RESUME

The literature on functionalized supramolecules like calixpyrrole and their analytical applications has been comprehensively covered. The aim and scope of the present work has been discussed.
# TABLE OF CONTENTS

1. **Introduction to Supramolecular Chemistry** 004

2. **The Chemistry of Calixpyrrole** 008
   2.1. Historical development 009
   2.2. Mechanism 011
   2.3. Different conformers of calix[4]pyrrole cycles formed 012

   3.1. One-pot [1+1+1+1] condensation 013
   3.2. [2+2] Condensation 016
   3.3. [3+1] Condensation 017

4. **Modification in Calix[4]pyrrole by Functionalization** 021
   4.1. Modification at the N-rim 021
   4.2. Functionalization at the β-position (C-rim) 022
   4.3. Functionalization at the meso-position (bridge position) 027

5. **Functionalized Calix[4]pyrroles and their Applications** 039
   5.2. Calix[4]pyrrole-based electrochemical sensors 052
   5.3. Calix[4]pyrrole-based HPLC support 057
   5.4. Polymer-bonded calix[4]pyrrole and their chelating properties 058
   5.5. Miscellaneous applications of calix[4]pyrrole macrocycles 060

6. **Synthesis of Higher order Calixpyrroles** 063
   **Aim and Scope** 065
   **References** 067
1. INTRODUCTION TO SUPRAMOLECULAR CHEMISTRY

Supramolecular chemistry, as it is now defined, is a young discipline dating back to the late 1960s and early 1970s. However its concepts and roots and indeed many simple (and not-so-simple) supramolecular chemical systems, may be traced back almost to the beginning of modern chemistry [1]. Strictly speaking, a supramolecule is beyond the normal concept of a molecule. As a large engineered “molecule”, a supramolecule has many subunits, each designed to perform a specific task. Therefore, while a supramolecule is still a single molecule, it is engineered to function like a large complex compound. In a supramolecular system the components are held reversibly by intermolecular forces, but not by covalent bonds. These intermolecular forces include Van der waals molecular interaction, electrostatic interaction and hydrogen bonding [2]. Recent research progress in supramolecular science is so striking that it has attracted the attention of many scientists from both the physical sciences and the biological sciences division. Supramolecular materials have astonishing applications from quantum dots to biomedicine and bioinformatics, from artificial intelligence to virtual reality. With such widespread application, scientists have argued that supramolecules will be the chemical building blocks of the future [3]. On the back cover of Nobel Laureate Lehn’s book, Supramolecular Chemistry: Concepts and Perspectives, the following inspiration on supramolecular science is offered [3].

“Supramolecular chemistry embodies the creative power of chemistry.
By its very essence, by its ability to create and through the beauty of their object, chemistry is an art as well as a science. Indeed, it fashions entire new world that do not exist before they are shaped by the hand of the chemist, just as matter, shaped by the hand of the sculpture, becomes a work of art.”
Introduction

The aim to amalgamate a variety of host molecules is a demanding task in the field of molecular recognition chemistry because of the implausible qualities manageable by forming supramolecular complexes from the host and guest molecules [4]. In other form we can say, the advent of a new host compound is crucial for development of highly advanced functional materials such as high performance catalyst, extremely sensitive sensors, ultra fine separation materials etc. For a compound to make a useful host it is necessary that the basic molecular scaffold should have impending aptitude for molecular recognition with ready feasibility to the varying chemical modifications for drawing out the best performances of the molecule for a specific application. Thus a hopeful candidate, host compound should be not only readily synthesized in large quantities but also easily modified for maximizing molecular recognition power towards relevant guest molecules [5].

One such host molecule which perfectly matches above requirements is calix[4]arenes, chemistry of which has been one of the most extensively developed in the field of supramolecular chemistry during the span of last 20 years [6]. Calix[n]arene, a macrocyclic compound, composed of phenolic units is linked with methylene groups at the o, o’ positions [6]. Calixarenes have been actively studied and utilized as the third generation of host compounds in addition to the well known crown ethers [7] and cyclodextrins (Figure 1) [8].
Figure 1 Structure of cyclodextrin (I), crown ether (II), calix[4]arene (III), calix[4]pyrrole (I) and porphyrin (2).

Calixarenes, a class of cyclic phenolic compounds, are called so due to their shape and structure [6]. The term calixarene was given by C. D. Gutsche [1] in 1978. The name “calixarene” is derived from Greek word, *calix* meaning *vase or cone* shaped conformation. Calixarenes are often described as “macrocycles with almost unlimited possibilities [9] due to their versatility and utility as host molecules, which is seen from the ease in the synthesis of the basic platform and well set functionalization at both the rims, so as to build a new modified three dimensional structures [6], two different zones can be distinguished in calixarenes, viz. the region...
of phenolic hydroxy groups and the *para*-position of the phenols, which are called the ‘lower rim’ and the ‘upper rim’ of the calixarene respectively (Figure 2).

![Figure 2](image-url) Different zones of calix[4]arene.

Calixarenes may be modified by tuning its size, depth or conformation of π e-rich cavity and functionalization at rim(s), provide receptors with targeted properties [6]. The replacement of their phenolic unit(s) by heterocycle(s), constitute heterocalixarenes [11] classified according to the category of the subcycle(s). The nature of subcycle(s) reveals electron rich or deficient cavity and varied transformation profile for hetero-calixarene systems. Therefore, calixarenes may be further divided into following two broad classes,

1) **Hetero-calixarenes**: When organic moiety is replaced by pyrrole, furan, pyridine etc. they are known as hetero-calixarenes.

2) **Hetera-calixarenes**: When methylene junctions occupy elements like S, O, N etc. they are known as hetera-calixarenes.

Thus, a range of rational design of hetero-calixarene receptors, with possibilities of wider range of non-covalent interactions and consequent recognition events than calixarenes, can be predicted. These hetero-calixarenes possess unique supramolecular characteristics and present interesting chemical and physicochemical properties as well as wide applications [10].
Calix[4]pyrrole belongs to the family of hetero-calixarene macrocycles, which has four pyrrole units instead of phenolic units (Figure 1). Various reviews have appeared on their synthetic methodologies and applications during last 10 years [11-14]. Synthesis and applications can be viewed from these reviews published during last decade.

2. THE CHEMISTRY OF CALIXPYRROLE

Calix[4]pyrrole 1, formally known as “pyrrole-acetone” are venerable class of tetra-pyrrolic macrocycles. Originally coined meso-octasubstituted porphyrinogens. Porphyrinogens [15] are naturally occurring colourless macrocycles consisting of four pyrrole rings linked through α (i.e. pyrrolic 2 and 5) or meso like positions by sp³-hybridized carbon atoms. The most common formulation of this system is a result of the condensation of acetone and pyrrole, which leads to the formation of a tetra-pyrrolic macrocycle structurally similar but electronically different than porphyrin in such a way that 18π electron aromatic structure cannot be formed in calix[4]pyrrole. This imparts drastically different properties to it (Scheme 1), where each pyrrole is electronically independent and consequently, can donate one hydrogen bond.

Calix[4]pyrroles are easy to make class of neutral macrocycles and differ from the porphyrin. Calix[4]pyrrole (non-aromatic system) and porphyrin (aromatic system) are obtained from the condensation of pyrrole with an electrophile. In case of calix[4]pyrrole, the electrophile is a ketone whereas in the case of porphyrin it is generally aldehyde (Scheme 1). Calix[4]pyrrole macrocycles can not be oxidized to their corresponding aromatic porphyrin.
Scheme 1 Schematic representation showing the different behavior of calix[4]pyrrole 1 and porphyrin 2 with respect to oxidation.

