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THE CHEMISTRY OF CALlXPYRROLES

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Abstract - The calixpyrroles (*meso*-octasubstituted porphyrinogens), which are easy to make and functionalize, are a class of old but new hetero-calixarene analogue. This comprehensive review summarizes the progress made in chemistry of calixpyrroles in terms of their synthesis, structure, conformation, functionalization and applications in various fields.

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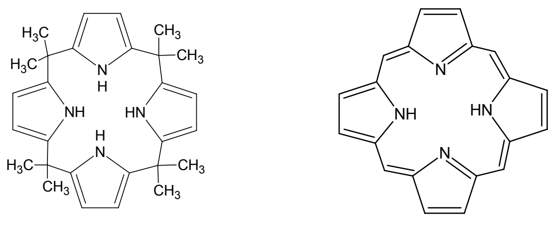
1. INTRODUCTON

Calix[4]pyrrole belongs to the family of hetero-calixarene[1] macrocycles, which has four pyrrole units instead of phenolic units. These heterocalixarene possess unique supramolecular characteristics and present interesting chemical and physicochemical properties as well as wide application possibilities. The replacement of calixarene phenolic unit(s) by heterocycle(s), constitute hetero-calixarenes 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. Thus a range of rational design of heterocalixarene receptors, with possibilities of wider range of noncovalent interactions and consequent recognition events than calixarene, can be envisaged. Various reviews,[2-8] patents,[9-11] and book chapter[12] on calixpyrrole have appeared in past. With the increasing number of research groups worldwide thereby regularly increasing number of publications, covering many areas of chemistry of calixpyrrole, we thought it worth to present comprehensive review article which covers the important work of all the research group across the world. The works done in the area of calixpyrrole have been reviewed mainly in terms of progress made in synthetic strategies, functionalization and application in various fields. We have not given any account of N-confused calixpyrroles as they have already been reviewed by Anzenbacher *et al.*[13] in 2006.

2. CALIXPYRROLE AND PORPHYRIN

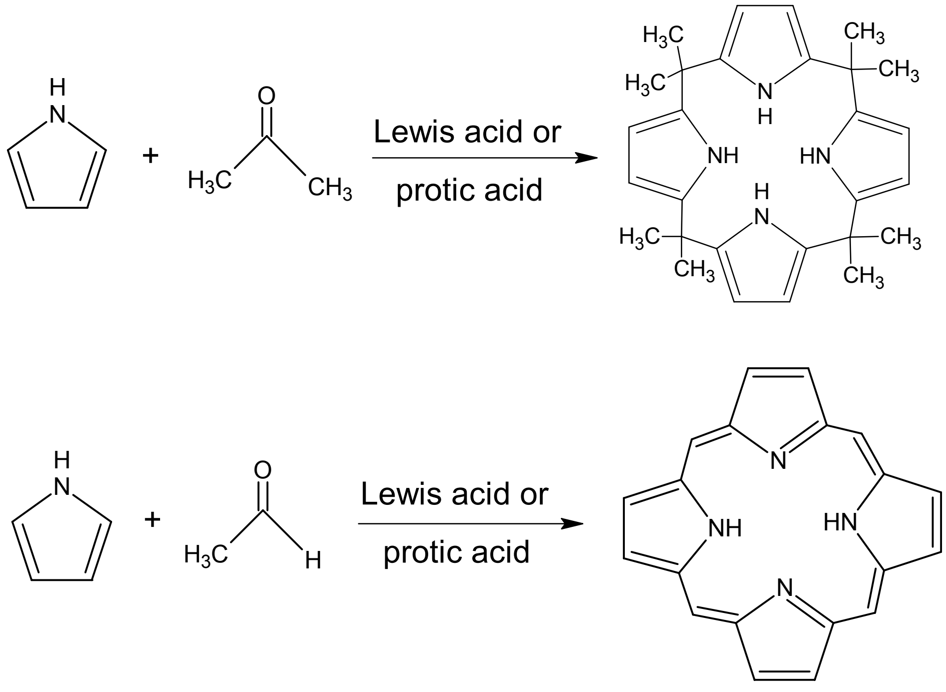
Calix[4]pyrrole **1**, originally named "Pyrrole-acetone" and formally known as *meso*-octaalkylporphyrinogens are a venerable class of tetrapyrrolic macrocycles. It was first synthesized by Baeyer[14] in the nineteenth century by condensing pyrrole and acetone in the presence of an acid. Porphyrinogens[2] are naturally occurring colorless macrocycles consisting of four pyrrole rings linked through the α (i.e. pyrrolic 2 and 5) or *meso* like positions by sp^3-hybridized carbon atoms. Originally coined *meso*-octasubstituted porphyrinogens, the most common formulation of this system is a result of the condensation of acetone and pyrrole, which leads to the formation of a tetrapyrrolic macrocycle structurally similar but electronically different than porphyrins in such a way that an **18π electron** aromatic structure cannot be formed in calix[4]pyrrole. This imparts drastically different properties to it **(Figure-1)**, where each pyrrole is electronically independent and consequently, each can donate one hydrogen bond.



1 2

Figure-1 Structure of calix[4]pyrrole **1** and porphyrin **2**.

The synthesis of calixpyrroles bears analogy to that of porphyrins[15] (aromatic system) in that they are obtained from the condensation of pyrrole with an electrophile. In the case of calixpyrroles (non-aromatic system), the electrophile is a ketone, whereas in the case of porphyrins, it is generally an aldehyde **(Scheme-1)**.



Scheme-1 Formation of porphyrins and octamethylcalix[4]pyrrole, the *'Parent'* Structure in the Calixpyrrole 'Family.'

3. HISTORICAL DEVELOPMENT

In 1886, Baeyer[14] synthesized a white crystalline material by condensing pyrrole with acetone in the presence of hydrochloric acid. Subsequent to the work of Baeyer, Dennstedt and Zimmermann (1886) also studied this reaction, using "Chlorzink" as the acid catalyst.[16] Thirty years later, during the First World War, Chelintzev and Tronov repeated this reaction and proposed (correctly) a cyclic tetrametric porphyrinogen structure for the product, which later proved to be correct. In 1955, Rothemund and Gage[17] improved this synthesis by using methanesulfonic acid as the acid catalyst. Other than these important findings, this class of compounds were studied, most of which merely focused on the refined syntheses of these macrocycles and their *meso*-substituted derivatives but not their applications.[18-20]

In the early 1970s, Brown *et al.*[21] reported a refined procedure that permitted them to obtained tetraspirocyclohexylcalix[4]pyrrole, a compound that had previously been reported by Chelintzev, Tronov and Karmanov,[18] in 1916, in decent yield. They condensed cyclohexanone with pyrrole in a 1:1 ratio in the presence of acid to obtained tetraspirocyclohexylcalix[4]pyrrole **3 (Figure-2).**

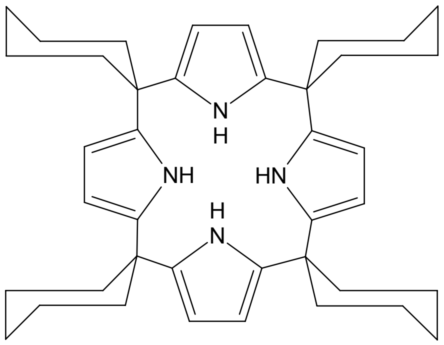


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Figure-2 Structure of tetraspirocyclohexylcalix[4]pyrrole **3.**

After being virtually dormant in the literature for nearly a century, interest in these macrocycles was renewed in the 1990s by the extensive work of Floriani and co-workers[22] on the metallation and attendant synthetic chemistry of deprotonated- calixpyrroles.

In the mid-1990s Sessler and co-workers[23] discovered that the NH array present in these species can act as a binding site for anionic and neutral guest species. They prepared the compound **1** using known literature procedures. Single crystal suitable for X-Ray crystallographic analysis showed that the molecules adopt a 1, 3-alternate conformation in the solid state wherein adjacent rings are oriented in opposite directions. However, X-Ray crystal analysis of the tetramethylammonium chloride complex of compound 1, revealed that the formation of an anion-calixpyrrole complex is accompanied by a dramatic change in the conformation of the macrocycle **(Figure-3)**.

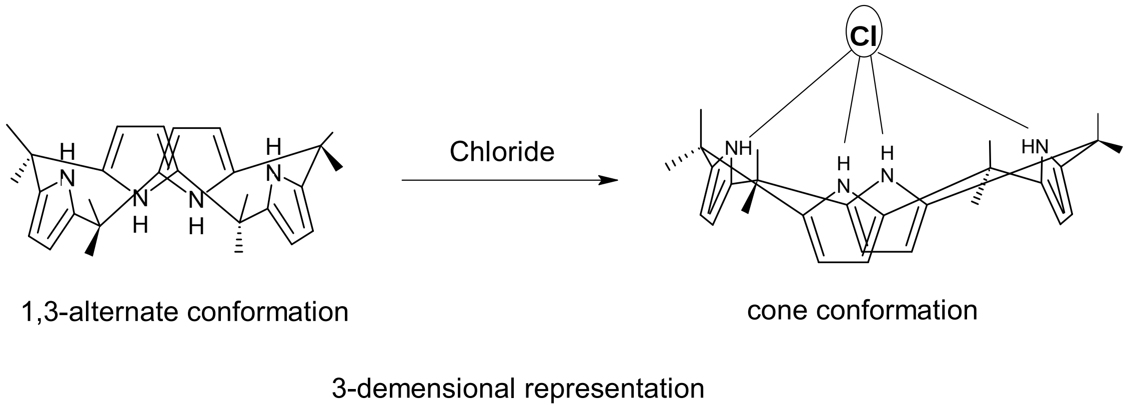


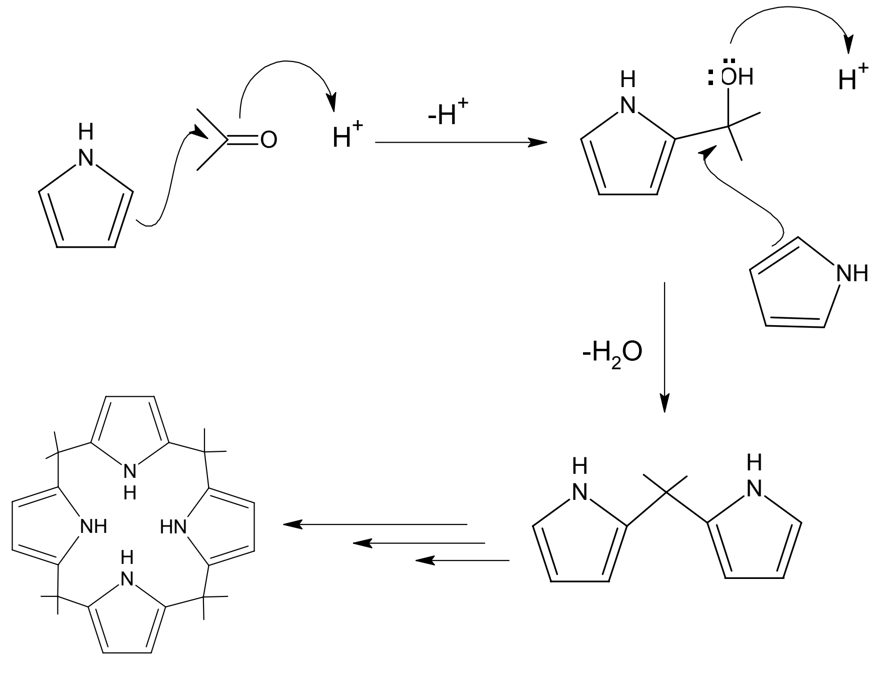
Figure-3 3-demensional representation of calix[4]pyrrole **1** in the absence and presence of chloride anion.

In this case the calix[4]pyrrole ligand adopts a cone like conformation such that the four NH protons can bind to the halide anion by hydrogen bond. Interestingly, unlike the calix[4]arene, calix[4]pyrrole has no scope for the formation of a hydrogen bonded array between the various pyrrolic NH groups.

These macrocycles which had been known as porphyrinogens, their interesting conformational behavior drew the 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 eight 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.***

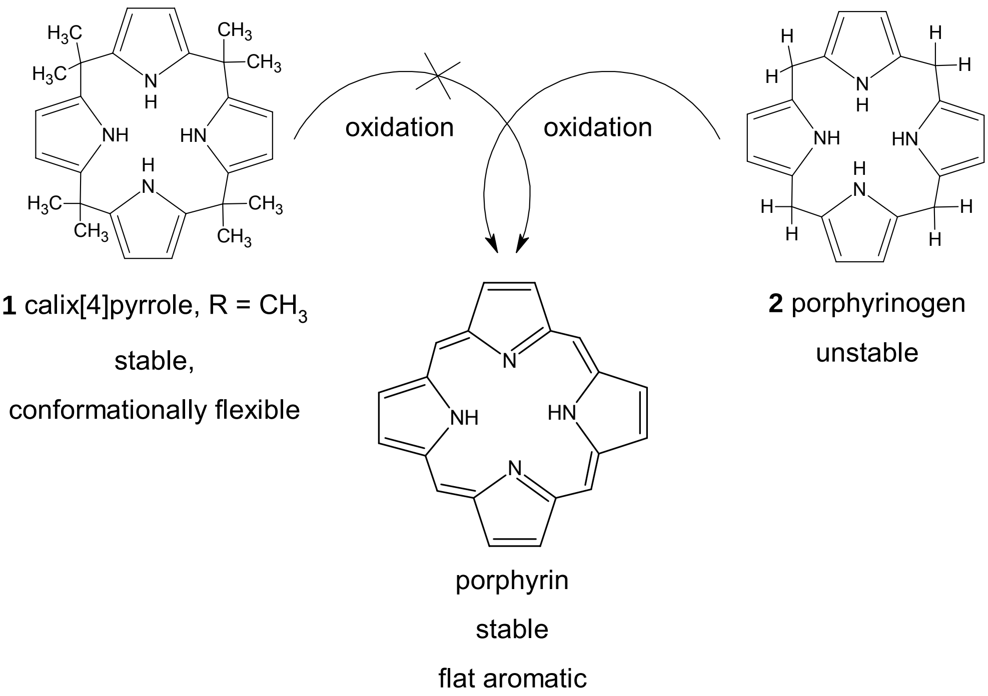
4. MECHANISM

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



Scheme-2 Synthetic mechanism of calix[4]pyrrole macrocycle.

Calixpyrroles, an easy-to-make class of neutral macrocycles, differ from the true porphyrinogens in that they can not be oxidized to their corresponding *aromatic porphyrin* forms **(Scheme-3)**. Their solid state structure also suggests that these *meso*-octamethylporphyrinogens are more aptly named calixpyrroles to emphasize their structural similarities to other members in the calixarene family.



Scheme-3 Schematic representation showing the different behavior of calix[4]pyrrole **1** and porphyrinogens **2** with respect to Oxidation.

