SYNTHESIS OF NEW CALIX(n)ARENES FOR IONIC AND MOLECULAR RECOGNITION

THESIS SUBMITTED
IN FULFILMENT FOR THE REQUIREMENTS
OF THE DEGREE OF
DOCTOR OF PHILOSOPHY

by

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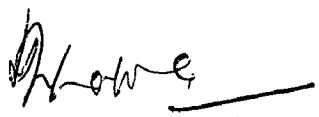
Dedicated to
My
Parents

CERTIFICATE

This is to certify that the thesis entitled ***Synthesis of New Calix(n)arenes for Ionic and Molecular Recognition*** being submitted by **Mr. K.Srinivas** to Indian Institute of Technology, New Delhi, for the award of the degree of Doctor of Philosophy is a record of bonafide research work carried out by him.

Mr. K.Srinivas 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 full to any other University or Institute for the award of any degree or diploma.



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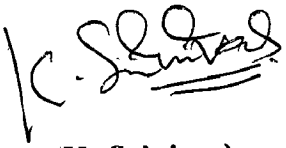

(K. Srinivas)

ABSTRACT

The thesis entitled ***Synthesis of New Calix(n)arenes for Ionic and Molecular Recognition*** has been divided into six chapters.

Chapter I summarizes the chemistry of calix(n)arenes and results obtained on the regioselective methylation of calix(n)arenes to obtain their mono-, di-, tri- and tetramethylated derivatives using different reagents (methyl iodide, dimethyl sulphate and methyltosylate) and bases (K_2CO_3, NaH, BaO,$Ba(OH)_2.8H_2O$ and CaH_2) in different solvents (acetone, acetonitrile, DMF, THF/DMF and toluene). It has been observed that the metal ion template effects noted in calix(4)arenes are not operative in regioselective methylation of hexahydroxycalix(6)arenes and octahydroxycalix(8) arenes and partial alkylation of higher calixarenes can be accomplished by varying the reaction conditions (*i.e.*, by changing the base, the reagent and the solvent etc.).

Chapter II describes the attempted and successful routes employed in our laboratory for obtaining calix(n)arene based new chromogenic molecular receptors. It was stipulated that calix(n)arenes should undergo a coupling reaction with diazonium salts at low temperatures to yield calixarene based synthetic dyes but the reaction when carried out in the laboratory led to the coupling of diazonium salts with excess of amine in solution. After several attempts on diazotization and coupling of various *p*-substituted anilines (X-  -NH_2, X=CH_3, NO_2, H) with calixarenes under a variety of conditions, chromogenic calix(n)arenes were finally achieved in good yields during the coupling of diazotized 4,4'-diaminobiphenyls with tetrahydroxycalix(4)arene and octahydroxycalix(8)arene. Details of the procedures adopted for the synthesis and

characterization of new chromogenic calixarenes by NMR, UV and IR spectral analysis and chemical derivatization is the subject matter of Chapter II.

Chapter III describes experiments conducted for achieving selective recognition of monoamines, diamines and polyamines by chromogenic calix(n)arenes (n=4,8) obtained through the procedures described in the previous chapter. Application of Jobs continuous variation methods, conductometric, photometric, potentiometric and NMR titrations to the study of interaction of amines with diazocalixes has established that the examined amines (R-NH_2, R=CH_3, C_2H_5, n-C_3H_7... etc) form 1:1 molecular complexes with chromogenic calixarenes in DMSO. The results achieved shed light on the proposed mechanism of exo to endo transformation in calixarene-amine complexation.

Recent studies on the ability of calixarenes to form supramolecular species with a range of small molecules and ions in our laboratory as well as elsewhere have stressed the need for availability of calixarenes with larger and deeper cavity in their molecular architecture. Though the reaction of 2,4,5-triphenylimidazole derivatives with calix(n)arenes provided selective lower rim functionalized imidazolylcalix (6)arenes, the yields of the wider cavity products were low and their recognition characteristics could not be studied. An alternative route involving the condensation of *p*-formylcalix(n)arenes (n=4,6,8) with benzil has,however,led to the formation of new *p*-imidazolyl calixarenes which have a much deeper and a wider hydrophobic cavity than that present in the structure of their parent analogs as revealed by CPK models and they can stabilize in the winged or the flower vase conformations. Chapter IV describes the details of synthetic procedures adopted to obtain such deep cavity calixarenes and their characterization by IR, UV and NMR spectroscopy. The

synthesized wider cavity *p*-imidazolylcalixarenes were also examined for ion recognition through solvent extraction procedures. It has been observed that some of the new calixarenes do provide selectivity for specific metal ions.

Towards our long term goal of exploring the mechanism of photooxidative deactivation of certain enzymes and their conjugates, the reaction of singlet oxygen with 2,4,5-triphenylimidazoles and calix-imidazoles has been examined. Chapter V describes the reaction modes of singlet oxygen with oxygen and nitrogen heterocycles and our experiments on its reaction with several 2,4,5-triphenylimidazoles and calix-imidazole derivatives. The identity of triphenylimidazole substrates and products of their photooxygenation have been established by UV, IR, NMR and mass spectral analysis. A plausible mechanism involved in the reaction has been postulated.

Chapter VI reports our efforts to obtain new calix-coumarin fluoro probes. The results obtained so far indicate that one of the synthesized calix-coumarins can function as a sensor materials for discriminating Na^+/K^+ ions while other derivatives are not suitable for the purpose.