2.1. Historical development

In 1886, a white crystalline material was synthesized by condensing pyrrole with acetone in the presence of hydrochloric acid by Baeyer [16]. Later considering the same work of Baeyer, Dennstedt and Zimmermann (1886) [17], also studied this reaction, using “Chlorzink” as the acid catalyst. Thirty years later, Chelintzev and Tronov repeated this reaction and proposed a cyclic tetrametric porphyrinogen structure for the product, which later proved to be correct.
In 1955, Rothemund and Gage [18] improved this synthesis by using methane-sulfonic acid as the acid catalyst. Other than these important findings, this class of compounds were studied, most of which merely focused on the refined synthesis of these macrocycles and their meso-substituted derivatives [19-20]. In early 1970s, Brown et al. [19] modified the procedure of Chelintzev et al. [20] which resulted in getting tetra-spirocyclohexylcalix[4]pyrrole 3 (Figure 3) in decent yield by condensing cyclohexanone and pyrrole in the presence of acid.

Figure 3 Tetra-spirocyclohexylcalix[4]pyrrole 3

In 1990s interest in these macrocycles was renewed by the extensive work of Floriani and co-workers [21] on the metallation and attendant synthetic chemistry of deprotonated-calixpyrroles. Mid of 90s Sessler and co-workers [22] discovered that the NH array present in these species can act as a binding site for anionic and neutral guest species. These calix[4]pyrrole macrocycles which were known as porphyrinogens because of their interesting conformational behaviour it drew attention to the clear differences in analogy between them and the calix[4]arenes. This analogy coupled with the fact that as these species carry alkyl or aryl groups in the meso-positions and hence are not susceptible to oxidation (to produce either porphyrin or less oxidized macrocyclic products), led them to propose that they should be re-named as calix[4]pyrroles.
Recently, Ballester and co-workers showed interest in current trend of endowing supramolecular gels with stimuli responsive functionality that could be the basis of smart materials useful in areas such as controlled drug release, sensing or tissue engineering among others [22].

2.2. Mechanism

The mechanism for the formation of calix[4]pyrrole by the acid catalyzed condensation reaction [23-24] has been studied in detail. Calix[4]pyrrole - a non-conjugated macrocycle, is formed by electrophilic α-substitution of pyrrole by ketone, acid-catalyzed oligomerization and spontaneous non-template cyclization wherein four pyrrole units are combined (Scheme 2). The synthetic methodologies for calix[4]pyrrole are generally simple, but the yield obtained is considerably less due to the formation of linear by products and/or polymerization. The reaction conditions and substituents at the ketone functionality also play a significant role in achieving quantitative recovery of calix[4]pyrrole.

2.3. Different conformers of calix[4]pyrroles

Calix[4]pyrrole adopts similar conformations same as to calix[4]arenes: 1,3-
alternate; 1,2-alternate; partial cone and cone (Figure 4). The most stable form
predicted and having experimentally lowest energetic is the 1,3-alternate
conformation where the pyrrole rings are found to be alternate in an up-down-up-
down setup [25].

Figure 4 Representation of the limiting possible conformations conceivable for

Jorgensen [25] investigated the complexation of compound 1 with anions by
carrying out energy minimizations in the gas phase and via Monte Carlo simulations
in a dichloromethane milieu using the OPLS force field. The gas phase calculations
revealed that 1,3-alternate conformation of compound 1 was most stable in the
absence of a halide anion, while in the presence of halide anions the cone
conformation was the most stable among all possible conformations (Figure 5).

Figure 5 Cone like halide complex of compound 1.
Wu et al. [26] also studied the conformation features and anion binding properties of compound 1 theoretically. Both, gas phase and solution phase (CH$_2$Cl$_2$) studies revealed a predicted stability sequence for the various conformers: 1,3-
alternate > partial cone > 1,2-alternate > cone.

3. VARIOUS SYNTHETIC TECHNIQUES FOR CALIX[4]PYRROLE MACROCYCLES

There are four major synthetic techniques for the synthesis of calix[4]pyrrole:

3.1 One-pot [1+1+1+1] condensation
3.2 [2+2] Condensation
3.3 [3+1] Condensation
3.4 Eco-friendly synthesis of calix[4]pyrroles using different catalysts

Where the numbers in the brackets refer to the number of pyrrolic subunits in the precursors involved. Among these, one-pot approach is most popular for preparing simple calix[4]pyrrole.

3.1. One-pot [1+1+1+1] condensation

The one-pot synthesis of calix[4]pyrroles involves the condensation of pyrrole(s) and ketone(s) in 1:1 ratio in the presence of an acid catalyst e.g. hydrochloric acid, methanesulfonic acid, trifluoroacetic acid, and boron trifluoride diethyl etherate. Solvents generally used for the reactions are methanol, ethanol, acetonitrile, and dichloromethane, but in some reactions, ketones are used both as reactant as well as solvent for condensation with pyrrole. Depending on how many types of pyrroles or ketones are used in the reaction, one-pot condensation can be categorized into:

- Homo-condensation
- Mixed condensation

### 3.1.1. Homo-condensation

In this type of condensation (homo-condensation) a specific pyrrole reacts with a specific ketone. According to the symmetry of the pyrrole or ketone components, these homo-condensations can be further classified as *symmetric homo-condensations* and *asymmetric homo-condensations*.

#### Symmetric homo-condensations

A symmetric homo-condensation represents a reaction involving a symmetric pyrrole and a symmetric ketone. Generally such reactions produce an easy to separate major product in good yield. One typical example of symmetric homo-condensation is the synthesis of *meso*-octamethylcalix[4]pyrrole 1 *via* the condensation of pyrrole with acetone in a 1:1 ratio in methanol using methanesulfonic acid as an acid catalyst [22]. Column chromatography separation affords 1 in 60-80% yields by symmetric homo-condensation (Scheme 1).

#### Asymmetric homo-condensations

An asymmetric homo-condensation normally involves the reaction of pyrrole with an asymmetric ketone. For example, condensation of pyrrole with 4-hydroxyacetophenone, 3-hydroxyacetophenone and 3, 5-dihydroxyacetophenone in methanol in the presence of methanesulfonic acid resulting the desired calix[4]pyrrole [27-28] 4a, 4b and 4c respectively in good yield (Scheme 3). The product actually consists of a mixture containing different configurational isomers; which are difficult to separate and may require tedious separation procedures including careful column chromatography.

3.1.2. Mixed condensation

Mixed condensation involves the condensation of more than one kind of pyrrole with a specific ketone or of a specific pyrrole with more than one kind of ketone. In this type of condensation reactions, mixtures of products are formed, so the reactant ratio must be carefully controlled in order to optimize the yield of the desired products. However, once separated, the various calix[4]pyrroles can often find application in a variety of areas, because mixed condensation product provides a good platform for selective functionalized systems.

Calix[4]pyrrole with a carboxylate pendant arm (monoester) 5 [29] was obtained by acid catalyst condensation of ethyl pyruvate and acetone with pyrrole, in a 1:3:4 ratio. Column chromatography (silica gel; dichloromethane/hexane, eluent) afforded 5 in 14% yield (Scheme 4).

Calix[4]pyrrole 6 containing monoester group on meso position was synthesized by co-condensation of methyl-4-acetyl benzoate pyrrole and acetone (Scheme 5) in a ratio of 1 : 4 : 3 with methanesulfonic acid as an acid catalyst, stirred in methanol [30]. Yield of the product obtained was about 12%


3.2. [2+2] Condensation

Acid-catalysed condensation of two dipyrromethane units with ketone units comes under [2+2] condensation method. In this method dipyrromethane units are synthesized by condensation of a pyrrole unit with a single ketone unit (normally different from those used in the synthesis of the dipyrromethanes) to achieve the predicted product. This [2+2] approach represents an important means of constructing
a variety of calix[4]pyrrole macrocycles, which otherwise can not be obtained by one-pot condensation.