5. STRUCTURAL ASPECTS OF CALIX[4]PYRROLE

A closer look at the structure of calix[4]pyrrole leads to an appreciation that they can adopt four limiting conformations like calix[4]arene: 1,3-alternate, 1,2-alternate, partial cone, and cone **(Figure-4)**. The form predicted to be most stable, and experimentally lowest energetic, is the 1,3-alternate conformation, where the pyrroles are found to alternate in an up-down-up-down setup.[25]

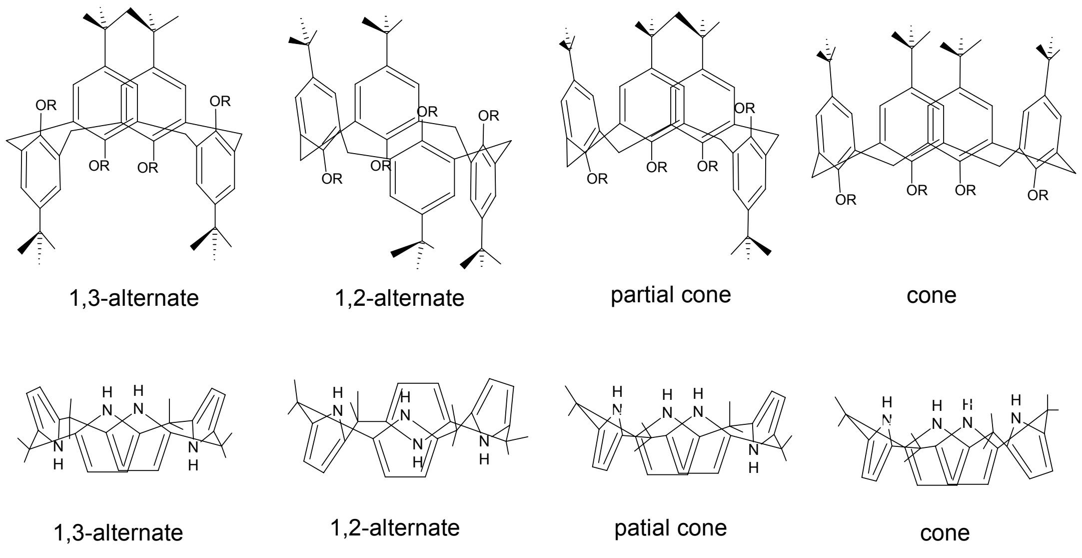


Figure-4 Representation of the limiting possible conformations conceivable for calix[4]pyrrole.

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 the most stable one in the absence of a halide anion, while the cone conformer was not stable under this condition. However, in the presence of halide anions the cone conformation was the most stable among all possible conformations **(Figure-5)**.

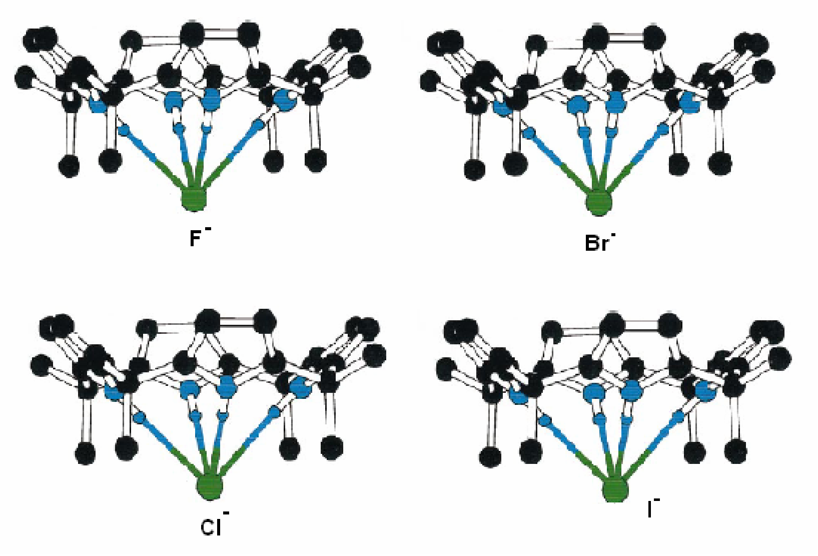


Figure-5 Cone like halide complex of compound **1** energy-minimized in the gas phase.

Wu *et al.*[26] also studied the conformation features and anion binding properties of compound **1** theoretically. Both gas phase and solution phase (CH_2Cl_2) studies revealed a predicted stability sequence for the various conformers of **1, 3-alternate > partial cone > 1, 2-alternate > cone**. This theoretical study also showed that in the case of fluoride anion binding, a 1:1 anion-binding mode would be favored over a 1:2 binding mode. It also predicted a calculated binding energy for chloride anion complexation that was in good agreement with the experimental data.

6. SYNTHETIC APPOROACHES TOWARDS CALIXPYRROLE MACROCYCLES

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

1. One-pot [1+1+1+1] condensation
2. [2+2] condensations
3. [3+1] condensations
4. State of the art approach

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.

6.1 One-pot condensation

As commonly practiced, the one-pot synthesis of calix[4]pyrroles involves the condensation of pyrrole(s) and ketone(s) in a 1:1 ratio in the presence of an acid catalyst eg. hydrochloric acid, methanesulfonic acid, trifluoroacetic acid, and boron trifluoride diethyl etherate. Generally used solvents are methanol, ethanol, acetonitrile, and dichloromethane, but in some of the reactions various ketones used for condensation with pyrrole can be used as solvent also. Depending on how many types of pyrroles or ketones are used in the reaction. One-pot condensation can be categorized into

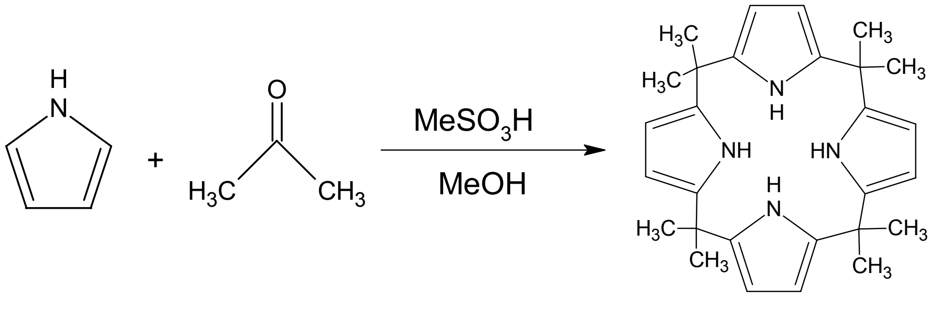
- homo-condensation and
- mixed condensation

6.1.1 Homo-condensation

The term homo-condensation can be defined as the reaction of a specific pyrrole with a specific ketone. According to the ***symmetry*** of the pyrrole or ketone components, these homo-condensations can be further categorized/classified as *symmetric homo-condensations* and *asymmetric homo-condensations*.

- Symmetric Homo-condensations:

A symmetric homo-condensation represents a reaction employing a symmetric pyrrole and a symmetric ketone. Generally such reaction produces an easy-to-separate major product in good yield. One typical example of symmetric homo-condensation is the synthesis of *meso*-octamethylcalix[4]pyrrole[23] **1** *via* the condensation of pyrrole with acetone in a 1:1 ratio in methanol using methanesulfonic acid as the acid catalyst. Column chromatography (silica gel, dichloromethane /hexanes 1:1, eluent) affords **1** in yields ranging between 60% and 80% by symmetric homo-condensation. **(Scheme-4)**



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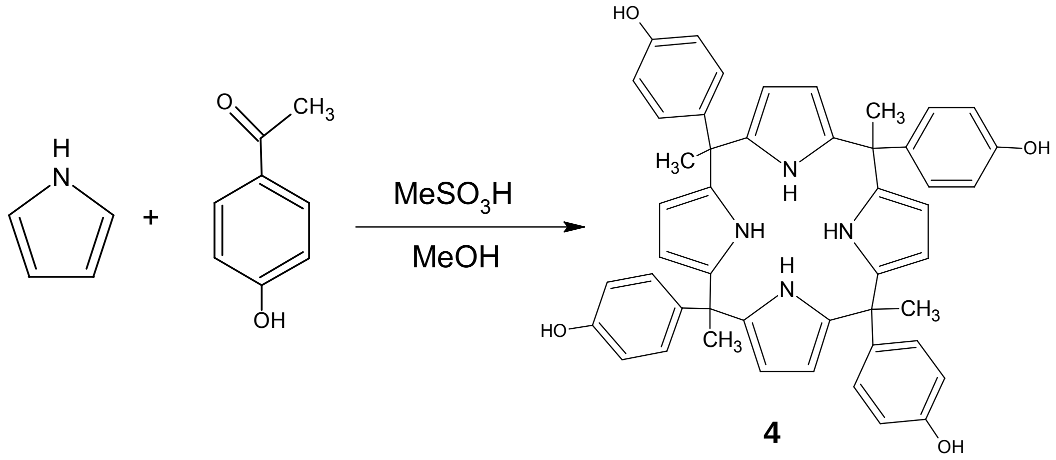
Scheme-4 A synthetic scheme of symmetric homo-condensation as illustrated *via* the synthesis of *meso*-octamethylcalix[4]pyrrole **1**.

- Asymmetric Homo-condensations:

An asymmetric homo-condensation normally involves the reaction of a pyrrole with an asymmetric ketone. For example, condensation of pyrrole with *p*-hydroxyacetophenone in methanol in the presence of methanesulfonic acid afforded the desired calix[4]pyrrole[27] **4** in 62% yield **(Scheme-5)**. Since each of the four *meso* bridges formed under the conditions contain both a methyl and aryl substituents, the product actually consists a mixture containing four different configurational isomers; which are difficult to separate and may require tedious separation procedures including careful column chromatography or HPLC techniques.

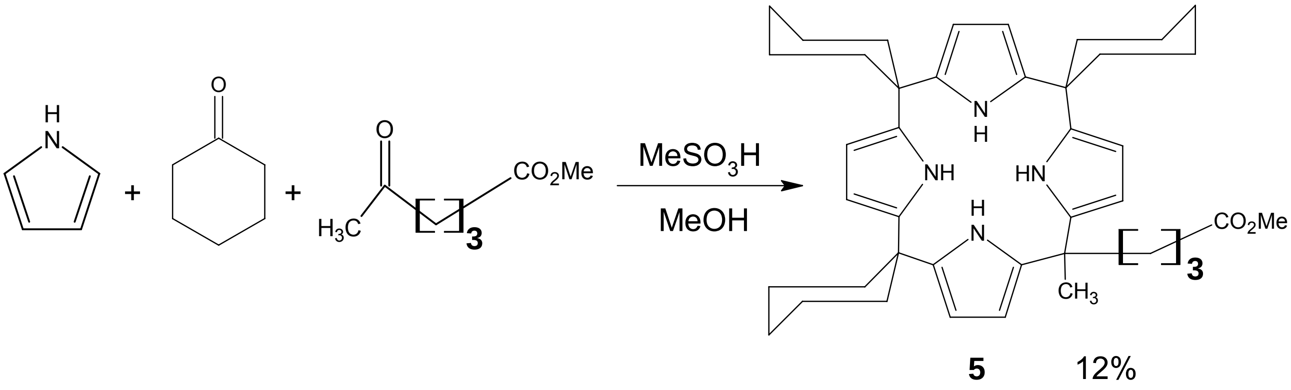


Scheme-5 A typical asymmetric homo-condensation: synthesis of the tetraphenolic calix[4]pyrrole **4**.

6.1.2 Mixed-condensation

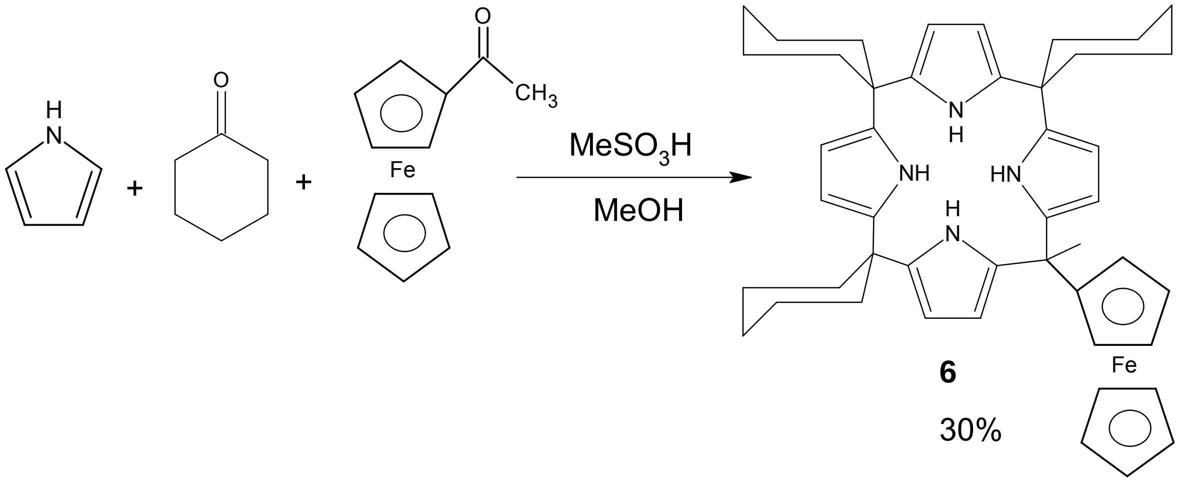
Mixed condensations involve the condensation of more than one kind of pyrrole with a specific ketone **or** of a specific pyrrole with more than one kind of ketone. Mixed condensations have low yields of individual products due to the fact that a mixture of products is formed. As a result, the reactants ratio must be carefully controlled so as 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 condensations provide a good entry into functionalized systems.

Calix[4]pyrrole with a carboxylate pendant arm (monoester)[28] **5** was obtained by acid catalyst condensation of methyl 4-acetylbutyrate and cyclohexanone with pyrrole, in a 1:1:2 ratios. Column chromatography (silica gel; dichloromethane, eluent) afforded **5** in 12% yields **(Scheme-6)**.



Scheme-6 Mixed condensation of calix[4]pyrrole monoester **5**.

Ferrocene substituted calix[4]pyrrole[29] **6** was synthesized by co-condensation of acetylferrocene, pyrrole and cyclohexanone **(Scheme-7)** and a catalytic quantity of methanesulfonic acid were added to methanol and stirred under nitrogen overnight. The mono-ferrocene calix[4]pyrrole **6** was separated by column chromatography (silica gel; dichloromethane, eluent), in 30% yield.

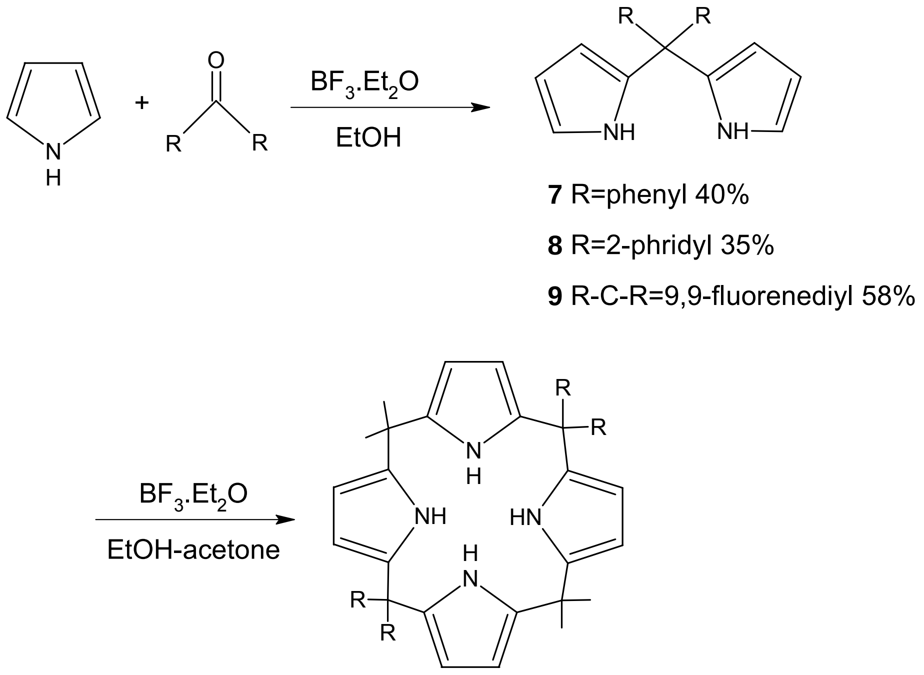


Scheme-7 Synthetic scheme of mono substituted ferrocene-calix[4]pyrrole **6**.

