3.6. UV-visible spectrum of 23b <sub>2</sub> in CHCl <sub>3</sub> .....	74
Figure 2.3.7. <sup>1</sup> H NMR spectrum of 23e <sub>5</sub> .....	75
Figure 2.3.8. UV-visible spectrum of 23f <sub>3</sub> in CHCl <sub>3</sub> .....	76
Figure 3.1.1. X-ray structure of tetrahydroxycalix[4]arene in 1,2-alternate conformation.....	104
Figure 3.1.2. Crystal Structure of 4 (encapsulated MeOH in cavity of 1) and 3 (CHCl <sub>3</sub> outside the cavity of 1).....	105
Figure 3.1.3. Crystal structure of 2.....	105
Figure 3.1.4. Crystal structure of Cd(II) and Pd(II) complexes of 5.....	106
Figure 3.1.5. Crystal structure of 7.....	107
Figure 3.1.6. Crystal structure of partial cone conformer of 8.....	108
Figure 3.1.7. Crystal structure of 9 and 10 (dimer).....	109
Figure 3.3.1. <sup>1</sup> H-NMR spectrum of 15 in CDCl <sub>3</sub> .....	117
Figure 3.3.2. <sup>1</sup> H-NMR of 14a in CDCl <sub>3</sub> .....	117

Figure 3.3.3. Crystal structure of 14a.....	118
Figure 3.3.4. H-Bonding interactions in Crystal Lattice of 14a.....	120
Figure 3.3.5. <sup>1</sup> H NMR spectrum of 18a.....	124
Figure 3.3.6. Crystal structure of 18a.....	125
Figure 3.3.7. <sup>1</sup> H-NMR spectrum of 18b.....	125
Figure 3.3.8. <sup>1</sup> H-NMR of 21 in CDCl <sub>3</sub> .....	127
Figure 3.3.9. <sup>1</sup> H-NMR of 22a in CDCl <sub>3</sub> .....	127
Fig.4.1.1. Wavelength changes of 3 upon the addition of varying amounts of Ca(ClO <sub>4</sub> ) <sub>2</sub> .....	154
Fig.4.1.2. UV-visible spectral change of 10a (1x10 <sup>-5</sup> M) (1) on addition of the following concentrations of <i>t</i> -butylamine: (2) 1x10 <sup>-7</sup> ; (3) 2x10 <sup>-7</sup> ; (4) 1.3x10 <sup>-6</sup> ; (5) 6.3x10 <sup>-6</sup> ; (6) 1.63x10 <sup>-6</sup> ; (7) 5.0x10 <sup>-5</sup> ; (8) 2.63x10 <sup>-4</sup> ; (9) 1.26x10 <sup>-4</sup> ; (10) 3.26x10 <sup>-4</sup> ; (11) 5.26x10 <sup>-3</sup> ; (12) 2.56x10 <sup>-3</sup> ; (13) 7.52x10 <sup>-3</sup> M.....	158
Fig. 4.1.3. UV absorption spectra of 16a (3x 10 <sup>-5</sup> M, CHCl <sub>3</sub> ) upon extraction with aqueous metal chloride solution [Ca <sup>2+</sup> ]= 0.05M, [Sr <sup>2+</sup> ] = [Ba <sup>2+</sup> ] = [Na <sup>+</sup> ] = 0.1M.....	160
Figure 4.1.4. UV-visible absorption spectra of (a) 17a, (b) 17a-Pb <sup>2+</sup> , (c) 17b and (d) 17b-Pb <sup>2+</sup> in CH <sub>2</sub> Cl <sub>2</sub> .....	162
Figure 4.1.5. Schematic representation of a redox switch.....	162
Figure.4.3.1. UV-visible absorption spectrum of 20 (curve 1) in CHCl <sub>3</sub> and its change upon the addition of Pd(II) (curve 2), Hg(II) (curve 3) and Cu(II) (curve 4).....	166

Figure 4.3.2. UV-visible absorption spectrum of 21 (curve 1) in CHCl <sub>3</sub> and its change upon the addition of Pd(II) (curve 2), Hg(II) (curve 3) and Cu(II) (curve 4).....	168
Figure 4.3.3. <sup>1</sup> H NMR spectrum of 21.....	170
Figure 4.3.4. <sup>1</sup> H NMR spectrum of 21-Pd complex.....	170
Figure 4.3.5. UV-visible absorption spectrum of 21-Pd complex in different solvents.....	172
Figure 4.3.6. Mole-ratio plot for interaction of 20 with Pd(II).....	174
Figure 4.3.7. Job's Plot for interaction of 20 with Pd(II).....	174
Figure 4.3.8. Mole-ratio plot for interaction of 20 with Hg(II).....	175
Figure 4.3.9. Job's plot for interaction of 20 with Hg(II).....	176
Figure 4.3.10. Mole-ratio plot for interaction of 21 with Pd(II).....	177
Figure 4.3.11. Job's plot for interaction of 21 with Pd(II).....	177
Figure 4.3.12. Mole-ratio plot for interaction of 21 with Hg(II).....	178
Figure 4.3.13. Job's plot for interaction of 21 with Hg(II).....	179
Figure 5.1.1. Chromatogram of an HPLC analysis of a crude product from an acid-catalyzed reaction of <i>p-tert</i> -butylphenol and <i>s</i> -trioxane.....	206
Figure 5.1.2. Chromatograms showing the retention of <i>p-tert</i> -butylcalix[n]arenes on Si-C <sub>60</sub> and Si-C <sub>70</sub> using CH <sub>2</sub> Cl <sub>2</sub> + 0.5% isopropanol as mobile phase, UV detection at 280nm.....	208
Figure 5.3.1. <sup>1</sup> H NMR spectrum of 9k.....	212
Figure 5.3.2. <sup>1</sup> H NMR spectrum of 9l.....	212
Figure 5.3.3. HPLC chromatograms (A) Pure 9k (B) Pure 9l.....	220