Compounds 7-8 may be obtained readily using a [2+2] approach. These particular products were synthesized from the dipyrrmethane precursors (Scheme 6). These precursors were in turn prepared from the condensation of pyrrole with aryl ketones in presence of trifluoro acetic acid using boron trifluoride diethyletherate as the catalyst. Once obtained, these precursors were condensed with acetone, acting both as a reactant as well as a solvent. This gave cyclic products 7-8 in decent yield. [31].

![Scheme 6 Synthesis of compounds 7-8 via [2 + 2] condensation.](image)

**Scheme 6** Synthesis of compounds 7-8 via [2 + 2] condensation.

3.3. [3+1] Condensation

[3+1] Condensation involves the reaction of a tripyrrane or its derivative with a pyrrole or its derivative in the presence of an acid catalyst. The reaction products are generally obtained in low yield due to the poor stability of most tripyrranes in the presence of acid. Infact, no true calix[4]pyrroles have been synthesized using this method.

Jeppesen et al. [32] reported that a “pseudo” calix[4]pyrrole 11 was synthesized using the [3+1] method (Scheme 7). Tripyrranediethanol 9c was
synthesized by reducing the corresponding tripyrranedialdehyde 9b, which was synthesized by formylation of tripyrrane 9a [33] with sodium borohydride in a mixture of tetrahydrofuran (THF) and methanol. Treatment of the resulting tripyrrane diol with the tetrathiafulvalene-containing pyrrole 10 in dry acetonitrile using boron trifluoride diethyl ether as an acid catalyst afforded the mono-tetrathiafulvalenecalix[4]pyrrole 11 in 21% yield.


Jeppesen et al. [34] later synthesized the two mono-TTF calix[4]pyrroles 17 and 18 shown in (Scheme 8). Both derivatives were functionalized with an alkanethiol anchor group (protected with an acetyl group). Mono pyrrole tetrathiafulvalene MPTTF derivatives 12, 13 with approximately two equivalents of the tripyrrane 14 synthesized by above literature procedure, in a mixture of Me₂CO
and CH₂Cl₂, in the presence of one equivalent of tetrabutylammonium chloride (TBACl) and excess trifluoroacetic acid (TFA) resulted in the mono-TTF calix[4]-pyrroles 15 or 16 in 23 and 22% yield, respectively. The precursors were heated under reflux temperature in the presence of excess potassium thioacetate (KSAc) in anhydrous THF which afforded the corresponding thioesters 17 or 18 in 88 and 69% yield, respectively.


To achieve calixpyrrole macrocycles in high yield by an environmentally clean process is of topical interest so as to meet the increasing demand for reducing the pollution hazards caused by the usage of homogeneous acid catalysts [35]. Heterogeneous catalytic synthesis is known to be one of the most effective ways to the selectivity of calixpyrroles with high yield and it has the potential to be scaled up at relatively low cost. Properly functionalized and structurally ordered mesoporous molecular sieves such as MCM-41 was found to be the most effective heterogeneous...
catalyst for the synthesis of calix[4]pyrrole. Various metal ion substituted MCM-41 samples were synthesized and were used to improve the yields of calix[4]pyrrole. Co-MCM-41 was found to give maximum yields. The effects of varying Si/Al ratio in MCM-41, molar ratio of various reactants, and the role of solvent towards this macrocyclization reaction have also been studied [35]. Calixpyrroles were also synthesized using zeolite based molecular sieves as catalyst and sorbents in thin layer chromatography (TLC) to achieve in single step by in situ synthesis from pyrrole with and ketones under microwave irradiation [35]. Different zeolite catalysts such as HZSM-5, HY and mesoporous Al-MCM-41 molecular sieves were used for above same reactions.

A facile, highly efficient and eco-friendly protocol for the synthesis of calix[4]pyrrole in excellent yield is reported by Sarkar et al. [36]. The binding of methanol, ethanol and N,N-dimethylformamide to meso-tetra(methyl) tetrakis(ethyl)calix[4]pyrrole in both solid and solution with the exhibition of multifashion hydrogen bonding as shown by X-ray crystallography were also studied. The thermodynamic stability of these host-guest inclusion complexes [36] were determined by exploiting thermal gravimetric analysis (TGA) and differential thermal analysis (DTA). Recently, S. M. S. Chauhan et al. [37] have developed a facial and efficient protocol for the synthesis of calix[4]pyrroles and N-confused calix[4]pyrroles in moderate to excellent yield by reaction of dialkyl or cycloalkylketones with pyrrole, catalyzed by reusable AmberlystTM-15 under eco-friendly conditions.
4. MODIFICATION IN CALIX[4]PYRROLE BY FUNCTIONALIZATION

Calix[4]pyrroles have been found to have good complexing affinity towards anions and neutral guests through hydrogen of pyrrolic nitrogen atoms. Complexes of calix[4]pyrroles with anions and neutral atoms were not very stable. To improve the binding abilities, the three potential sites available with calix[4]pyrrole skeleton namely, the β-position (C-rim), the meso-position (bridge-position) and N-rim which can be used for the introduction of different functionality.

4.1. Modification at the N-rim

Modification at N-rim in calix[4]pyrroles has been reported by Takata et al. [38] meso-octaethylcalix[4]pyrrole 19 on reaction with sodium hydride and methyl iodide in the presence of 18-crown-6 in THF resulted in formation of variety of N-methylated calixpyrroles 20-25 (Figure 6). The variation of product was dependent on the concentration of methyl iodide. When one equivalent of methyl iodide was used, the main product was the mono-N-methylated derivative 20. On the other hand, use of 2 equivalent methyl iodide resulted in predominant formation of 22, 23, and 24, where 22 was isolated predominantly. The authors have also studied the X-Ray diffraction analysis of 22. The resulting structure revealed that the macrocycle adopts a 1,3-alternate conformation in the solid state.

Alkylation with ethyl iodide resulted in the isolation of the mono-ethyl derivative 25 only. Takata et al. considered that, in solution, reaction of calix[4]pyrrole 19 with butyl lithium results in the formation of a tight ion pair between the deprotonated calix[4]pyrrole nitrogen atoms and the lithium cations. Under this reaction conditions, Takata et al. proposed that the 18-crown-6 serves to break up this ion pair, thereby allowing N-alkylation to occur. While far from
established, important support for this hypothesis comes from the solid state structural analysis of Floriani [39].

![Figure 6 N-methylated calixpyrroles.](image)

**Figure 6** N-methylated calixpyrroles.

### 4.2. Functionalization at the β-position (C-rim)

Functionalization at β-positions, also called C-rim functionalization, has been extensively explored by Sessler at el. [40] and S.M.S Chauhan et al. [41] recently. The most popular C-rim functionalization is β-mono functionalization and β-octa functionalization, since they produce only one dominant product. β- functionalization procedures in between these two extremes have not been extensively explored due to the production of multiple products, poor reaction control and difficulties in achieving product separation.

During the last two decades, studies have flourished on functionalized calix[4]pyrroles to understand, improve and tuning the binding affinity and selectivity of different anions. Recently S.M.S. Chauhan and co-workers [41] reported synthesis
of 2-arylazo-meso-octamethylcalix[4]pyrroles 28-33 functionalized at β–position and their role in binding of different anions under different conditions (Scheme 9).

It is found that development of anion sensors and receptors is an important area of supramolecular chemistry in chemical and biological processes. S.M.S. Chauhan et al. [42] has developed two novel 3,12- and 3,7-bis(4'-nitrophenyl)-azo-5,5,10,10,15,15,20,20-octamethyl calix[4]pyrroles 34,35, introducing the chromogenic group at two different position and studied them as potential anion binders due to their rich and unique complexation behaviour (Figure 7).