6.2 [2+2] Condensation

[2+2] Condensations refer to acid-catalyzed condensations of two dipyrromethane units, generally synthesized in a predictive step from pyrrole and a ketone, with two ketone units (normally different from those used in the syntheses of the dipyrromethanes). 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 **10-12** are typical of the kinds of products[30] that may be obtained readily using a [2 + 2] approach. These particular products were synthesized from the dipyrromethane precursors **7-9 (Scheme-8)**. These precursors were, in turn, prepared from the condensation of pyrrole with diaryl ketones in ethanol using boron trifluoride diethyl etherate as the catalyst. Once in hand, these precursors were condensed in a mixed solvent system consisting of ethanol and acetone (1:1 v/v), with the acetone acting both as a solvent and as a reactant. This gave the cyclic products **10-12** in decent yields. By contrast, **7-9** were found not to react further with the original aromatic ketones, either to form linear polymers or cyclic calixpyrrole-type products, even after prolonged reaction times or *via* the use of elevated temperature. This lack of reactivity may be explained by the steric effect caused by the aryl groups.



7 R=phenyl 40%
8 R=2-phridyl 35%
9 R-C-R=9,9-fluorenediyl 58%

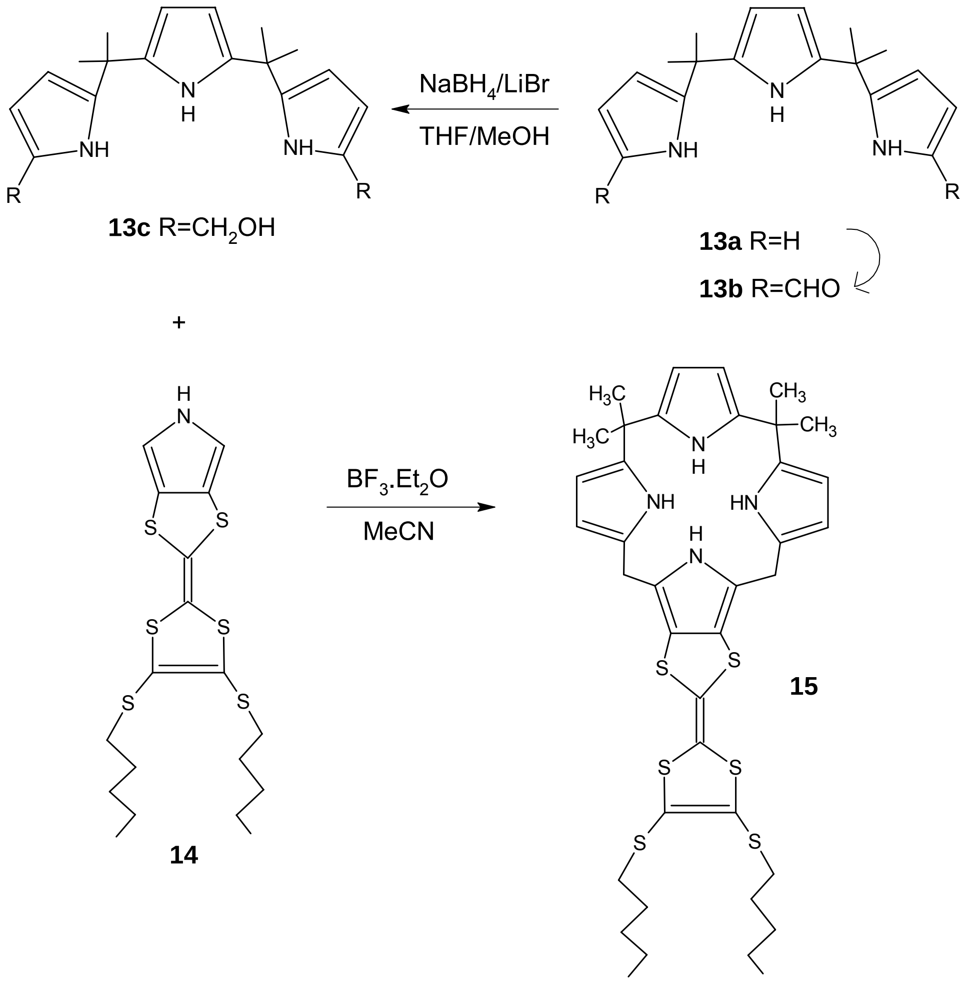
10 R=phenyl 56%
11 R=2-phridyl 20%
12 R-C-R=9,9-fluorenediyl 38%

Scheme-8 [2 + 2] Condensation syntheses of compounds **10-12**.

6.3 [3+1] Condensation

[3+1] Condensations involve the reaction of a tripyrrane or tripyrrane derivative with a pyrrole or pyrrole derivative in the presence of an acid catalyst. Due to the poor stability of most tripyrranes in the presence of acid, the reaction products are generally obtained in low yield. In fact, no true calix[4]pyrroles have been synthesized using this method.

Jeppesen *et al.*[31] reported that a "pseudo" calix[4]pyrrole **15** was synthesized using the [3+1] method **(Scheme-9)**. Tripyrrane dimethanol **13c** was synthesized by reducing the corresponding tripyrrane dialdehyde **13b**, which was synthesized by formylation of tripyrrane[32] **13a**, with sodium borohydride in a mixture of THF and methanol. Treatment of the resulting tripyrrane diol with the tetrathiafulvalene-containing pyrrole **14** in dry acetonitrile using boron trifluoride diethyl ether as an acidic catalyst afforded the mono- tetrathiafulvalene calix[4]pyrrole **15** in 21% yield.



Scheme-9 Synthesis of a “pseudo” calix[4]pyrrole **15** *via* a [3 + 1] condensation approach.

6.4 State of the art approach

Selective synthesis of calixpyrroles in high yield by an environmentally clean process[33] is of topical interest, so as to meet the increasing demand of reducing the pollution hazards caused by the usage of homogeneous acid catalysts. Heterogeneous catalytic synthesis is known to be one of the most effective ways to the selectivity to calixpyrroles with high yield and it has the potential to be scaled-up at relatively low cost. The synthesis of calixpyrroles over mesoporous materials, such as MCM-type silica and alumina catalyst has highlighted the future application of these materials for the synthesis of macrocycles. 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 been studied.

The same author previously prepared these calixpyrrole macrocycles using zeolite catalyzed synthesis in liquid phase under microwave irradiation. The reactions are carried out with different zeolite catalysts such as HZSM-5, HY and mesoporous Al-MCM-41 molecular sieves.[34] These mesoporous Al-MCM-41 molecular sieves (MCM-41) opened a new era in the zeolite catalysis and many reports are available on their use as catalyst for the oxidation, alkylation, cyclization and also in photo catalysis.[35-37]

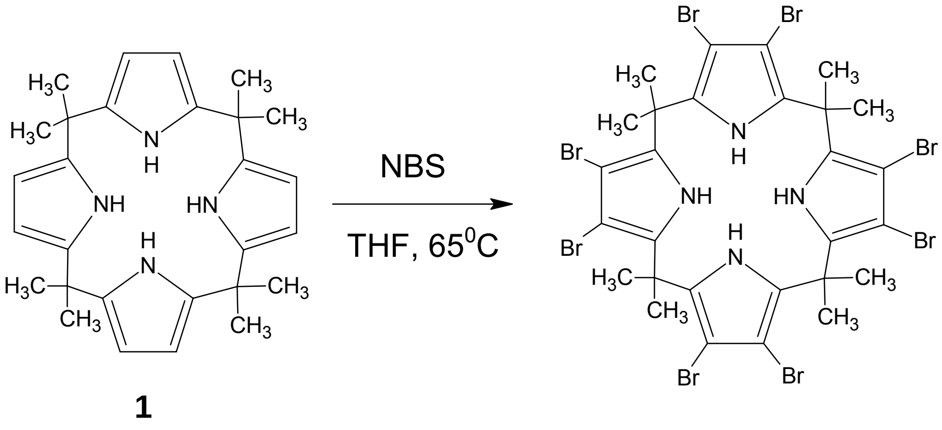
Recently, a facile, highly efficient and eco-friendly protocol for the synthesis of calix[4]pyrrole in excellent yields is reported by Sarkar *et al.*[38] A wide variety of catalysts including chlorzink, *p*-toluenesulfonic acid, glacial acetic acid and zeolites were employed.

7. POST-MACROCYCLIZATION MODIFICATIONS

Calix[4]pyrroles which are complexation agents for anion and neutral guest through hydrogen bond with pyrrolic nitrogen atoms. However, the stability of the complexes is not high enough for analytical use. To improve the binding abilities of basic calix[4]pyrrole skeleton can be functionalized at either the *β-position (C-rim)* or *meso position*.

7.1 Functionalization at the β-position (C-rim)

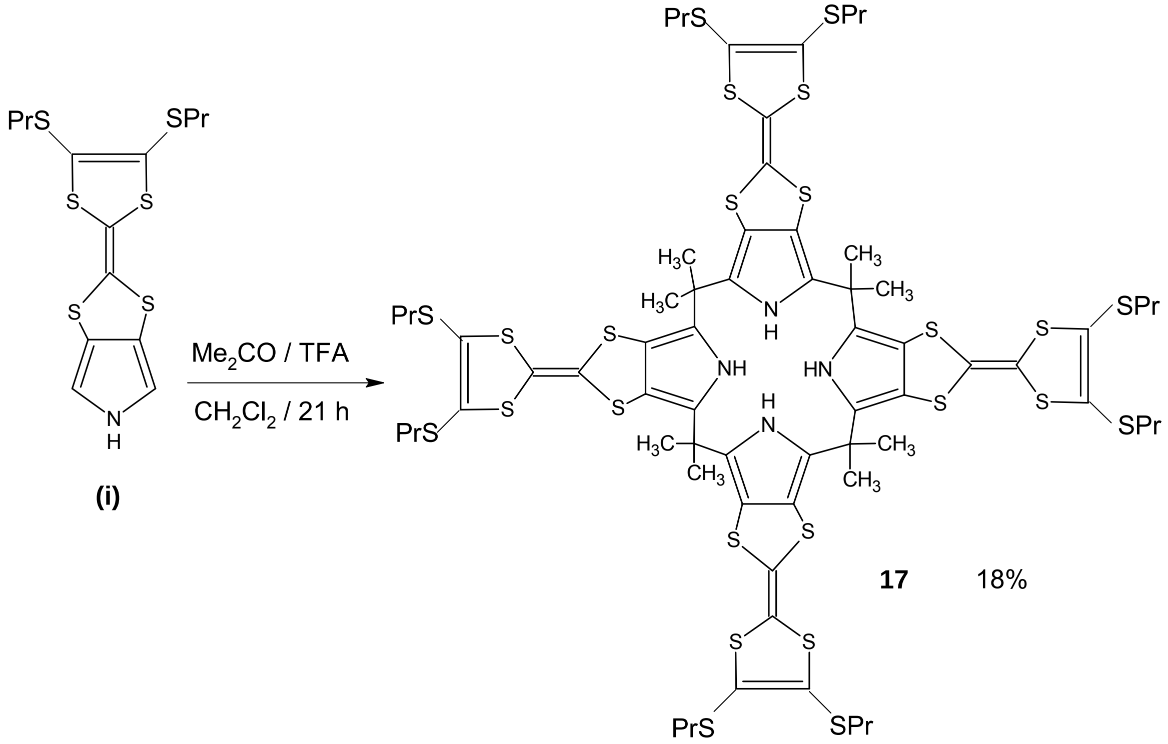
Functionalizations at β–positions, also called C-rim functionalization, have been extensively explored by Sessler *et al.*[39] The most popular C-rim functionalizations are β-octa functionalizations and β-mono functionalizations since they produce only one dominant product. β-functionalization procedures 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.



Scheme-10 C-rim functionalization synthesis of compound **16**.

β – Octabromocalix[4]pyrrole **16** was synthesized in 90% yield by heating **1** with eight equivalents of NBS reagents in THF at reflux for five hours **(Scheme-10)**. This represents an alternative and highly effective synthesis of compound **16**, as compared to that synthesized by the standard one-pot condensation of 3,4-dibromopyrrole with acetone which proved unproductive, presumably due to the instability of 3,4-dibromopyrrole under the reaction conditions.

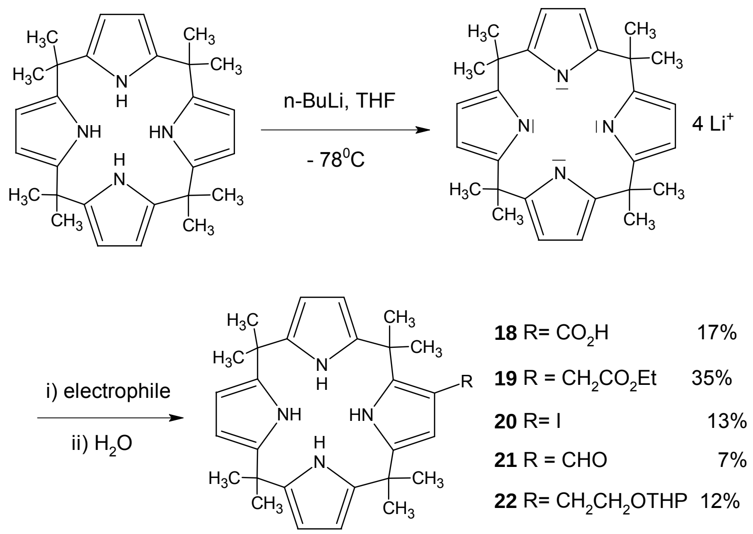
The synthesis of the tetra-tetrathiafulvalene calix[4]pyrrole[40] **17** was obtained by monopyrrolo-TTF (i) with an excess of TFA in a mixture of CH_2Cl_2 and Me_2CO, in 18% yield **(Scheme-11).** This system can act as an effective receptor for neutral electron acceptors, such as 1,3,5-trinitrobenzene, tetrafluoro-*p*-benzoquinone, tetrachloro-*p*-benzoquinone, and p-benzoquinone.



Scheme-11 Synthesis of tetra TTF-calix[4]pyrrole **17**.

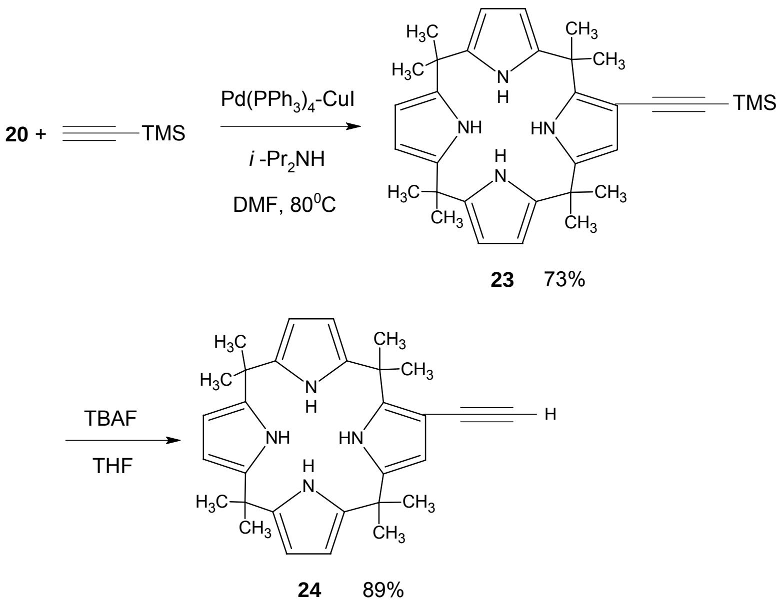
Only two types of carboxyl-functionalized calix[4]pyrroles were reported, one type of carboxyl-functionalized calix[4]pyrrole was replaced at C-rim of parent moiety and the other was reported at *meso* position of calix[4]pyrrole by Sessler *et al.*[28,41]

Sessler et al prepared β-mono substituted calix[4]pyrrole **(Scheme-12)**. However, their synthesis proved somewhat unusual and served to illustrate an interesting feature of calix[4]pyrrole chemistry. In particular, it was found that lithiation of compound **1** with four equivalents of *n*-butyllithium in THF at –78 °C produced a polyanion intermediate, which upon treatment with a suitable electrophile followed by quenching with water, gave the β-monosubstituted calix[4]pyrroles[41] **18-22.** This method provided a variety of elaborated calix[4]pyrroles, among which systems **18-20** have proved particularly useful as building blocks for further elaboration.