Figure 5.3.4. HPLC chromatograms of reaction mixtures obtained from Table 5.3.2. (C) 30 ml THF (D) 60 ml THF (E) 70 ml THF (F) 50 ml THF-2 ml DMF (G) 50 ml THF-3 ml DMF (H) 60 ml THF-5 ml DMF.....	221
Figure 5.3.5. <sup>1</sup> H NMR spectrum of 9s.....	224
Figure 5.3.6. <sup>1</sup> H NMR spectrum of 9r.....	224
Figure 5.3.7. HPLC chromatograms of 9t (I) and 9r (J).....	225
Figure 6.1.1. Possible sites for functionalization in calixarenes.....	240
Figure 6.3.1. <sup>1</sup> H NMR spectrum of 10.....	249
Figure 6.3.2. <sup>1</sup> H NMR spectrum of 11.....	251
Figure 6.3.3. <sup>1</sup> H NMR spectrum of 12.....	252
Table 1.1.1. Yield [%] of calix[n]arenes in one-pot synthesis from <i>p</i> -substituted phenols. Values given in the following table refer to chromatographically isolated yields.....	5
Table 1.1.2. pK values for <i>p</i> -sulfonatocalix[4]arene and <i>p</i> -nitrocalix[4]arene.....	13
Table 1.1.3. Absorptivities ( $\epsilon_{\max}$ , mol <sup>-1</sup> cm <sup>-1</sup> ) of calixarenes in the indicated solvent at 280 nm and 288 nm.....	15
Table 1.1.4. Spectral patterns for different conformations of <i>p</i> - <i>tert</i> -butylcalix[4]arene.....	18
Table 2.3.1: IR and NMR characteristics of chromogenic calix[4]arene compounds.....	70
Table 2.3.2: IR and NMR characteristics of chromogenic calix[6]arene compounds.....	76

<b>Table 3.3.1. Showing H-bond interactions (Å and O).....</b>	<b>120</b>
<b>Table 4.3.1. Change in <math>\lambda_{\max}</math> of UV-visible spectra of 21-Pd adduct on the addition of solvent.....</b>	<b>171</b>
<b>Table 4.5.1. Optical Density of solutions of different compositions of 20 and Pd(II) solutions at <math>\lambda_{\max}</math> 525nm.....</b>	<b>183</b>
<b>Table 4.5.2. Optical Density of solutions of different compositions of 20 and Pd(II) solutions at <math>\lambda_{\max}</math> 525nm.....</b>	<b>184</b>
<b>Table 4.5.3. Optical Density of solutions of different compositions of 20 and Hg(II) solutions at 500 nm.....</b>	<b>185</b>
<b>Table 4.5.4. Optical Density of solutions of different compositions of 20 and Hg(II) solutions at <math>\lambda_{\max}</math> 500nm.....</b>	<b>186</b>
<b>Table 4.5.5. Optical Density of solutions of different compositions of 21 and Pd(II) solutions at 525nm.....</b>	<b>187</b>
<b>Table 4.5.6. Optical Density of solutions of different compositions of 21 and Pd(II) solutions at <math>\lambda_{\max}</math> 525nm.....</b>	<b>188</b>
<b>Table 4.5.7. Optical Density of solutions of different compositions of 21 and Hg(II) solutions at <math>\lambda_{\max}</math> 540nm.....</b>	<b>189</b>
<b>Table 4.5.8. Optical Density of solutions of different compositions of 21 and Hg (II) solutions at <math>\lambda_{\max}</math> 540nm.....</b>	<b>190</b>
<b>Table 5.1.1. Literature for the LC methods for calixarenes and related compounds.....</b>	<b>198</b>
<b>Table 5.3.1. Effect of base on the esterification of <i>p-tert-butylcalix[4]arene</i>.....</b>	<b>215</b>

**Table: 5.3.2. Effect of reaction time and solvent on the synthesis of *p-tert*-butylcalix[4]arene tetraester using NaH as a base.....217**

**Table: 5.3.3. % purity of 9l in different samples of reaction mixtures as determined by HPLC.....222**