Scheme 9 Synthesis of 2-arylazo-meso-octamethylcalix[4]pyrroles functionalized at β–position
β-Octabromocalix[4]pyrrole 36 [40] was synthesized by reacting 1 with eight equivalents of NBS reagent in THF and reflux for five hours and yield obtained was 90%. The method adopted was an alternative method to the earlier method of one-pot condensation of 3,4-dibromopyrrole with acetone which proved to be unproductive due to the instability of 3,4-dibromopyrrole under the occurring reaction conditions.

(Scheme 10)

The reaction of monopyrrolo-TTF with an excess of TFA and a mixture of CH₂Cl₂ and Me₂CO yielded 18% of tetrathiafulvalene calix[4]pyrrole 37 (Scheme 11)
This system can act as an effective receptor for neutral electron acceptors such as 1,3,5-trinitrobenzene, tetrafluoro-\(p\)-benzoquinone, tetrachloro-\(p\)-benzoquinone, and \(p\)-benzoquinone.

\[
\begin{align*}
\text{PrS} & \quad \text{SPr} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{N} & \quad \text{NH} \\
\text{C} & \quad \text{CH} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{NH} \\
\text{C} & \quad \text{CH} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{PrS} & \quad \text{SPr} \\
\end{align*}
\]


Miyaji et al. [44] synthesized a series of halogen bearing \(\beta\)-rim mono-substituted calix[4]pyrroles 37-40 by adding an appropriate electrophilic halogen source in a finely tuned manner to form mono-functionalized calix[4]pyrroles as shown in Scheme 12. This study emphasized the importance of electron withdrawing or donating groups on the \(\beta\)-rim periphery in terms of regulating the anion affinity of calix[4]pyrroles.

Chupakhin et al. [45] reported the first example of direct heterylation of calix[4]pyrroles in 2004. Heterylation of calix[4]pyrroles was obtained by reacting 1, 2, 4-triazines derivatives (belonging to the most electrophilic heterocycles) with calix[4]pyrrole to give stable nucleophilic addition products 41 and 42. The heterylation of calix[4]pyrrole was done keeping in mind to increase the complexing ability of calix[4]pyrrole by introduction of heterocyclic fragments (Scheme 13).

Scheme 13 Heterylation of calix[4]pyrroles

Augusto C. Tome et al. used 3-(octamethylcalix[4]pyrrol-2-yl)propenal 43 used as precursors of azomethine ylides which was trapped in situ with a range of
dipolarophiles, such as 1,4-benzoquinone, 1,4-naphthoquinone. Azomethine ylides generated by reaction of 43 with N-methylglycine could be trapped with dipolarophiles to afford new β- substituted octamethylcalix[4]pyrrole derivatives 44, 45 in moderate yields [46]. These cycloadducts showed high affinity constants for fluoride anions and selectivity for acetate anions when compared with dihydrogen phosphate anions.


4.3. Functionalization at the meso-position (bridge position)

Functionalization at bridge position or meso position of calix[4]pyrrole by introduction of aryl or other rigid groups influences the increase in binding capacity
for selectivity of cations, anions or neutral guest molecules. Modifying the calix[4]pyrrole skeleton by different functional groups can also hold great potential to act it as a ditopic receptor.

Calix[4]pyrrole with a carboxylate pendant arm (monoester) 46 [47] was obtained by acid catalyst condensation of methyl 4-acetylbutyrate and cyclohexanone with pyrrole, in a 1:1:2 ratio. Column chromatography (silica gel; dichloromethane, eluent) afforded 46 in 12% yield (Scheme 15). A good example of meso-modification was provided by the first type of carboxyl-functionalized calix[4]pyrrole [44] When the proper ratios were used, taking into account the slow reactivity of the δ-ketoester, the meso-“hooked” calixpyrrole (Scheme 15) was formed in reasonable yield. Hydrolysis of the ester generated the free carboxylic acid functionalized calix[4]pyrrole 47 (Figure 8), which could be used for further derivatisation.

Scheme 15 Calix[4]pyrrole with a carboxylate pendant arm

Figure 8 Carboxylic acid functionalized calix[4]pyrrole.
Revising the approach for synthesis of Calixpyrrole, Sessler et al. [48] produced amine functionalized calixpyrroles. Specifically, condensation of benzyloxy carbonyl (Cbz) protected 3-aminoacetophenone, 3-pentanone and pyrrole in the presence of BF₃·Et₂O was found to afford the mono-functionalized calix[4]pyrrole 48. Subsequent deprotection by Pd–C gave the mono-amine functionalized calixpyrrole 49 in 23% yield (Scheme 16).


In an effort to further improve the selectivity of calixpyrrole derivatives for particular anions and especially the chloride-over-phosphate selectivity, calix[4]pyrrole systems bearing substituted aryl groups in the meso-positions were prepared and their anion coordination properties had been examined [27]. As detailed in reported paper, calix[4]pyrrole 50a consists of four isomers that can be separated via column chromatography. According to the relative position of the bulky substituted phenyl group, these isomers were identified as being the αβαβ, ααββ,
αααβ, and αaaa configurational isomers, where the “α” and “β” nomenclature follows the standard porphyrin convention (Scheme 17).

For instance, each of the isomers of 50a was found to display a considerably higher affinity for anions than did the corresponding isomers of the methoxy substituted system, 50b. Further, as a general rule the anion affinities of both species were found to be less than those of parent calix[4]pyrrole 1. This was an unexpected result that contradicts author’s expectation that the deep cavities of 50a and 50b would serve to increase anion affinities in absolute terms.

Further modification at meso-position was obtained by reaction of compound 50a with ethylbromoacetate in dry acetone in presence of K₂CO₃ with heating at reflux for 5 days [49]. The tetraester derivative 51 was isolated as a white powder in 76.5% yield. Amide macrocycle 52 was synthesized by reaction of compound 50a with 2-chloro-N,N-dimethylacetamide and potassium iodide in dry acetone with

---

**Scheme 17** Isomers of “deep cavity” calix[4]pyrrole.
stirring for 5 days and was isolated in 50% yield (Scheme 18). These extended cavity ester and amide calix[4]pyrrole macrocycles have shown to bind fluoride exclusively in DMSO-$d_6$ solution.


methyl-tetra[N-(2-phenoxyethyl)-N'-phenylurea]calix[4]pyrrole \textit{53d}, \textit{meso}-tetra methyl-tetrakis(thiophene)calix[4]pyrrole \textit{53e}, and \textit{meso}-tetramethyl-tetrakis{4-[2-(ethylthio) ethoxy]phenyl}calix[4]pyrrole \textit{53f} in non-aqueous media have been discussed by Angela et al. (Figure 9) [50]. Given that these derivatives have potential to interact with anion and cation (through the donor atoms of the pendant arms of the di-substituted methylene bridges), their complexation with anions and cations have been investigated through \textsuperscript{1}H NMR, conductance and calorimetric studies.

\textbf{Figure 9} Calix[4]pyrrole derivatives.

Novel deep cavity calix[4]pyrroles \textit{54} and \textit{55} derived from steroidal ketones were synthesized and studied for their ability to effect the selective recognition of appropriate sized organic anions (Figure 10) [51]. One good receptor, the polyhydroxylated \textit{aaaaβ} configurational isomer of \textit{55b}, was found to bind both, tartaric acid and mandelic acid selectively, while \textit{54} and \textit{55a} were found to be far less
effective as receptors for these guests. These findings were rationalized in terms of a combination of both, specific anion-pyrrole NH hydrogen bonding interactions and less well-defined steroid-substrate interactions.