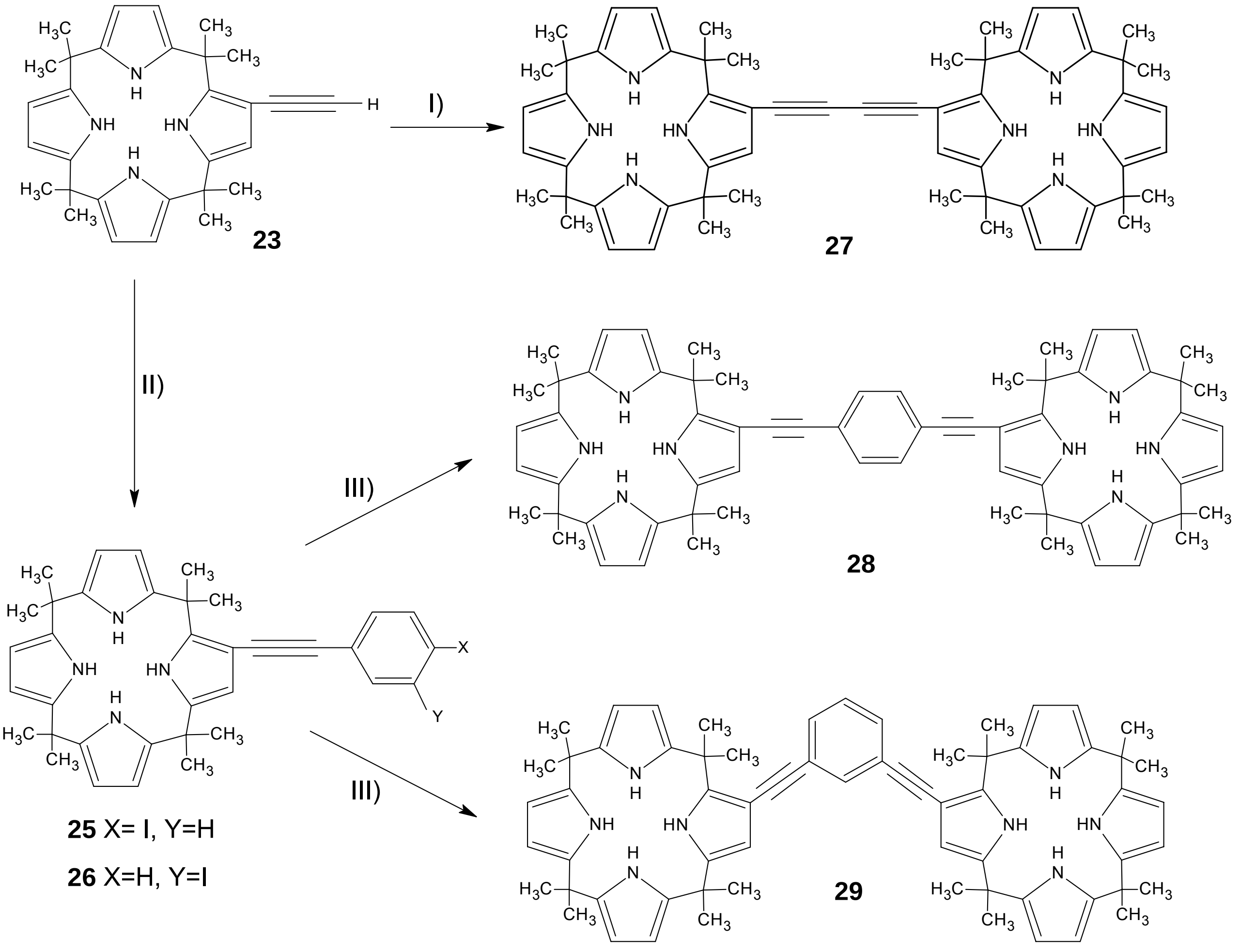


Scheme-12 C-rim functionalization synthesis of compounds **18-22**.

For instance, the monoiodo derivative **20** was used to produce the β-monoethynylcalix[4]pyrrole[42] **24**, a species that , in turn, has serves as a versatile building block **(Scheme-13).** The compound **24** was synthesized by first reacting **20** with excess TMS acetylene in diisopropylamine-DMF at 80 °C in the presence of $Pd(PPh_3)_4$-CuI, to give the TMS protected alkynyl derivative **23** in 73% yield.[42] In second step, this intermediate was subjected to deprotection using tetrabutylammonium fluoride in THF at room temperature; this gave **24** in 89% yield. This material served as a key precursor for the synthesis of calixpyrrole based anion sensors. Palladium catalyst coupling of compound **24** leads to the formation of a linear calixpyrrole dimer[43] **27** , whilst a stepwise coupling with 1,3- or 1,4-diiodobenzene (**25** or **26**) respectively, leads to the formation of the elongated calixpyrrole dimmer[43] **28** or the "bent" **29** dimer for improved anion binding ability of calixpyrrole parent compound **(Scheme-14)**.

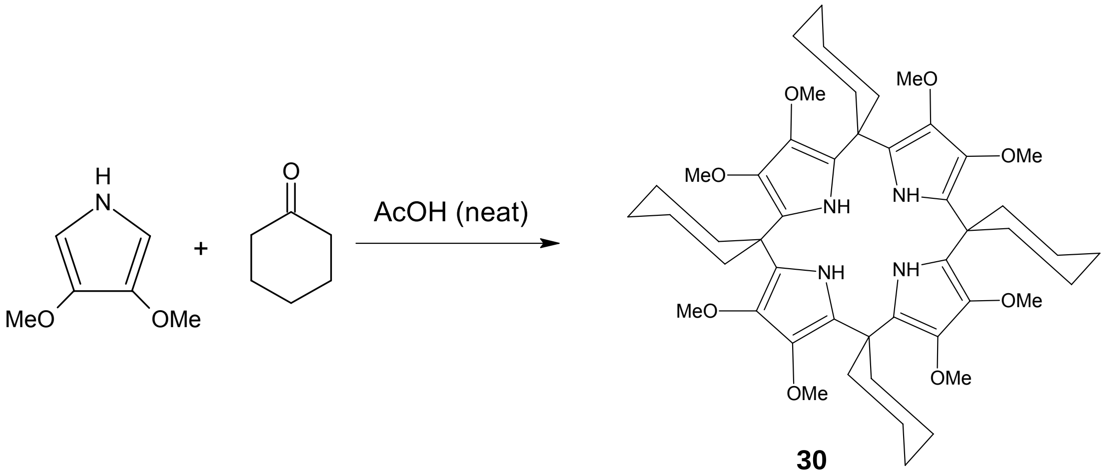


Scheme-13 Two step synthesis of building block **24**.



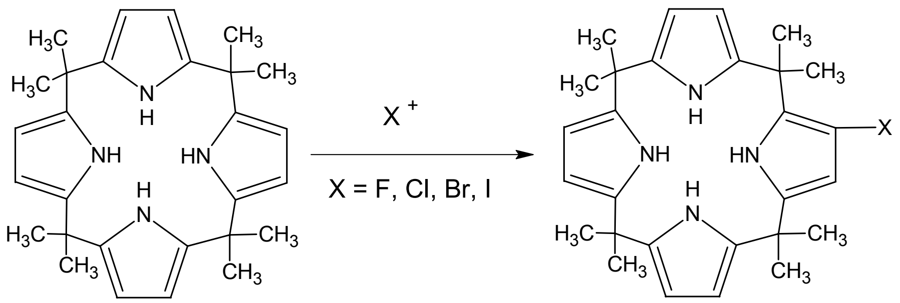
Scheme-14 i) Pd $(PPh_3)_4$, CuI, *i*-Pr_2NH-DMF (91%); ii) $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH-DMF, 1,4-diiodobenzene (for **25**: 87%), 1,3-iodobenzene (for **26**: 82%); iii) **23** (0.5 equiv.), Pd $(PPh_3)_4$, CuI, *i*-Pr_2NH-DMF (**28**:43%; 29:41%).

An additional example, β-octa-methoxy-*meso*-tetraspirocyclohexylcalix[4]pyrrole **30** was prepared *via* the condensation of 3, 4-dimethoxypyrrole with cyclohexanone under slightly modified conditions[39]**(Scheme-15)**. The resulting calix[4]pyrrole was then isolated in 8% yield after column chromatography. The anion binding affinity of compound **30** was studied by ^{1}H NMR spectroscopic titrations. As expected, decrease in binding affinity was seen for the electron rich methoxy version, compared to the parent form of calix[4]pyrrole.



Scheme-15 Synthesis of electron rich β-octamethoxycalix[4]pyrrole using a modified preparative strategy, wherein acetic acid was employed as the solvent.

Another study, published by Miyaji *et al.*,[44] served to underscore the importance of electron withdrawing or donating groups on the β-rim periphery in terms of regulating the anion affinity of calix[4]pyrroles. In this study, a series of halogen-bearing β-rim monosubstituted calix[4]pyrroles **31-34**, were made by adding an appropriate electrophilic halogen source in a finely tuned manner to form preferentially the mono- functionalized calix[4]pyrroles as shown in **Scheme 16**.

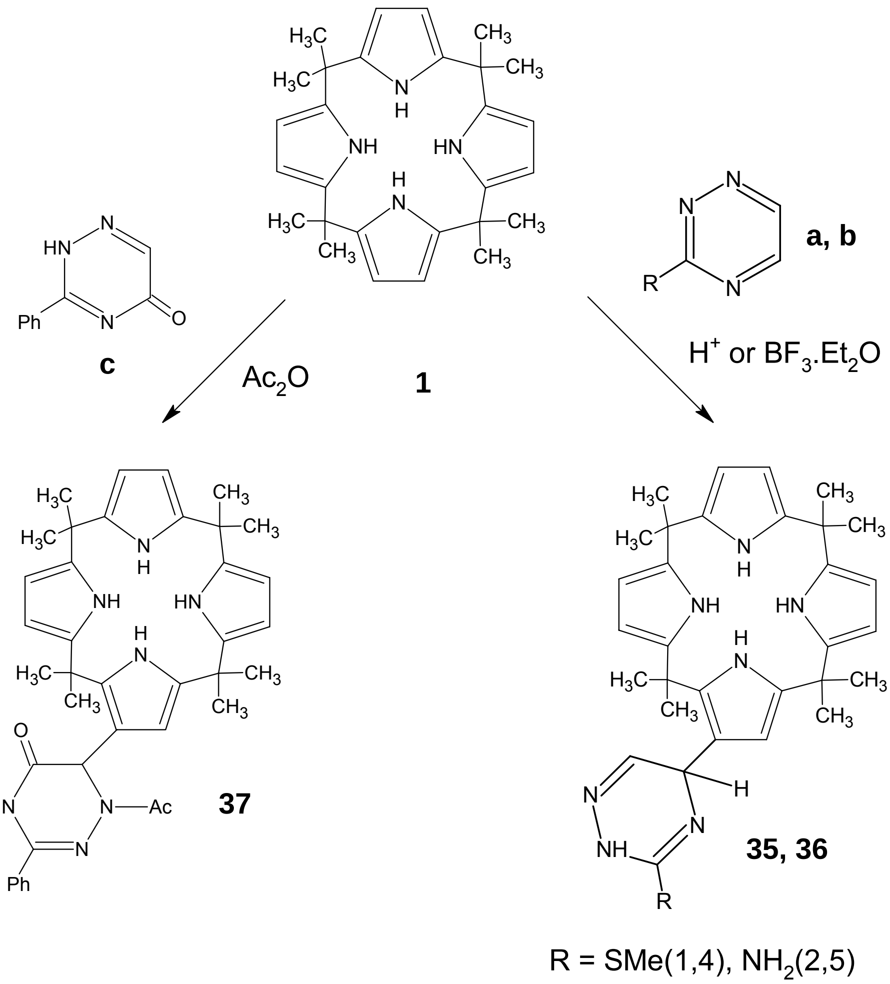


31 X = F
32 X = Cl
33 X = Br
34 X = I

Scheme-16 Generic scheme for the monohalogenation of calix[4]pyrrole.

One of the newest approaches towards functionalization at β positions (C-rim), have been extensively explored in 2004 by Chupakhin *et al.*[45] who reported the first example of direct heterylation of Calixpyrrole. For heterylation of calixpyrrole, introduction of heterocyclic fragments not only creates additional sites for complexation but also proves its molecular conformation.

1, 2, 4-Triazines as such do not react with calixpyrrole. However, Protonic or Lewis acids activate the triazine ring, and the reactions of protonated 3-methylthio **a** and 3-amino-1, 2, 4-triazines **b** with calixpyrrole **1** in H^+ or $BF_3.Et_2O$ gave adducts **35** and **36.** The reaction of calixpyrrole **1** with 3-phenyl-1, 2, 4-triazin-5(2*H)*-one **c** in the presence of acetic anhydride as an activator affords monoadduct **37** **(Scheme-17).**

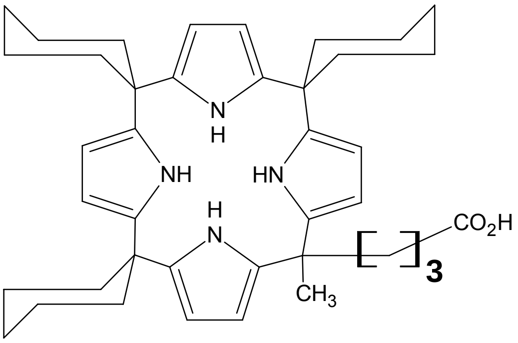


Scheme-17 Direct heterylation of calix[4]pyrrole.

7.2 Functionalization at the *meso*-position (bridge position)

Introduction of aryl or other rigid groups into the *meso*-like positions of calix[4]pyrroles serves not only to change the intrinsic anion selectivity of the calix[4]pyrrole skeleton, but also, in appropriate cases to introduce *secondary binding sites* that might allow binding for selective recognition of cationic, anionic, or neutral guests.

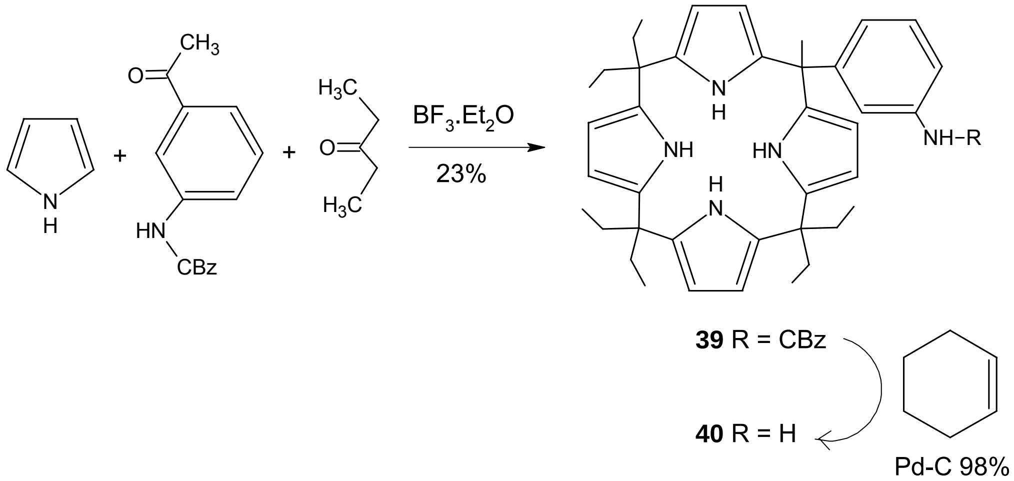
A good example of *meso*-modification was provided by the first type of carboxyl-functionalized calix[4]pyrrole[28] which was produced from the mixed condensation of pyrrole with cyclohexanone and ethyl acetobutyrate. When the proper ratios were used, taking into account the slow reactivity of the δketoester, the *meso*-"hooked" calixpyrrole **(Scheme-6),** was formed in reasonable yields. Hydrolysis of the ester generated the free carboxylic acid functionalized calix[4]pyrrole **38 (Figure-6)**, which could be used for further derivation.