RESEARCH PAPERS PUBLISHED/PRESENTED

1. Molecular Diagnostics: Synthesis of new Chromogenic calix(8)arenes as potential reagents for detection of amines, H.M. Chawla and K. Srinivas, *J. Chem. Soc., Chem. Commun.*, 1994, 2593-2594.
2. Synthesis of new chromogenic calix(8)arenes, H.M. Chawla and K. Srinivas; *Tetrahedron Letters*, 1994, **35**, 2925.
3. Synthesis of new fluorescent ionophores: First examples of calix-coumarin analogs, H.M.Chawla and K.Srinivas, *J. Inst. Sci.*, 1994, **74**, 515.
4. Calix-quinone interactions: Molecular recognition of 2,6-naphthoquinone by 5,11,17,23,29,35-Hexatert-butyl-37,38,39,40,41,42-hexahydroxycalix(6)arene, H.M.Chawla and K.Srinivas, *Tetrahedron*, 1995, **51**, 2709.
5. Molecular recognition of 2,6-naphthoquinone by 5,11,17,23,29,35-Hexatert-butyl-37,38,39,40,41,42-hexahydroxycalix(6)arene, H.M.Chawla and K.Srinivas, *Ind. J. Chem.*, 1995, **34B**, 230.
6. Synthesis of 25,26,27-Tris(ethoxycarbonylmethoxy)-28-(4'-methyl-7'-coumarin yloxycarbonylmethoxy)calix(4)arenes, H.M. Chawla and K. Srinivas, *Ind. J. Chem.*, 1993, **32B**, 1162-1164.
7. Synthesis of new chromogenic calix(4)arenes bridged at the upper rim through bisazobiphenyl linkages, H.M. Chawla and K. Srinivas, *J. Org. Chem.* (In Press).
8. Molecular receptors for recognition: Synthesis of new triple storey calix(n)arenes H.M. Chawla and K. Srinivas; *Proc. 10th Int. Symp. on Organic Synthesis*, Bangalore, Dec. 11-16, 1994, p.225.

9. Molecular Diagnostics: Synthesis and evaluation of new chromogenic calixarenes as potential molecular diagnostics for recognition of amines. H.M. Chawla and K. Srinivas; *Proc. Int. Symp. on Perspectives in Bio-organic Chemistry*, New Delhi, Dec. 8-9, 1994, p.59.

10. Synthesis and characterization of new fluorescent calix-coumarins, H.M. Chawla and K. Srinivas, *Proc. 2nd Int. Workshop on Calixarenes and Related Compounds*, Japan, June 2-4, 1993, p.18.

11. Molecular recognition of 2,6-naphthoquinone by 5,11,17,23,29,35-Hexatert-butyl-37,38,39,40,41,42-hexahydroxycalix(6)arene, H.M.Chawla and K.Srinivas, *Proc. 2nd Int. Workshop on Calixarenes and Related Compounds*, Japan, June 2-4, 1993, p.35.

12. Synthesis of new deep cavity calixarenes for selective extraction of silver metal cation, H.M. Chawla and K. Srinivas; *J. Chem. Soc., Chem. Commun.*, (Communicated).

13. Synthesis of new bisazobiphenyl capped calix(4)arenes and their bearing on the mechanism of calixarenes with amines, H.M.Chawla and K.Srinivas, *Supra molecular Chemistry* (communicated).

14. Remarkable effect of reaction parameters on regioselective methylation of calix(n)arenes, H.M.Chawla and K.Srinivas; *Tetrahedron Letters* (communicated).

15. Chromogenic calixarenes: New reagents for detection and discrimination of amines., *J. Chem. Soc., Chem. Commun.*, 1995 (communicated).

NOTES

1. All the 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 or chloroform on a [5-DX] Nicolet FT-IR spectrophotometer. The abbreviations such as s,w,m,sh,bs,w-sh and m-sh refers to strong, weak, medium, sharp, broad and strong, weak and sharp, medium and sharp respectively.
4. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-D_6 on Jeol JNM-FX100 (IIT Delhi) and Varian XL-300 (RSIC, Bombay) FT-NMR spectrometers using TMS as an internal standard and value reported are in δ scale. The abbreviationssuch as s,bs,d,t,q and m indicate singlet, broad singlet, doublet, triplet, quartet and multiplet respectively.
5. Mass spectra were recorded on [Jeol-JMS D300/JMA-2000] Gas Chromatograph-Mass Spectrometer at 15 eV.
6. The molecular mass of several calix(n)arenes synthesized was determined by vapour pressure osmometry using vapour pressure osmometer (Knauer, W.Germany).
7. Elemental Analysis was carried on Perkin Elmer's 240C CHN Analyzer.
8. The completion of the reaction and the purity of the synthesized compounds were checked by TLC performed on silica gel (BDH, Bombay) plates using iodine for visualizing the spots.

9. The solvents used were purified and dried before use.

10. Pet. ether refers to the fraction with boiling point range of 60-80°C.

11. For the sake convenience, the names of calixarenes used in this thesis have been further shortened. For example, 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetra hydroxycalix(4)arene has been usually referred as p-tert-butylcalix(4)arene while 5,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexahydroxycalix(6)areneand 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-tetrahydroxy calix(4)arene, 37,38, 39,40,41,42-hexahydroxycalix(6)arene and 49,50,51,52,53,54,55,56-octahydroxy calix(8)arene have been shortened to tetrahydroxycalix(4)arene, hexahydroxy calix(6)arene and octahydroxycalix(8)arene respectively.

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