In 2003, Gale et al. [52] reported the synthesis of a new meso-modified calix[4]pyrrole, namely the pentapyrrolic calix[4]pyrrole 57 (Scheme 19). The fifth pyrrole unit, attached synthetically to a meso-position, was expected to act as an ancillary hydrogen bonding donor, thereby enhancing the anion affinities of 57 relative to simple calix[4]pyrroles. Tripyrrolylmethane 56 was synthesized via methanesulfonic acid catalyzed condensation of pyrrole with 2-acetyl-3,4,5-tribromopyrrole. But, the [2+2] mixed condensation of 56 with dimethyl dipyrrromethane in acetone afforded 57 in 14% yield.

![Figure 10](image_url)  
**Figure 10** Structure of steroidal calix[4]pyrroles.
Ballaster et al. recently designed new calix[4]pyrroles having extended aromatic cavities using 4 ureas in the para position of the meso phenyl positions. This elaboration of the upper rim was completed in two synthetic steps starting from \( \alpha \alpha \alpha \) tetranitro isomer 58 of the calixpyrrole obtained by acid catalysed condensation of p-nitro methyl ketone and pyrrole (Scheme 20). These derivatives 60, 61, 62 were specially designed to form a capsule and encapsulate 4, 4-bipyridine bis N-oxide [53].
Scheme 20 Synthesis of calix[4]pyrrole with extended aromatic cavities

Novel adamantane derivatives 63-67 of calix[4]pyrroles (Scheme 21) were synthesized by Kate Mlinaric-Majerski and co-workers and characterized by X-ray powder diffraction method. Calix[4]pyrrole derivative binds with Cl\(^-\) ion in DMSO solution and also in solid state. Kata Mlinaric-Majerski and co-workers were first to report complexation with anion in solid state [54].
Drasar et al. [55] synthesized two new steroidal spiroannulated calix[4]pyrroles 69 and 71, derived from bile acids (lithocholate). These calix[4]pyrroles were prepared by the acid catalyzed condensation of methyl-3,3-bis(pyrrol-2-yl)-5β-cholan-24-oate with carbonyl compounds and with 2,2'-propane-2,2-diylbis(1H-pyrrole), respectively (Scheme 22).

Pavel Drasar et al. [56] have prepared first calix[4]pyrrole 74 containing unprotected carbohydrate moiety directly linked to meso-position of oligopyrrole by stable “C-glycosidic” bond (Scheme 23).

**Scheme 21** Admantine derivatives of calix[4]pyrroles
Scheme 23 Calix[4]pyrrole containing unprotected carbohydrate

Ahmet Akar et al. synthesized novel *meso*-tetracarboxylic acid and *meso*-tetraester functionalized calix[4]pyrroles by condensation of pyrrole with levulinic acid and ethyl pyruvate in sufficient yields. In addition, mixed condensation products were also be synthesized using this method [57].

72 +  

\[
\begin{align*}
\text{MeSO}_3\text{H} & \quad \text{MeOH} \\
\text{MeSO}_3\text{H} & \quad \text{MeOH}
\end{align*}
\]

74

73

75
Scheme 24 Novel meso-tetracarboxylic acid and meso-tetraester calixpyrrole.

5. FUNCTIONALIZED CALIX[4]PYRROLE AND THEIR APPLICATIONS

Literature survey reveals that calixpyrroles have been used for various applications e.g. as optical sensors, electrochemical sensors, HPLC supports, anion transporting agents, chelating polymer and nonlinear optical materials etc.

Two main approaches (Scheme 25) have been used to get calix[4]pyrrole-based optical anion sensors,

In Covalent attachment approach a colorimetric or fluorescent reporter group is linked covalently to the calix[4]pyrrole skeleton. Perturbation of the electronic properties of these reporter groups upon anion complexation then produces a response detectable by visual or fluorescence-based means. Since 1999, numbers of covalently linked calixpyrrole-based optical sensor systems have been synthesized. Sessler et al. [58] reported a new library of covalently linked calixpyrrole derivatives, which showed that they could find application as anion sensors.

a) Covalent attachment

![Covalent attachment diagram](attachment_diagram.png)

Change in optical properties

b) Displacement assay

![Displacement assay diagram](displacement_diagram.png)

Change in optical properties of anion A₁

Scheme 25 Two approaches for optical sensors.

Augusto C. Tomé et al. [47] synthesized new calix[4]pyrrole derivatives 44 and 45, the azomethine yield generated from aldehyde 43 were successfully trapped in 1,3-
dipolar cyclo-additions with fumaronitrile and quinones. The resulting cycloadducts showed high affinity constants for fluoride anion and a significant selectivity for acetate when compared with dihydrogen phosphate.

The synthesis of new calixpyrrole derivatives were obtained from (E)-3-(meso-octamethylicalix[4]pyrrol-2-yl)propanol and its use in Knoevenagel reactions are described (Scheme 26). The resulting compounds display sharp changes in colour in the presence of fluoride, acetate, and dihydrogen phosphate anions. Compounds 78–81 showed quite different absorption spectra, displaying blue, orange, and yellow colours. The addition of fluoride, chloride, and acetate anions to sensor 79 resulted in an impressive change in colour while minor changes were observed for compounds 80 and 81. The addition of nitrate, nitrite and bromide anions caused almost no change in the colour of the four sensor solutions, indicating a low affinity for these anions [59].

Scheme 26 Calixpyrrole derivatives obtained from (E)-3-(meso-octamethylicalix[4]pyrrol-2-yl)propanal

(a) 1,3-bis(dicyanomethylidene)indane, AC₂O, reflux, 30 min; (b) indane-1,3- dione, Et₃N, THF, rt, 24 h; (c) malononitrile, Et₃N, CH₂Cl₂, rt, 24 h; (d) ethyl cyanoacetate, Et₃N, CH₂Cl₂, rt, 24 h.
A comparative study of the halide and benzoate anion binding properties of a series of phenyl, pyrrole and furan-strapped calix[4]pyrroles 82, 83 and 84 were carried out by J. L. Sessler et al. [60]. They found strapped calix[4]pyrrole derivatives to bind bromide and benzoate anion (studied as the corresponding tetra butyl ammonium salts) with near equal affinity in acetonitrile, although less well than chloride, as determined from NMR spectroscopic titrations. Out of three anions for which quantitative data were obtained (i.e. Cl⁻, Br⁻, PhCO₂⁻), the pyrrole-strapped system displayed the highest affinity, in the specific case of fluoride anion binding to the pyrrole-strapped receptor, two modes of interaction are inferred, with the first consisting of binding to the calix[4]pyrrole via NH-anion hydrogen bonds, followed by a process that involves deprotonation of the strapped pyrrolic NH proton.

Figure 11 A series of phenyl, pyrrole, and furan-strapped calix[4]pyrroles
A strapped calix[4]pyrrole bearing a 1,3-indanedione group at a β-pyrrolic position 85 has been synthesized and studied as a ratiometric cyanide selective chemosensor by C. H. Lee et al. [61]. A concentration-dependent bleaching of the initial yellow colour was observed upon addition of the cyanide anion. The bleaching, which was observed exclusively with the cyanide anion occurred even in the presence of other anions. Spectroscopic studies provide support for a mechanistic interpretation wherein the cyanide anion forms a complex with the receptor. A minimum inhibitory effect from other anions was observed, a feature that could be beneficial in the selective sensing of the cyanide anion.

Figure 12 A strapped calix[4]pyrrole bearing a 1,3-indanedione group at a β-pyrrolic position

A new catechol derived strapped calix[4]pyrrole 86 (Figure 13) bearing diether strap linked via alkyl chains have been synthesized and characterized for the first time. The strap with 1,2-diether link provided a relatively constrained geometry on its side of the calix[4]pyrrole moiety. This calix[4]pyrrole also exhibits enhanced
binding towards halide anions compared to simple calix[4]pyrrole apart from showing binding towards dihydrogenphosphate and acetate ions. The association constants were found to be quite similar to that found for orcinol strapped calix[4]pyrrole towards halide anions in general, but having a higher preference for chloride than bromide ion in particular. Further it showed very strong preference towards fluoride ion [62].