38

Figure-6 carboxylic acid functionalized calix[4]pyrrole **38**.

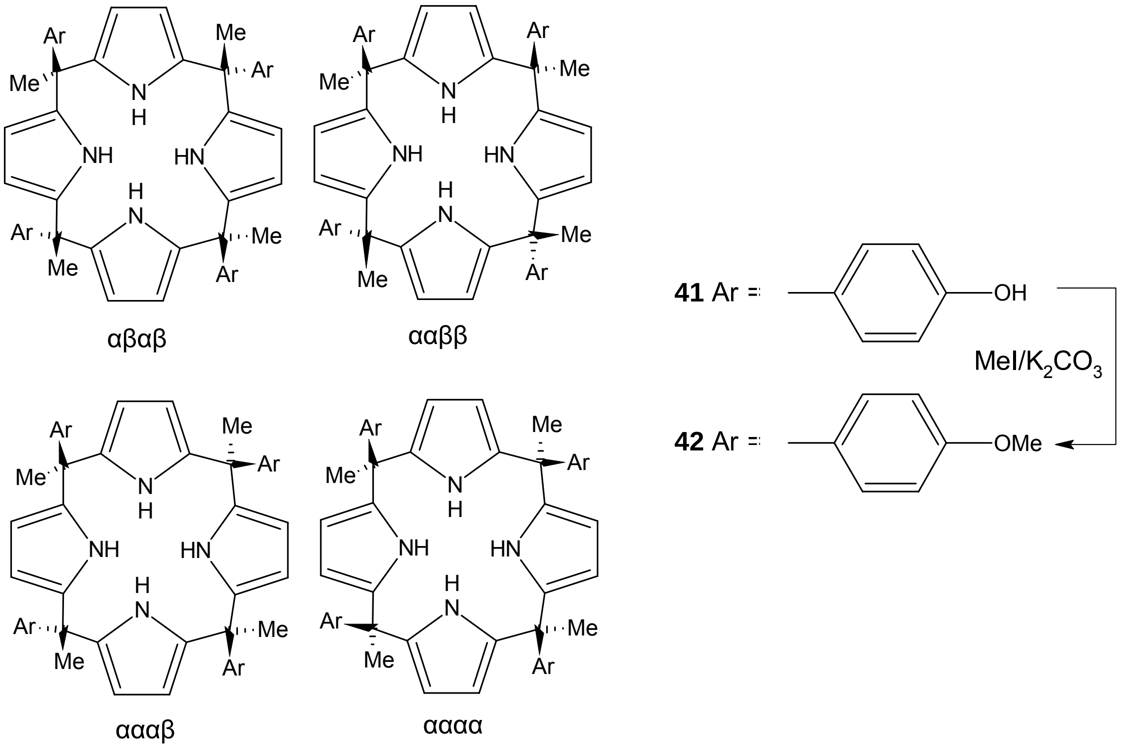
Sessler *et al.*[46] have revised this approach and used it to produce amine functionalized calixpyrroles. Specifically, condensation of Cbz-protected 3-aminoacetophenone, 3-pentanone and pyrrole in the presence of $BF_3{\cdot}Et_2O$ was found to afford the mono-functionalized calix[4]pyrrole **39**. Subsequent deprotection by Pd–C gave the mono-amine functionalized calixpyrrole **40** in 23% overall yield **(Scheme-18)**.



Scheme- 18 Synthesis of mono-amine functionalized calix[4]pyrrole.

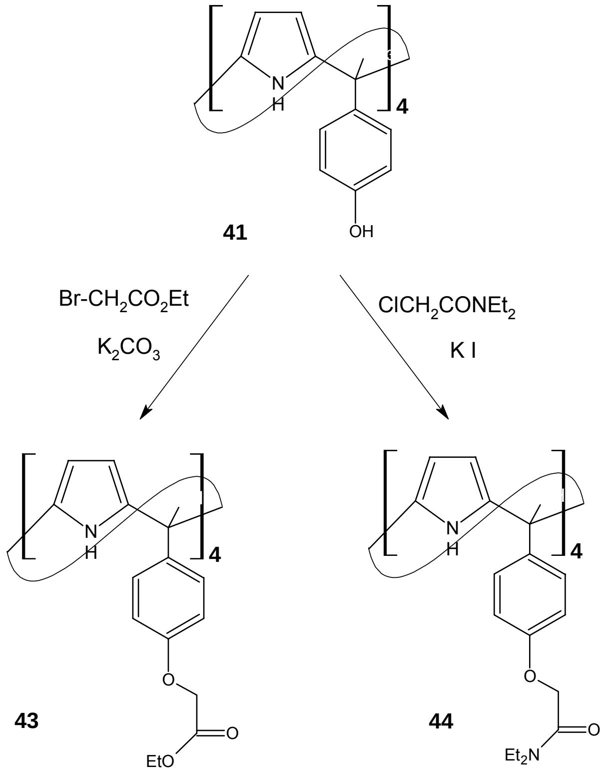
In an effort to improve further the selectivity of calixpyrrole derivatives for particular anions and especially the chloride-over-phosphate selectivity, calix[4]pyrrole systems bearing substituted aryl groups in the *meso*-positions were prepared and their anion coordination properties had been examined.[27] As detailed in reported paper, calix[4]pyrrole **41** 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 αααα configurational isomers, where the "α" and "β" nomenclature follows the standard porphyrin convention **(Scheme-19)**.

For instance, each of the isomers of **41** was found to display a considerably higher affinity for anions than did the corresponding isomers of the methoxy substituted system, **42**. 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 authors expectation that the deep cavities of **41**and **42** would serve to increase anion affinities in absolute terms.



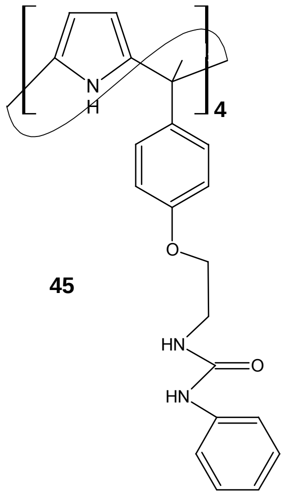
Scheme-19 Structure isomers of "deep cavity" calix[4]pyrroles **41** and **42**.

Further modification at *meso*-position was obtained by reaction of compound **41** with ethylbromoacetate in dry acetone in presence of K_2CO_3 with heating at reflux for 5 days.[47] The tetraester derivative **43** was isolated as a white powder in 76.5% yield. And amide macrocycle **44** was synthesized by reaction of compound **41** with 2-chloro-*N,N*-dimethylacetamide and potassium iodide in dry acetone with stirring for 5 days and was isolated in 50% yield[47] **(Scheme-20)**. These extended cavity ester and amide calix[4]pyrrole macrocycles has shown to bind fluoride exclusively in d_2- DMSO solution.



Scheme- 20 Synthesis of novel, super extended deep cavity calix[4]pyrrole.

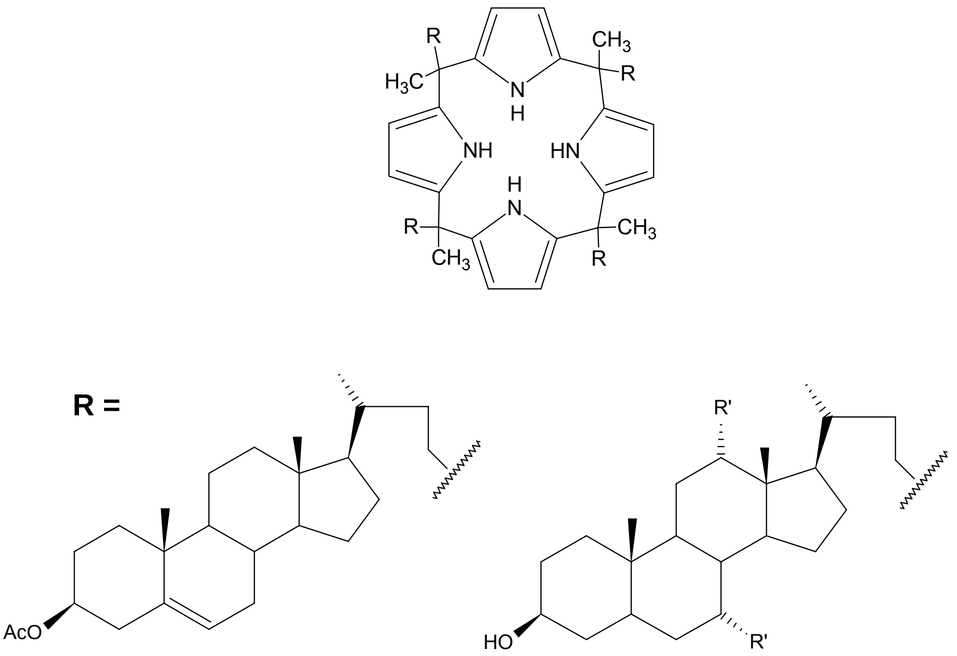
Danil de Namor *et al.*[48] were the first to show the power of this approach with their treatise on a double-cavity calix[4]pyrrole derivative, *meso*-tetramethyl-tetra[*N*-(2-phenoxyethyl)-*N*'-phenylurea]calix[4]pyrrole **45**, with enhanced hosting ability for the fluoride anion has been designed and characterized **(Figure-7).**



45

Figure-7 A double-cavity calix[4]pyrrole **45**.

Novel deep cavity calix[4]pyrroles **46** and **47** derived from steroidal ketones were synthesized and studied for their ability to effect the selective recognition of appropriate sized organic anions[49] **(Figure-8).** One good receptor, the polyhydroxylated αααβ configurational isomer of **47b**, was found to bind both tartaric acid and mandelic acid selectively, while **46** and **47a** 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.



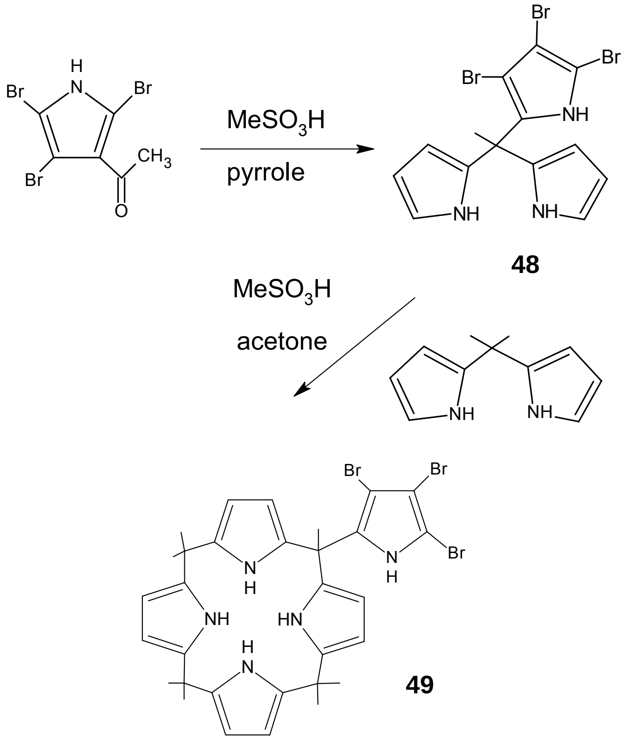
46

47a R'=H

47b R'=OH

Figure-8 Structure of steroidal calix[4]pyrroles.

In 2003, Gale *et al.*[50] reported the synthesis of a new *meso*-modified calix[4]pyrrole, namely the pentapyrrolic calix[4]pyrrole **49 (Scheme-21)**. The fifth pyrrole unit, attached synthetically to a *meso*-position, was expected to act as an ancillary hydrogen bonding doner, thereby enhancing the anion affinities of **49** relative to simple calix[4]pyrroles. Tripyrrolylmethane **48** was synthesized *via* a methanesulfonic acid catalyzed condensation of pyrrole with 2-acetyl-3, 4, 5-tribromopyrrole. But, the [2 + 2] mixed condensation of **48** with dimethyl dipyrromethane in acetone afforded **49** in 14% yield.



Scheme-21 *meso*-modified pentapyrrolic calix[4]pyrrole.

7.3 Modification at the *N*-rim

Takata and co-workers[51] have reported a method for modifying the calix[4]pyrrole at the *N*-rim. Reaction of *meso*-octaethylcalix[4]pyrrole **50** with sodium hydride and methyl iodide in the presence of 18-crown-6 in THF was found to give a distribution of *N*-methylated calixpyrroles **51-55 (Figure-9).** The variation of product was dependent on the concentration of methyl iodide. When 1 equiv. of methyl iodide was used, the main product was the mono-*N*-methylated derivative **51**. On the other hand, use of 2 equivalent methyl iodide resulted in predominantly formation of 53, 54, and 55, where 53 was isolated predominantly. The low yield of 54 and 55 were mainly due to their lower solubility to the eluent. The authors also studied the X-Ray diffraction analysis of **53.** 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 **56** only. The Takata et al. considered that, in solution, reaction of calix[4]pyrrole **50** with butyllithium 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 and co-workers propose 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 analyses of Floriani[52]; in the case of tetralithio-*meso*-

octaethylcalix[4]pyrrole these latter researchers observed an ion pair analogous to that proposed by Takata.[51]

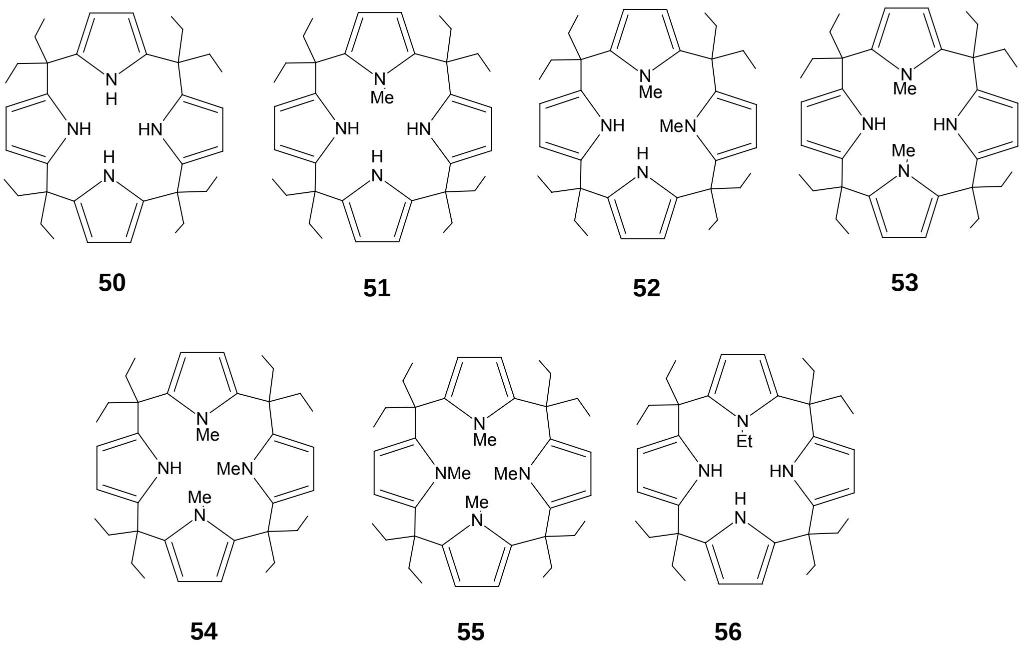


Figure-9 Structure of *N*-methylated calixpyrroles **51-56**.

8. FUNCTIONALIZED CALIXPYRROLES AND THEIR APPLICATIONS

Survey of the literature reveals that calixpyrroles have been used for a multitude of applications e.g. as optical sensors, electrochemical sensors, HPLC supports, anion transporting agents, chelating polymer and nonlinear optical materials etc.

8.1 Calixpyrrole-based Optical Sensors

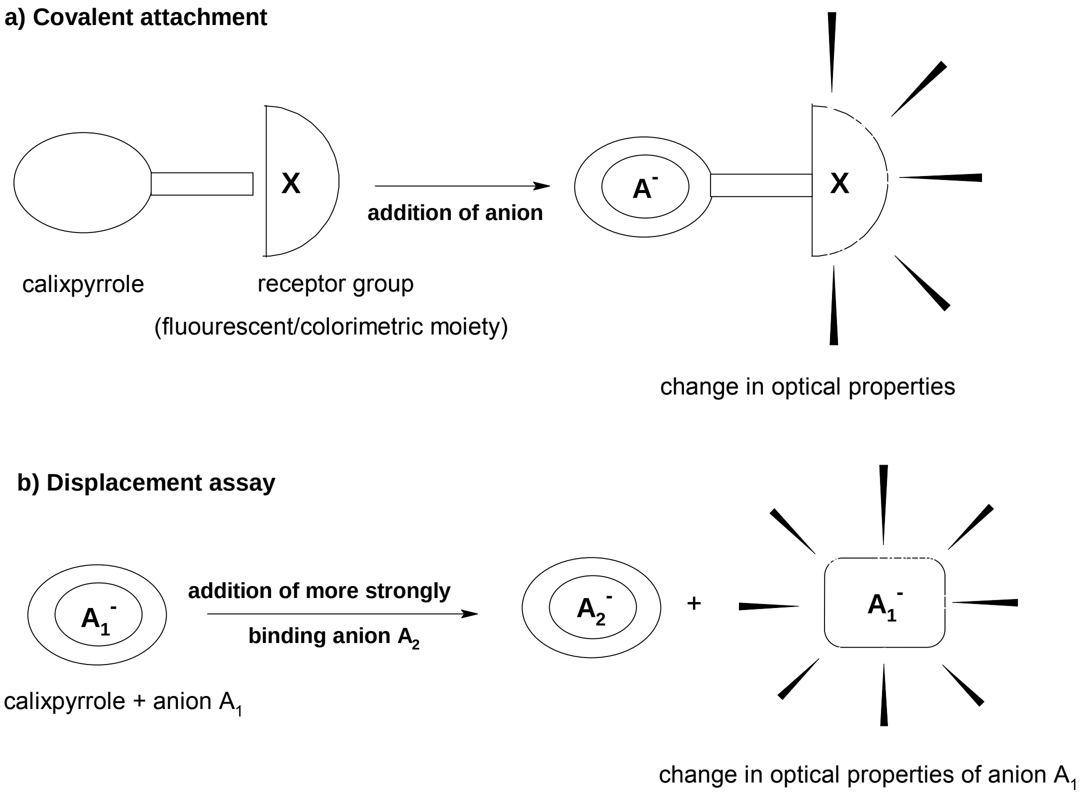
The synthesis of new molecular devices designed to sense and report the presence of a particular substrate is an area of analytical chemistry that is attracting intense current interest. Chromogenic sensors have attracted much attention due to their capability to detect analytes by the naked eye without resorting to any expensive instruments.

Two main approaches have been used in the production of calix[4]pyrrole based optical anion sensors,

I) First approach is based on the *covalent attachment* of a colorimetric or fluorescent reporter group 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. A number of covalently linked, calixpyrrole-based optical sensor systems have been synthesized in the last eight years. Sessler *et al.*[53] reported a new library of covalently linked calixpyrrole derivatives showed that they could find application as anion sensors.

II) Second approach centers on the use of displacement assay.[54] In this study, initially formed calix[4]pyrrole complex involving a colored anion is used that breaks upon the addition of a more strongly coordinating anionic analyte.

These approaches are shown schematically in **Scheme 22**.



Scheme-22 Two approaches used to get calix[4]pyrrole based optical sensors.

The first generation systems consisted of anthracene groups attached to the calix[4]pyrrole skeleton via amide bonds.[53] For example, the mono-acid derivative **18** was coupled to 1-aminoanthracene using dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) in DMF to afford a calix[4]pyrrole–anthracene conjugate[53] **57** that possesses a direct link between the calix[4]pyrrole anion binding site and the anthracene fluorophore.

Other calix[4]pyrrole–anthracene conjugates were synthesized by coupling the calix[4]pyrrole mono-acid derived by saponification of compound **19** with 1-aminoanthracene or 9-aminomethylanthracene using the benzotriazolyloxy-tris(dimethylamino)phosphonium (BOP) amide coupling reagent. This afforded the conjugate compounds **58** and **59** in 63 and 51% yields, respectively **(Figure-10).**

Recently, three new chromogenic calix[4]pyrrole sensors[55] **60-62** were synthesized and characterized. Sensor **60** was prepared by an electrophile aromatic substitution reaction of Octamethylcalix[4]pyrrole **1** with tetracyanoethylene. Sensors **61** and **62** were obtained by condensation of formyl-octamethylcalix[4]pyrrole **21** with 1-indanylidene-malononitrile and anthrone, respectively. The anion

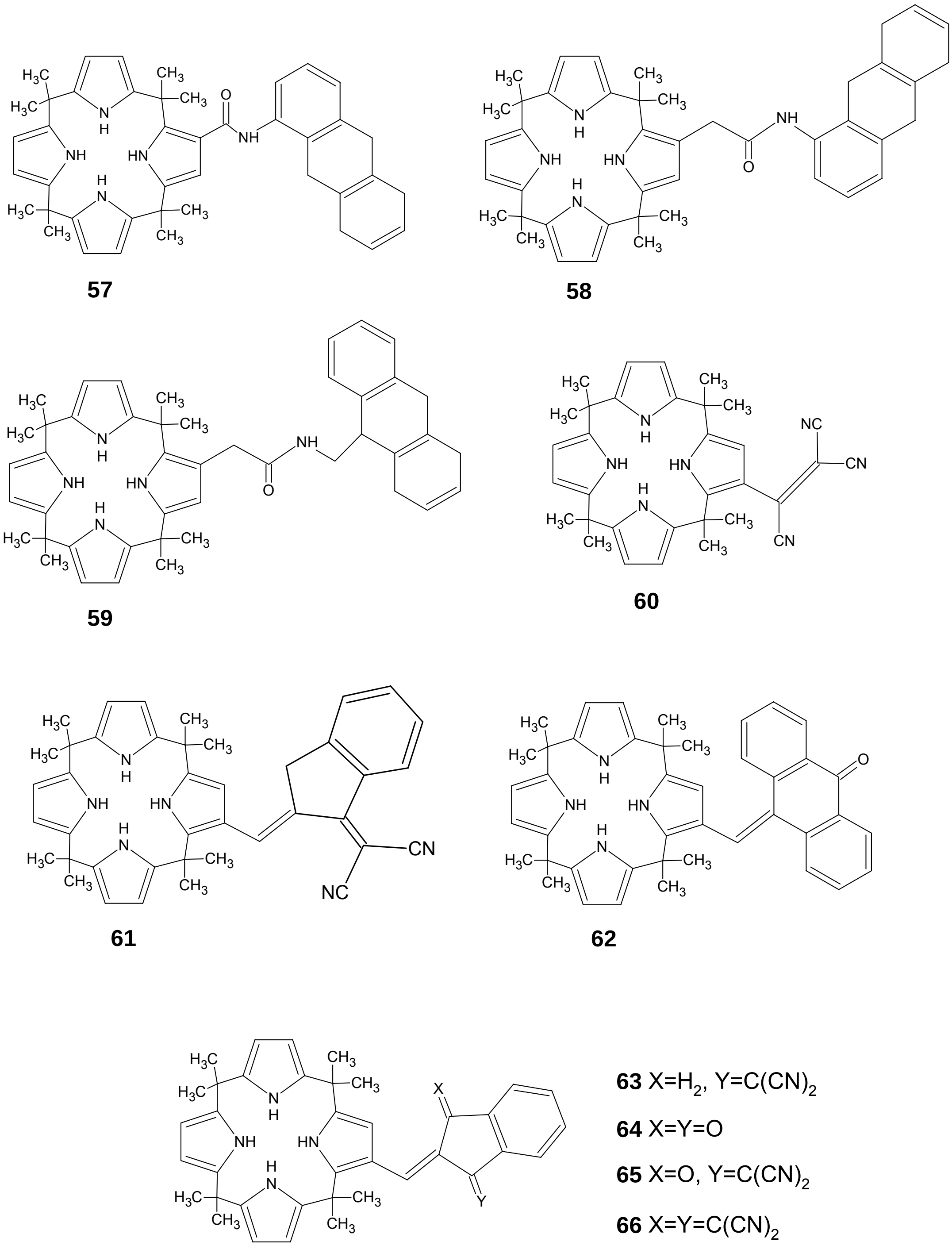
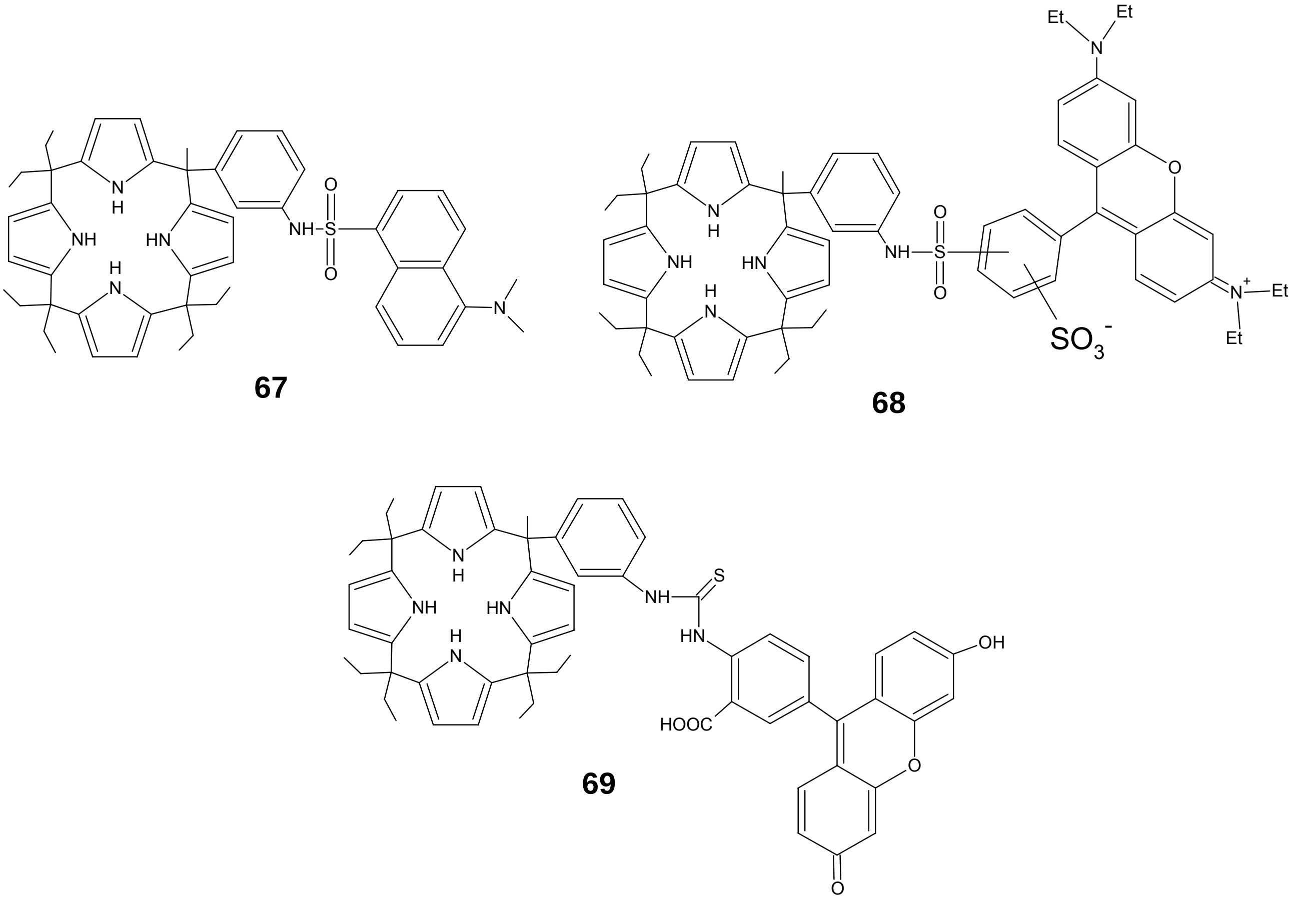


Figure-10 Structure of calix[4]pyrrole based optical sensors **57-66**.

sensing ability of sensors **60, 61** and **62** was studied on a qualitative level by visual examination of the anion-induced color changes in the solution of the sensors **60-62**. To demonstrate the relevance of sensors **60-62** to health care applications,[56] they performed the sensing experiments at a high electrolyte concentration and in blood plasma. Further more, studies with carboxylates of medical interest (salicylate, ibuprofen and naproxen) were performed using newly developed assay with sensors **60-62** embedded in polyurethane films.

Anzenbacher *et al.*[57] 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 **63-66**. The push-pull feature results in augmented signal output as well as in dramatic changes in anions selectivity exemplified by a 50-fold increase in acetate *vs* chloride selectivity compared to the parent calix[4]pyrrole.

A series of 'second generation' calix[4]pyrrole anion sensors[46] **67**, **68**, and **69** were synthesized by coupling *meso*-mono-amine calix[4]pyrrole **40** with commercially available dyes as fluorescent tags **(Figure-11)**. These adduct **67**, **68** and **69** 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 **67**, **68**, and **69**, were found to be quenched in the presence of anions.



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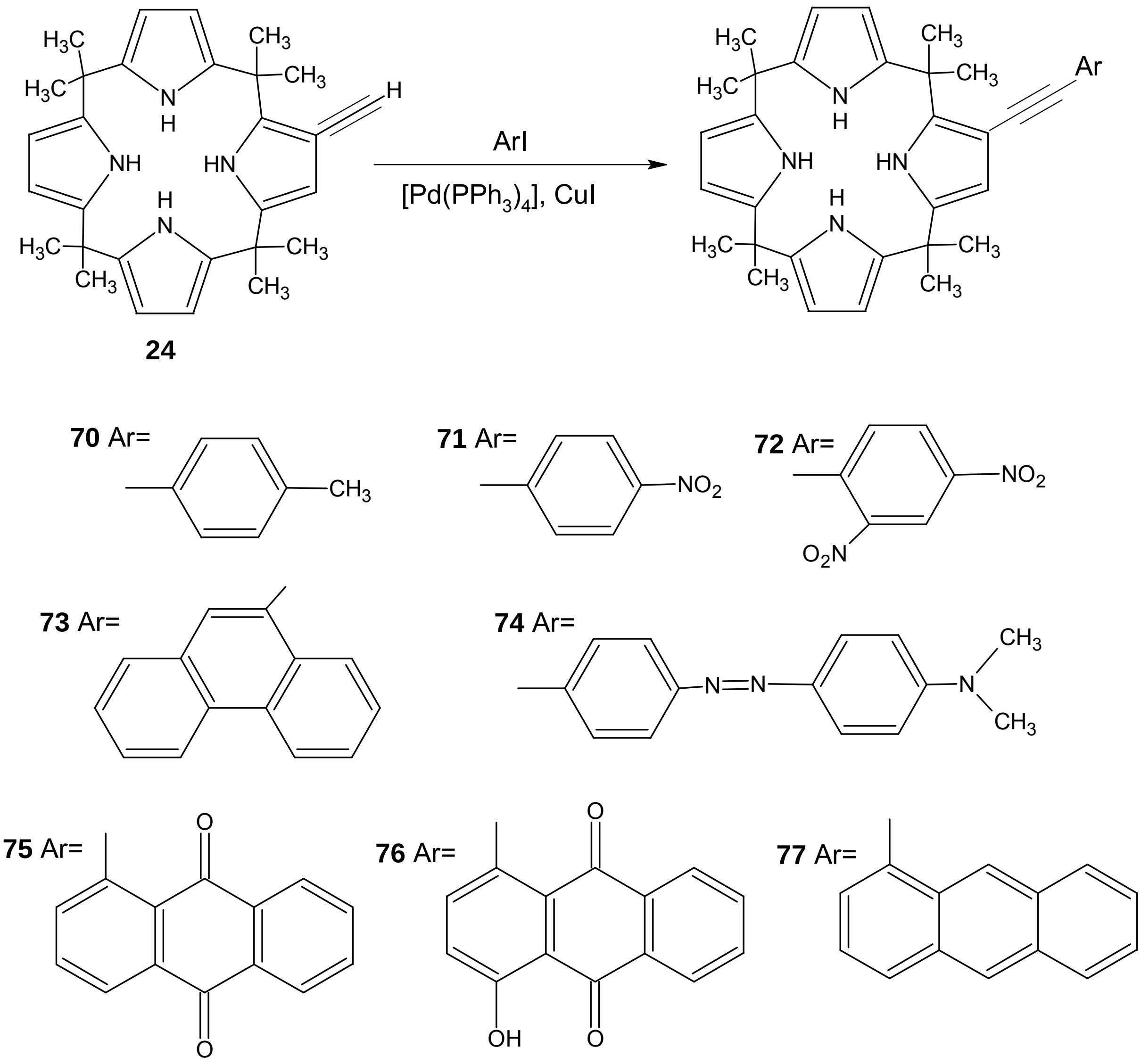
68

69

Figure-11 Three fluorescent calix[4]pyrroles prepared by attaching commercial dyes to the amino-functionalized species.