Three new chromogenic calix[4]pyrrole sensors 88-90 [63] were synthesized and characterized. Sensor 88 was prepared by an electrophilic aromatic substitution reaction of octamethylcalix[4]pyrrole 1 with tetra-cyanoethylene. Sensors 89 and 90 were obtained by condensation of formyl-octamethylcalix[4]pyrrole with 1-indanylidene-malononitrile and anthrone, respectively. The anion sensing ability of sensors 88, 89 and 90 was studied on a qualitative level by visual examination of the

![Figure 13 A new catechol derived strapped calix[4]pyrrole](image-url)
anion-induced colour changes in the solution of the sensors 88-90. To demonstrate the relevance of sensors 88-90 to health care applications [64] sensing experiments were performed in blood plasma at a high electrolyte concentration. Furthermore, studies with carboxylates of medical interest (salicylate, ibuprofen and naproxen) were performed using newly developed assay with sensors 88-90 embedded in polyurethane films (Figure 14).

Anzenbacher et al. [65] also synthesized, 1,3-indane-based chromogenic calixpyrroles with push-pull chromophores. The Knoevenagel condensation of 2-formyl-octamethylcalix[4]pyrrole with selected 1,3-indanedione derivatives gave sensors 91-94. The push-pull feature results in augmented signal output as well as in dramatic changes in anion selectivity exemplified by a 50 fold increase in acetate vs chloride selectivity compared to the parent calix[4]pyrrole (Figure 14).
The β-octaalkyl-substituted calix[4]pyrrole [66], the first to be prepared via a direct condensation reaction, was obtained by reacting the 3,4-alkyl-functionalized pyrrole with acetone in the presence of an acid catalyst. The synthesis and preliminary solution phase ion binding properties of the N-tosylpyrrolidine calix[4]pyrrole 95 are reported for first time. On the basis of $^1$H NMR spectroscopic analyses and isothermal titration calorimetry, it was concluded that, compared with the parent, β-unsubstituted calix[4]pyrrole 1, possesses significantly enhanced binding ability for halide anions in chloroform. Furthermore, 95 proved capable of solubilizing in chloroform solution the
insoluble salts like CsF and CsCl. These effects are ascribed to the interactions between the four tosyl groups present in 2 and the counter cations of the halide anion salts.

Figure 15 The β-octaalkyl-substituted N-tosylpyrrolidine calix[4]pyrrole

Two novel 3,12- and 3,7-bis(4'-nitrophenyl)-azo-5,5,10,10,15,15,20,20-octamethyl calix[4]pyrroles 34 and 35 were prepared and studied as potential anion binders for AcO⁻ and H₂PO₄⁻; the isomeric pair not only allowed for the colourimetric detection but also helped to discriminate these geometrically different anions from other anions [43].

Calix[4]pyrroles bearing appended pyrenyl groups 96, 97 at the meso-positions on one side of the calix[4]pyrrole have been synthesised and characterised by C. H. Lee et al. [67]. The host calix[4]pyrrole derivatives exhibited a selective increase in their fluorescence intensity upon the addition of Pb²⁺ or Cu²⁺. When excess chloride anion was added after subjecting the host to pre-complexation with
Pb\(^{+2}\), the cation-induced enhancement in fluorescence was sustained. On the contrary, no changes in fluorescence was observed when the calix[4]pyrrole host was first treated with chloride anion, followed by the addition of Pb\(^{+2}\). These results were found to be consistent with pre-complexation of Pb\(^{+2}\) not serving to inhibit the binding of chloride anion, while, by contrast, the initial interaction between a chloride anion and the calix[4]pyrrole cavity acts to inhibit the subsequent binding of Pb\(^{+2}\), possibly due to anion-binding-based constraints on the conformational flexibility (Figure 16).

![Figure 16](image)

**Figure 16** Calix[4]pyrroles bearing appended pyrenyl groups at the meso-positions

C. H. Lee et al. [68] synthesized and fully characterized calix[4]pyrroles bearing two fluorescent pyrenyl groups at the diametrical meso-positions on one side of the calix[4]pyrrole 98, 99. The preliminary solution phase anion-binding studies indicate that fluoride and chloride anion irreversibly binds to the pocket generated by the two pyrene pickets and the affinity for other anions is far less than those of fluoride anion resulting fast complexation/decomplexation kinetics. The observed higher affinity of chloride anion other than fluoride anion may be associated with stronger anion π interaction in the chloride complex with receptor (Figure 17).
A series of second generation calix[4]pyrrole anion sensors 100, 101, and 102 [48] were synthesized by coupling meso-monoaminecalix[4]pyrrole 37 with commercially available dyes as fluorescent tags (Figure 18). These adduct 100, 101, and 102 are based on dansyl, lisamine-rhodamine B and fluorescein, respectively. These were tested for their affinities towards the usual set of test anions via fluorescence quenching using a 0.01% v/v acetonitrile/water mixture. The presence of the second anion binding group alters the anion selectivity of the calix[4]pyrrole. Specifically, selectivity is enhanced for dihydrogenphosphate and pyrophosphate relative to chloride. The fluorescence of receptors 100, 101, and 102, were found to be quenched in the presence of anions.
Figure 18 Fluorescent receptors prepared by linking commercial dyes to the amino-functionalized calix[4]pyrroles.

The second displacement assay approach has not been explored much than the first approach. Still, it has been successfully exploited to produce different kind of colorimetric anion sensors [69, 70] which do not require any functionalization of the parent molecule. They discovered that when bound to meso-octamethyl calix[4]pyrrole 1, the 4-nitrophenolate anion X loses its intense yellow colour and the decrease in intensity was visible to the naked eye. Anions, such as fluoride, displaced the 4-nitrophenolate anion from the complex thereby restoring the native absorbance of the 4-nitrophenolate anion (Figure 19)
Figure 19  F⁻ dependent equilibrium between the meso-octa(methyl)calixpyrrole-4-nitrophenolate and meso-octa(methyl)calixpyrrole-fluoride.

An interesting example of a fluorogenic sensor based on displacement assays was discovered by Machado et al. [71] The interaction of Brooker’s merocyanine (BM), a merocyanine dye with calix[4]pyrrole 1 (CP) was studied in acetonitrile. BM is violet in solution, but its interaction with CP changes the colour of the solution due to the formation of CP–BM species associated through hydrogen bonding. A displacement assay was then carried out in the presence of different anions (F⁻, Cl⁻, Br⁻, I⁻, H₂PO₄⁻, HSO₄⁻ and NO₃⁻). It was verified that F⁻ and to a lesser extent Cl⁻ and H₂PO₄⁻, displace BM through the formation of a complex with CP. Addition of HSO₄⁻ makes the solution almost colourless because it is sufficiently acidic to transfer a proton to BM, removing it from the receptor site in CP and protonating the dye, thereby allowing the visual detection of the anion in relation to the other anions (Figure 20).
Figure 20 The competition between the anion and merocyanine solvatochromic dye for calix[4]pyrrole as a receptor site.

5.2. Calix[4]pyrrole-based electrochemical sensors

For the development of calixpyrrole-based electrochemical anion sensors, different approaches include the incorporation of calixpyrroles in ion-selective electrodes (ISEs), discrete redox active molecular receptors and chemically modified electrodes.

5.2.1. Ion-selective electrodes (ISEs)

selective electrodes to investigate the relationship between Ag(I) ion selectivity and the conformation of the porphyrinogen substituents.