In addition to the sensors noted above, The mono-alkynyl calix[4]pyrrole **24** has also been used as a basis for the construction of optical anion sensing agents. Palladium catalyzed coupling of a variety of aromatic species including nitroaromatics, anthraquinoines and pyrene with compound **24** afforded a new library of calix[4]pyrrole derivatives[42,58] **70-77 (Scheme-23)**.



Scheme-23 Examples of potential colorimetric calix[4]pyrroles **70-77**.

The second approach which is displacement-based has been explored less extensively than the first approach. Still, has been exploited successfully to produce a very different kind of colorimetric anion sensor was developed[59] which does not require any functionalization of the parent molecule. They discovered that when bound to *meso*-octamethylcalix[4]pyrrole **1**, the 4-nitrophenolate anion **X** loses its intense yellow color 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. This was observed as a colorless to yellow color change, with the intensity of the recovered yellow color being dependent upon the affinity of the calixpyrrole for the added anion and the anion concentration **(Figure-12)**.

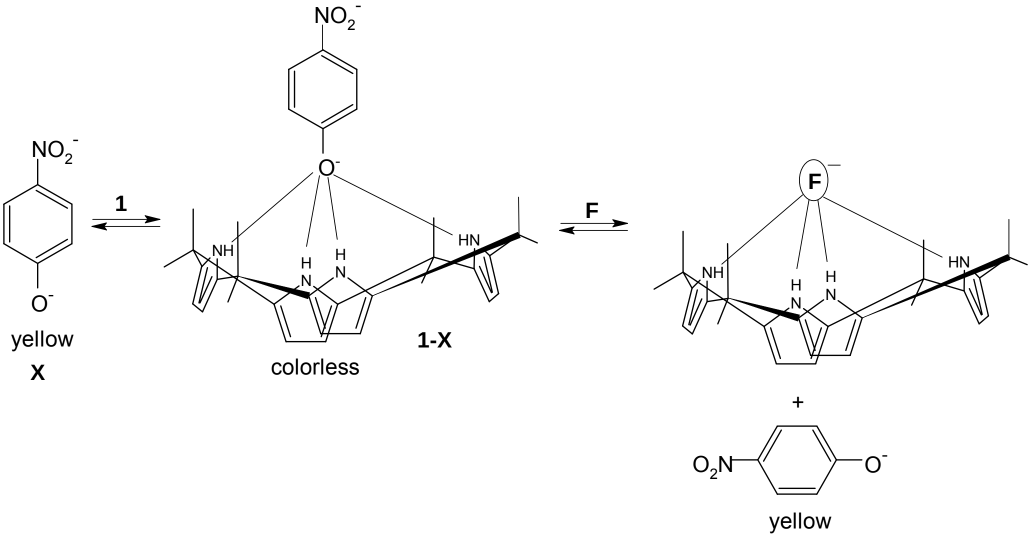


Figure-12 F^- dependent equilibrium between the *meso*-octamethylcalixpyrrole-4-nitrophenolate and *meso*-octamethylcalixpyrrolefluoride.

8.2 Calix[4]pyrrole-based Electrochemical Sensors

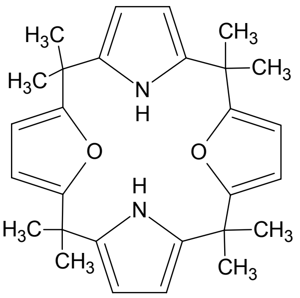
For the development electrochemical anion sensors based on calixpyrroles, different approaches include the incorporation of calixpyrroles in ion-selective electrodes (ISEs), discrete redox active molecular receptors and chemically modified electrodes.

Ion-selective electrodes (ISEs)

Kim *et al.*[60] reported that electrode based on the *meso*-tetracyclohexylcalix[4]pyrrole exhibit excellent electrochemical response characteristics and selectivity for Ag (I) ion.

They utilized the calix[m]pyrrole[n]furans (m+n=4), such as *trans*-octamethyl-calix[2]pyrroles[2]furans (**78**), *cis*-octamethylcalix[2]pyrroles[2]furans (**79**), and octamethyl-calix[1]pyrrole[3]furans (**80**) **(Figure-13)** as sensing materials in ion selective electrodes to investigate the relationship between Ag(I) ion selectivity and the conformation of the porphyrinogen substituents. The polymeric liquid membrane based on **78**, *trans*-N_2O_2 porphyrinogen gave the best results in terms of the working concentration range, Nernstian slope and selectivity towards interfering ions. The best performance[61] of the **78**-based electrode can be understood since its selectivity towards Ag (I) exhibited depends strongly on the geometrical arrangement of the nitrogen coordination centers in the porphyrinogen skeleton and its tendency for linear coordination.

Lee *et al.*[62] reported the potentiometric behavior of three types of newly synthesized calix[2]furano[2]pyrrole derivatives towards silver-ion **(Figure-13)**. PVC (polyvinyl chloride)-membrane electrodes incorporating the ionophores-**81, 82** and **83** exhibited the response to silver-ion. The best results were obtained with the membrane containing N and O atoms in the ligand (ionophore-**81**), bis(2-ethylhexyl sebacate) (DOS) as a plasticizer and potassium tetrakis(4-chlorophenyl borate) (KTpClPB) as a lipophilic additive. These silver-ion electrodes displayed very good selectivity for Ag^+ ion with respect to alkali and alkaline earth metal-ions, NH_4^+, and H^+.



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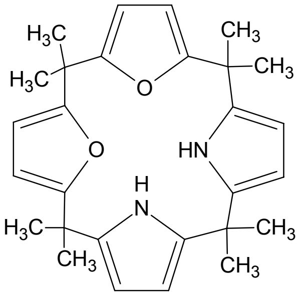

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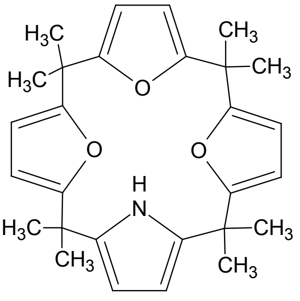

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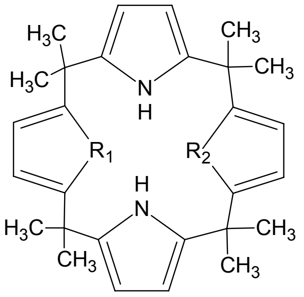


81: $R_1=R_2=O$

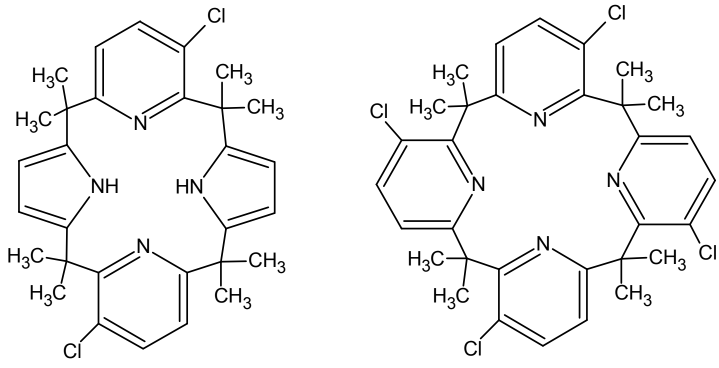
82: $R_1=R_2=S$

83: $R_1=S$, $R_2=O$

Figure-13 The chemical structures of ionophores **78-83**.

PVC based ISEs from *meso*-octamethylcalix[4]pyrrole **1** and analogue system was also prepared[63,64] namely dichlorocalix[2]pyrrole[2]pyridine **84** and teterachlorocalix[4]pyridine **85 (Figure-14)**.

ISEs derived from compound **1** displayed/showed strong anionic response towards Br^-, Cl^-, and $H_2PO_4^-$ and too much lesser extent towards F^- where as pH=9, compound **1** not only shows cationic response towards Cl^-, and Br^- anions but also selectively (that is $Br^- < Cl^- < OH^- \approx F^- < HPO_4^{2}$). That is non-Hofmeister in nature. ISEs derived from compound **84** and compound **85** were investigated towards a range of anions namely Br^-, Cl^-, F^-, $HPO_4^{-2}/H_2PO_4^-$ and were found to be pH depended.

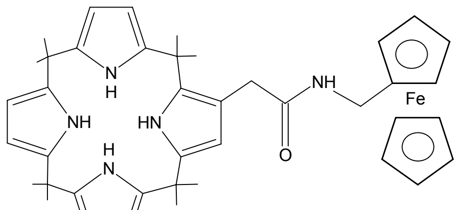


84 **85**

Figure-14 Structures of dichlorocalix[2]pyrrole[2]pyridine **84** and tetrachloro calix[4] pyridine **85**

Discrete redox-active molecular receptors

The development of discrete redox-active receptors[65] containing a guest-binding site coupled to a redox-active reporter group is an area of supramolecular chemistry that has attracted much attention. Beer and Gale[66] have synthesized a redox-active ferrocene group to the calix[4]pyrrole framework but anion binding properties of the resulting receptors are to be studied using electrochemical means. As with the optical sensors described above, this was done *via* both *meso* functionalization and modification of *β*-pyrrolic position. Thus, compound **86** and **87** were prepared by coupling the corresponding calix[4]pyrrole mono-acid species to aminomethyl-ferrocene using the benzotriazolyloxy-tris(dimethylamino)phosphonium (BOP) amide coupling reagent, while an alternate system, **88**, was synthesized via a mixed condensation involving pyrrole, cyclohexanone, and acetylferrocene[29] **(Figure-15)**.



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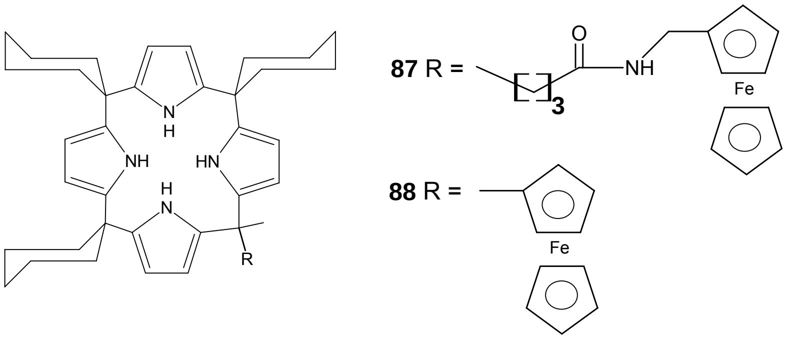


Figure-15 Ferrocene appended calix[4]pyrrole **86-88**.

^{1}H-NMR spectroscopic titrations in the same solvent system revealed that one ferrocene CH proton participated in hydrogen bonding interactions with calixpyrrole NH hydrogen-bonding interaction that are thought to stabilize the bound anion in complex are shown in **Figure-16**. The crystal structure of compound **88** revealed that it functions as electrochemical sensors and binds F^-, H_2PO_4 and Cl^- anions.[29]

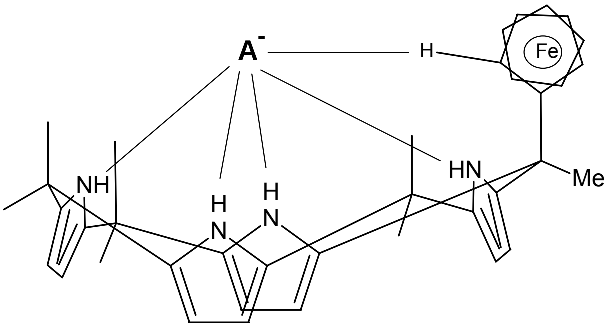


Figure-16 Proposed CH-anion interaction in complex.

Chemically modified electrodes

Out of the two ways of utilizing calixpyrroles in the production of modified electrodes, Gale *et al.*[67] prepared chemically modified electrode from calix[4]pyrrole monomers containing α-unsubstituted pyrrolic species and compounds **89** and **90 (Figure-17)**, were synthesized using methods analogous to those used to prepare **86** and **87**. 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.

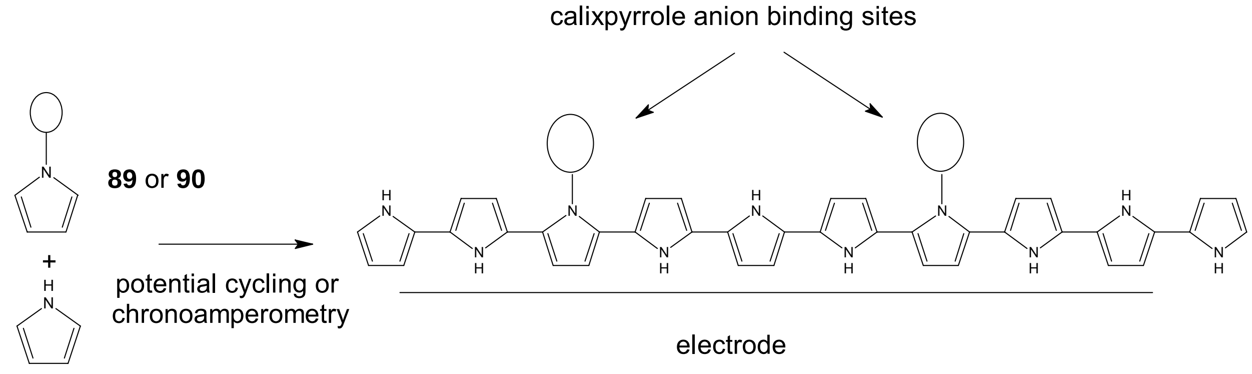
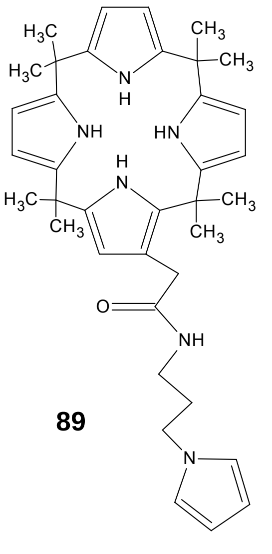
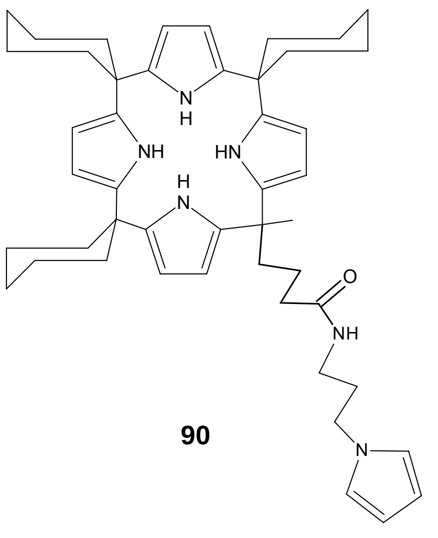


Figure-17 Polymerization of calixpyrrole monomers

They also investigated the use of these co-polymer films of **89**-pyrrole and **90**-pyrrole **(Figure-18)** as anions masks any perturbation due to the formation of calix[4]pyrrole-anion complexes on the cyclic voltammogram.