Lee et al. [74] reported the potentiometric behavior of three types of newly synthesized calix[2]furano[2]pyrrole derivatives towards Ag(I) ion (Figure 21). PVC (polyvinyl chloride) membrane electrodes incorporating the ionophores 106, 107 and 108 exhibited the response to Ag(I) ion. The best results were obtained with the membrane containing N and O atoms in the ligand (ionophore 106). These Ag(I) ion electrodes displayed very good selectivity for Ag(I) ion in comparison to alkali and alkaline earth metal ions, NH$_4^+$ and H$^+$. 

![Figure 21 Various ionophores for ion-selective electrodes.](image)

ISEs derived from compound 1 showed strong anionic response for Br\(^-\), Cl\(^-\) and H\(_2\)PO\(_4\)\(^-\) and to a much lesser extent for F\(^-\). ISEs derived from compound 109 and compound 110 were investigated towards these anions and were found to be pH dependent.

![Figure 22](image)


### 5.2.2. Discrete redox active molecular receptors

Novel calix[4]pyrrole bearing vic-dioxime ligand has been synthesized by the reaction of anti-chlorophenylglyoxime with 3-aminophenylcalix[4]pyrrole at room temperature. The mononuclear Cu(II), Ni(II) and Co(II) complexes of this vic-dioxime ligand were prepared and their structures were confirmed by elemental analysis, FTIR, TGA and magnetic susceptibility measurements; the HMBC, DEPT, \(^1\)H and \(^{13}\)C NMR spectra of the ligand were also reported. B. Taner et al. have investigated redox behaviors of Ni(II), Co(II) and Cu(II) complexes of ligand by cyclic voltammetry at glassy carbon electrode. Electrochemical data showed that nickel and copper complexes exhibit almost similar electrochemical behavior, with the irreversible reduction processes based on metal cations, while the Co(II) complex displays quasi-reversible one-electron transfer reduction process in the cathodic region based on metal [77].
The development of discrete redox active receptors [78] containing a guest binding site coupled to a redox active reporter group is an area in supramolecular chemistry that has attracted much attention. Beer and Gale [79] have synthesized a redox active ferrocene group to the calix[4]pyrrole framework 111-113 but anion binding properties of the resulting receptors are to be studied using electrochemical means. As with the optical sensors described earlier, this was done via both meso functionalization and modification of β-pyrrolic position (Figure 23) [80].

![Figure 23](image)

Figure 23 Ferrocene appended calix[4]pyrrole.

$^1$H-NMR titrations have revealed that one CH proton of ferrocene participated in hydrogen bonding interactions with calixpyrrole NH hydrogen bonding interaction that are thought to stabilize the bound anion in complex (Figure 24). The crystal structure of compound 113 revealed that it functions as electrochemical sensor and binds $F^-$, $H_2PO_4^-$ and $Cl^-$ anions [80].
Figure 24 Proposed CH-anion interaction in complex

5.2.3. Chemically modified electrodes

Gale et al. [81] prepared chemically modified electrode from calix[4]pyrrole monomers containing α-unsubstituted pyrrolic species and compounds 114 and 115 (Figure 25), were synthesized using methods analogous to those used to prepare 111 and 112. Specifically, they were made by coupling the relevant calix[4]pyrrole mono-acid species with 3-aminopropylpyrrole using the benzotriazolyloxy-tris(dimethylamino) phosphonium (BOP) amide coupling agent.

They also investigated the use of these co-polymer films of 114-pyrrole and 115-pyrrole (Figure 26) as anion masks and any perturbation due to the formation of calix[4]pyrrole-anion complexes on the cyclic voltammogram.

Figure 25 Chemically modified electrodes.
5.3. Calix[4]pyrrole-based HPLC supports

Reports on calix[4]pyrrole modified stationary phase are relatively few. The important one came from Sessler et al. [82] calix[4]pyrrole-modified silica gels (Gel B and Gel M) could act as new solid-phase HPLC supports. Under different conditions, they realized that this calix[4]pyrrole-modified silica gels were useful for the separation of some inorganic and organic anions, such as fluoride, chloride, Cbz-protected amino acids, phosphorylated derivatives of adenine, oligonucleotides, and some small neutral substrates. A mechanism for HPLC-based separation was proposed as resulting from the weak hydrogen bonding interactions between calix[4]pyrrole moieties and the anionic substrates. These weak interactions, which presumably differ in strength for each anionic substrate in question, lead to selective retention of the anions under conditions of isocratic elution using a competitive solvent system. For instance, HPLC separation of 5'-adenosine monophosphate (AMP), 5'-adenosine diphosphate (ADP), and 5'-adenosine triphosphate (ATP) on Gel M revealed that the more highly charged nucleotide is retained longer without the use of ion-pairing agents (Figure 27).

Figure 26 Polymerization of calix[4]pyrrole monomers.
Recently, Jiang et al. [83] explored the separation ability and mechanism of calix[4]pyrrole stationary phase, where two calix[4]pyrrole-modified silica gels (gel BM and BC in **Figure 27**) were synthesized and successfully applied to separate amino acids, phenols, benzene carboxylic acids, and some medicines. Calix[4]pyrrole-modified HPLC columns have the potential to separate some positional isomers and medicines, which would be helpful for further studies and applications in the fields of analytical and supramolecular chemistry.

5.4. Polymer-bonded calix[4]pyrrole and their chelating properties

The synthesis and preliminary sorption properties of three types of chelating resins containing calixpyrrole units (**Figure 28**) have been reported by Andrzej et al. [84] obtained by:

(i) Immobilization of calix[4]pyrrole on a polymeric support (vinylbenzyl chloride/divinylbenzene co-polymer),
(ii) Condensation of calix[4]pyrrole with formaldehyde to form insoluble polymeric materials and

(iii) Radical co-polymerization of calixpyrrole monomer with methylacralyte and divinylbenzene that led to cross-linked insoluble resin in the form of beads.

“Hetero” or “hybrid-calixpyrroles” are among the many new calixpyrrole receptors found. These hybrid systems contain thiophene or furan other than pyrrole heterocycles incorporated into macrocycles, presenting a new class of receptors with interesting anion and cation-binding potential. Andrzej et al. [85] presented the synthesis and batch-mode sorption characteristics of a novel chelating resin containing macrocyclic ligands calix[4]pyrrole[2]thiophene immobilized on a cross-linked vinyl benzyl chloride/divinylbenzene copolymer which played important role in selectively complexing precious metal cations.

It was observed that all resins demonstrated a preference for fluoride anions over other halides in static sorption studies. [86] Larger anions, like iodides, did not form complex with the resin due to difference between the size of the anion and the size of the binding site. Thus resins 1-3 (Figure 28) have been proved to be used as sorbents of anions from non-aqueous media and are promising materials for separation techniques.

A range of static sorption studies were performed on resin 4, (Figure 28) that demonstrated strong affinity towards cations of the noble metals (Au, Ag, Pt, Pd) over other transition metals. The sorption studies also revealed a considerable preference of the chelating resin for gold over other precious metals in binary mixtures, which might be useful in the removal of gold from scraps or ores containing other noble metals.
5.5. Miscellaneous Applications of Calix[4]pyrrole Macrocycles

F. L. Gu et al. [87] have investigated the structures and static (hyper)polarizabilities of the $[\text{Li}^+[\text{calix}[4]\text{pyrrole}]\text{Li}^-]^n$ dimer and trimer with C4v symmetry in details. The 2s electron of Li atom inside each calix[4]pyrrole unit were ionized to form the diffuse excess electron under the action of the lone pairs of its four N atoms. Compared to the corresponding $[\text{calix}[4]\text{pyrrole}]_n$ (n=5,2,3) without Li
atom, the first hyperpolarizabilities of dimer and trimer sharply increased up to 30–40 times by inserting Li atoms, which demonstrated that the excess electrons play an important role in these large static (hyper)polarizabilities. The detailed investigations about dimer, trimer, and even polymer of $[\text{Li}^+\text{[calix[4]pyrrole]Li}]_n$ were useful and helpful for designing new type of NLO materials.

The impact of anion receptor (1,1,3,3,5,5,5-meso-hexaphenyl-2,2,4,4,6,6-meso-hexamethylcalix[6]pyrrole) on physicochemical and ion transport properties of poly(ethylene oxide)-salt composites was studied by M. Siekierski et al. [88].

A DFT based methodology [89] was used to study the complexation of the alkali metal cations (Li$^+$, Na$^+$, K$^+$, Rb$^+$ and Cs$^+$) and alkaline-earth metal cations (Be$^{2+}$, Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$ and Ba$^{2+}$) with calix[2]furano[2]pyrrole 116 (Figure 29). This compound, which is a promising selective metal extracting agent, showed large flexibility, with 4.4 kcal mol$^{-1}$ for the maximum amplitude of conformational energy. Except for the case of lithium, all the metal ions are held at the centre of the ligand cavity, with the vertical position depending on the ion radius, small metal ions are found in inner positions and bigger ones are shifted progressively to the upper rim of the cavity. The coordination to the central ion is made by the oxygen atoms and the delocalized electronic density of the pyrrole rings. The binding strength of the ions to the calix[2]furano[2]pyrrole was found to increase with charge and decrease with their size.

![Figure 29 Calix[2]furano[2]pyrrole](image-url)
Poly(ethylene oxide) based electrolytes comprising LiCF$_3$SO$_3$ and calix[2]-p-benzo[4]pyrrole (CBP) as anion binder were prepared and subjected to DSC, ionic conductivity, cationic transport number and FTIR analysis [90]. The calix[2]-p-benzo[4]pyrrole (CBP) 117 prepared as an anion receptor in a PE was investigated for possible application in lithium batteries. The incorporation of CBP in a PEO environment considerably reduced the crystallinity of the polymer host. However, the ionic conductivity of electrolytes with CBP was found to be lower than that of a CBP-free electrolyte below the melting point of PEO. Interactions between the polymer host, CBP and lithium salt were further inferred from FTIR results (Figure 30).

![Figure 30 Calix[2]-p-benzo[4]pyrrole](image)

P. Ballester et al. [22] reported formation of gels, responsive to sodium cations or pH changes, in aqueous media by an aryl extended calix[4]pyrrole 50a receptor and the tetramethylammonium guest. It was observed that the addition of TMA bromide to a solution of 50a in aqueous NaOH afforded with time a transparent hydrogel.

Sessler et al. [91] examined cooperative relationship between tetrathiafulvalene (TTF)-calix[4]pyrrole 119-121 and several nitroaromatic guests and developed new allosteric systems that function as rudimentary colorimetric
chemosensors for common nitro aromatic based explosives, and which are effective even in the presence of potentially interfering anions (Figure 31).

![Figure 31](image)

**Figure 31** New annulated TTF-calix[4]pyrrole receptors

### 6. SYNTHESIS OF HIGHER ORDER CALIXPYRROLES

Calix[4]pyrroles are promising anion receptors, but due to the small size of their cavities, they bind only small anions, such as fluoride and chloride, effectively in aprotic solvents. Way to improve, or at least adapt, the anion binding properties of calix[4]pyrroles would be to expand them to produce so called higher order calix[n]pyrrole (n>4). Such systems are expected to bind larger anions selectively due to a change in the anion-receptor size or geometry match. However, these higher order structures are likely to prove more flexible than calix[4]pyrroles, which could also affect their anion binding properties.

Luis Chacón-García et al. [92] describe the first synthesis of the novel meso-pentaspirocyclohexyl calix[5]pyrrole 122. Anion–guest properties of the new
compound were evaluated with respect to fluoride, chloride, and bromide tetrabutylammonium salts by 1H NMR titration techniques in deuterated dichloromethane by following the induced shifts in the NH resonances upon complexation (Figure 32).

Figure 32 meso-pentaspiro-cyclohexyl calix[5]pyrrole

The first example of a stand alone higher order calix[n]pyrrole was calix[6]pyrrole. This synthesis was based on the use of the dipyrromethane building blocks 123 and 124. In particular, reaction of 123 or 124 in a mixture of dry acetone and ethanol (1:1 v/v) in the presence of trifluoroacetic acid gave rise to meso-hexa(phenyl)calix[5]pyrrole 125 and meso-hexa(2-pyridyl)calix[6]pyrrole 126, respectively (Scheme 27).
Scheme 27 Synthesis of the calix[6]pyrroles

Investigating into the role of the acid catalyst in the synthesis of 125 revealed that, in addition to acting as a catalyst for the reaction, the trihaloacid catalyst plays an independent role as a template, promoting the formation of the calix[6]pyrrole product [93]. $^1$H NMR-based anion binding studies in acetonitrile-chloroform (1:9) revealed that compared to parent molecule calix[4]pyrrole 1, 125 binds larger anions such as $\Gamma^-$, $\text{BF}_4^-$, and $\text{CF}_3\text{CO}_2^-$ quite effectively [94]. By contrast, this expanded system shows relatively reduced affinities for smaller anions, such as $\text{F}^-$, $\text{Cl}^-$, $\text{Br}^-$, and $\text{SCN}^-$.

AIM AND SCOPE

Supramolecules derived from calix[4]pyrroles are synthesized by acid catalyzed condensation of pyrrole with any aliphatic or aromatic ketone. As conventional method suffers from large amount of solvent, longer reaction time and low yield, therefore, microwave assisted organic synthesis has become an increasingly popular technique in academic and industrial research laboratories, due to certain advantages like (a) faster reaction time (b) higher yield (c) less quantity of solvent volume (d) improved purity (e) ease of work up after the reactions and (f) eco-friendly reaction conditions. Product obtained by the condensation of pyrrole with 3,5-dihydroxyacetophenone is likely to exhibit the properties of resorcinarene as well as calixpyrrole and its further functionalization with chelating group such as azo, may further enhance its complexing ability with various metal ions.
Aim of the work to be presented in thesis:


2. To synthesize two new functionalized Amberlite XAD-2 polymeric chelating resins, resin \textbf{I} and resin \textbf{II}, by covalently linking diazotized Amberlite XAD-2 with \textit{meso-tetra(methyl) meso-tetra(3, 5-dihydroxyphenyl) calix[4]pyrrole and meso-tetra(methyl) meso-tetra[(3, 5-dihydroxy phenyl-4-(2-diazenyl phenol)] calixpyrrole} respectively.

3. To study the complexation and selectivity behaviour of azo dyes of \textit{meso-tetra(methyl) meso-tetra(3, 5-dihydroxyphenyl) calix[4]pyrrole} with various rare earth metal ions like U(VI), Th(IV), La(III), Ce(III) and develop method for liquid-liquid extraction, preconcentration and transportation of selective metal ions.

4. To use resin \textbf{I} and resin \textbf{II} for the solid phase extraction, separation, preconcentration and trace determination of Cu(II), Zn(II), Cd(II), Ni(II), La(III), Ce(III), Th(IV) and U(VI) in synthetic as well as natural samples under optimum conditions.

5. To examine antimicrobial activity of azo derivatives of \textit{meso-tetra(methyl) meso-tetra(3, 5-dihydroxyphenyl) calix[4]pyrrole} against \textit{E. coli}, \textit{S. aureus} and \textit{A. niger}, \textit{Rhizopus sp.} To evaluate the dyeing performances of these dyes on fibers like cotton, wool, silk, acrylic, nylon and paper study their fastness properties towards water, sunlight, washing and perspiration.
REFERENCES