89



90

Figure-18 Chemically modified electrodes.

8.3 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.*[68] According to their report, 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, benzyloxycarbonyl(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 isochratic 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-19)**.

Recently, Jiang *et al.*[69] 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-19**) 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 the further studies and applications in the fields of analytical and supramolecular chemistry.

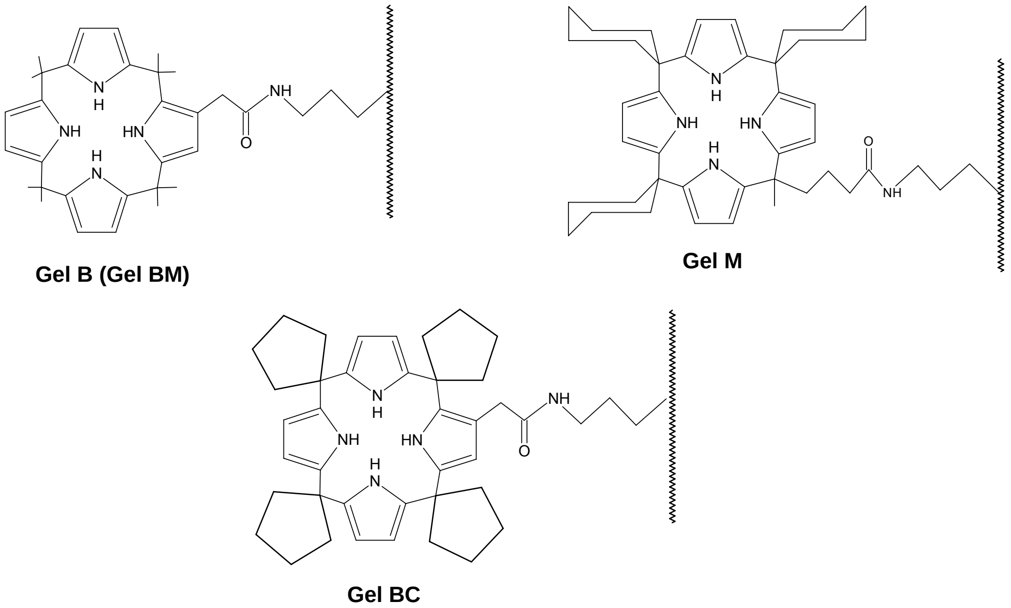
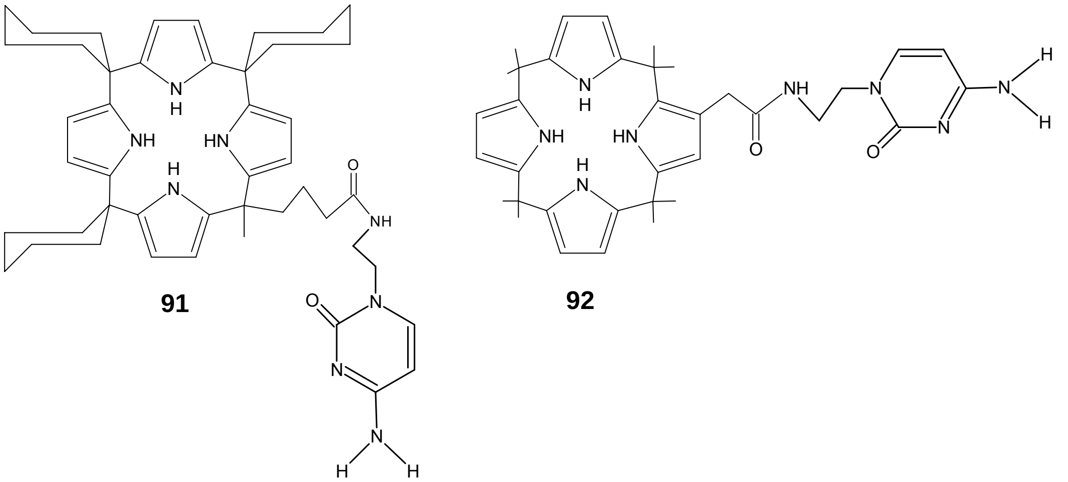


Figure-19 Sketch maps of the calix[4]pyrrole-modified silica gels [Gel B (Gel BM), Gel M and Gel BC].

8.4 Calix[4]pyrrole-based Anion Transporting Agents

Calix[4]pyrroles have been shown to act as anion carriers capable of transporting anions or anionic substrates through Pressman-type model membranes.[70] This transport ability was tested specifically *via* the synthesis of the two cytosine substituted calix[4]pyrroles, **91** and **92 (Figure-20)**. These systems were synthesized and studied as neutral receptors for 5’-guanosine monophosphate (5’-GMP). Transport studies revealed that good selectivity for 5’-GMP over 5’-cytocine monophosphate (5-CMP) and 5’-amino monophosphate (5’-AMP) was seen for compound **91**, which acts as a ditopic receptor by binding both the phosphate “head” of 5’-GMP with the calix[4]pyrrole core and its purine “center” with cytosine “tail” in a “two point” recognition manner.



91 **92**

Figure-20 Calix[4]pyrrole-cytosine conjugate (*meso* and *C-rim* linked).

8.5 Chelating properties of Polymer-bonded Calix[4]pyrrole

Andrzej *et al.*[71] have reported the synthesis and preliminary sorption properties of three types of chelating resins containing calixpyrroles units **(Figure-21)** which were obtained by:

(i) Immobilization of calix[4]pyrrole on a polymeric support (Vinyl benzyl-chloride/Divinylbenzene copolymer),

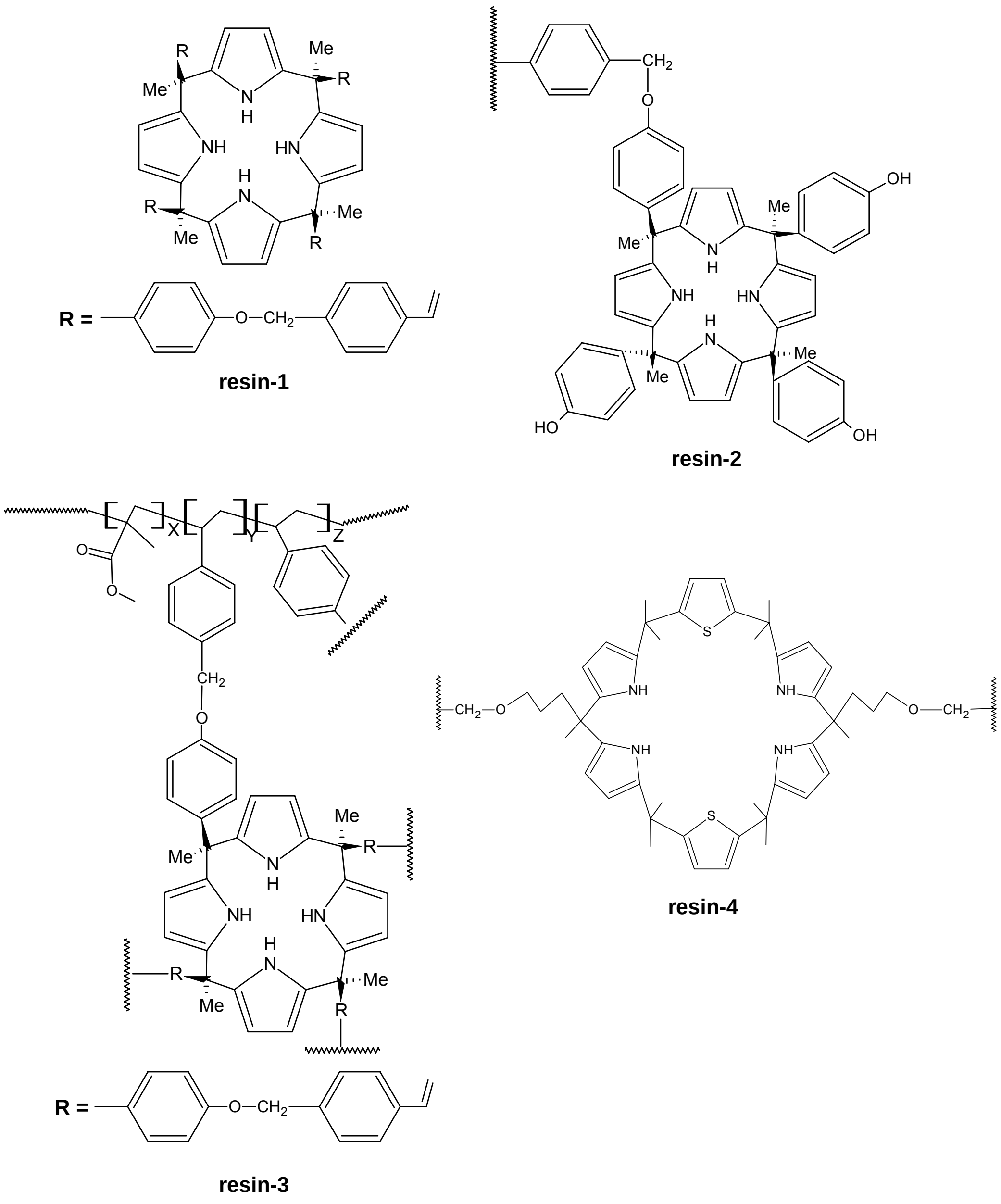
(ii) Condensation of calix[4]pyrrole with formaldehyde to form insoluble polymeric materials, and

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

Among many new calixpyrrole receptors, there is “hetero” or “hybrid-calixpyrroles”. These hybrid systems contain thiophene or furan other than pyrrole heterocycles incorporated into a macrocycles, presenting a new class of receptors with interesting anion and cation-binding potential. Andrzej et al[72] presented the synthesis and batch-made 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 plays role in complexing precious metal-cations.

A range of static sorption studies was performed on these materials **(resin 4) (Figure-21)** that demonstrated their strong affinity towards cations of the noble metals (Au, Ag, Pt, Pd) over other transition metal-cations, Pb(II), and Tl(I) was then the mismatch between the size of the macrocycle and these cations. 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.

Recently, the same authors[73] have mentioned that all resins demonstrated a preference for fluoride anions over other halides in static sorption studies. Larger anions, like iodides, were not complexed by the resin due to lack of fit between the size of the anion and the size of the binding site. Thus **resin1-3 (Figure-21)** can have proved to be used as sorbents of anions from non-aqueous media and are promising materials for separation techniques.



resin-1

resin-2

resin-3

resin-4

Figure-21 Novel chelating resin containing calixpyrrole macrocycles resin **1- 4**.

8.6 Nonlinear Optical Properties of Li@Calix[4]pyrrole

Zhi-Ru Li *et al.*[74] designed a new organic electride compound in theory, Li@calix[4]pyrrole. It may be stable at room temperature. The structure with C_{4v} symmetry resembles a cup-like shape. In the cup-like Li@calix[4]pyrrole, the Li atom is ionized to form a cation and an excess electron anion. The excess electron cloud was like a saucer underneath the cup. The authors presented the geometry structure, the Raman spectrum, and the electronic properties of Li@calix[4]pyrrole. It was found that the very large first hyperpolarizability of Li@calix[4]pyrrole was mainly due to the excess electron. The calculated results confirmed their prediction that this Li@calix[4]pyrrole electride had considerable large nonlinear optical (NLO) response, β= 7326 au, which was almost 20 times larger than that of calix[4]pyrrole without electride characteristics.

Recently they reported[75] a new type of alkalide compounds with the cup-like complexant, Li^+(calix[4]pyrrole)M^- (M=Li, Na, and K), which may also be stable at room temperature and found that this kind of compound with an alkali anion possessed considerably larger first hyperpolarizability. The alkali anion plays a crucial role in the large β which increases as the atomic number of the alkali anion increases.

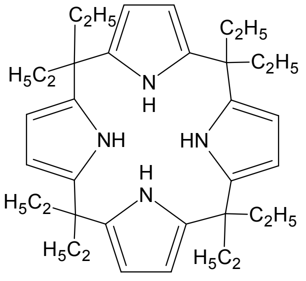
8.7 Poly(vinylidene difluoride)-based Calix[6]pyrrole Electrolytes.

Wieczorek *et al.*[76] have reported the effect of calix[6]pyrrole in polyethylene glycol (PEG) $LiBF_4$ poly electrolytes and showed that the addition of calix[6]pyrrole to polyether-based electrolytes doped with $LiBF_4$ demonstrated in a considerable increase in the cation transport number and has confirmed it by dc-ac current techniques as well as by PEG NMR studies. The increase Li transport number has shown to be associated with decreasing in ionic conductivity of composite polymer electrolytes. The author has found that this effect is weaker in these cases than electrolytes with calix[4]arene previously studied by them.[77,78] Kalita *et al.*[79] have studied composite electrolytes containing calix[6]pyrrole derivatives as an anion complexing agents for I^-, $CF_3SO_3^-$, and BF_4^-. They also collected the data for liquid systems based on polyethylene glycol dimethyl ether (PEODME) as a solvent with varying concentrations of the supramolecular additive. The observed decrease of conductivity was attributed to the anion complexation. The conductivity and electrochemical properties of poly (vinylidene difluoride)-based (PVdF-based) calix[6]pyrrole-containing gel electrolytes were also tested. They tried to establish correlation between the complexing ability of the macrocyclic additive and the properties of the electrolytes.

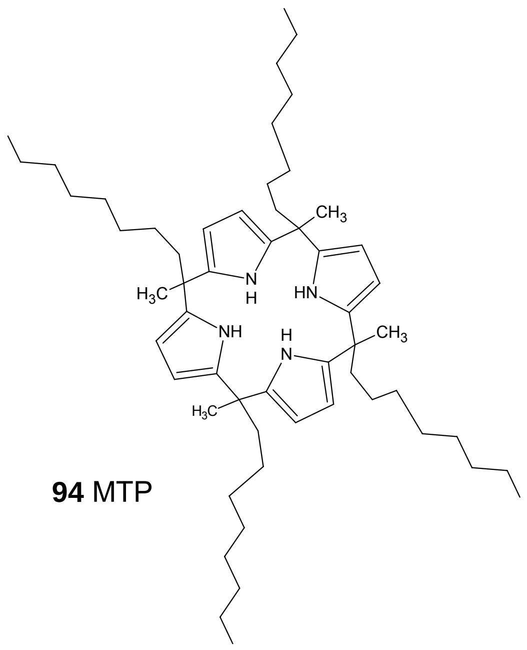
8.8 Calixpyrrole-based Langmuir-Schäfer films.

Valli *et al.*[80] have deposited thin film of *meso*-octaethyl-calix[4]pyrrole (MOP) **93 (Figure-22)** on suitable surface by the Lnagmuir-Blodgett (LB) technique in order to obtained optical sensors using the surface plasmon resonance (SPR) spectroscopy technique and have shown their application in optical gas sensing devices for the discrimination between methanol and ethanol vapours.

A new calix[4]pyrrole macrocycle, *meso*-tetra(methyloctyl)calix[4]pyrrole (MTP) **94**, has been synthesized and characterized[81] **(Figure-22)**. Thin films of MTP were transferred onto hydrophobized quartz and silicon oxide sheets by using the Langmuir-schäfer (LS) method (horizontal lifting). The results showed that although not chiral by themselves the MTP molecules within the film exhibited chirality induced by binding with the chiral guests. The authors showed that the tailoring of the calix[4]pyrrole with longer hydrophobic tails, together with application of the LS technique, gave rise to structurally ordered thin films.



93 MOP



94 MTP

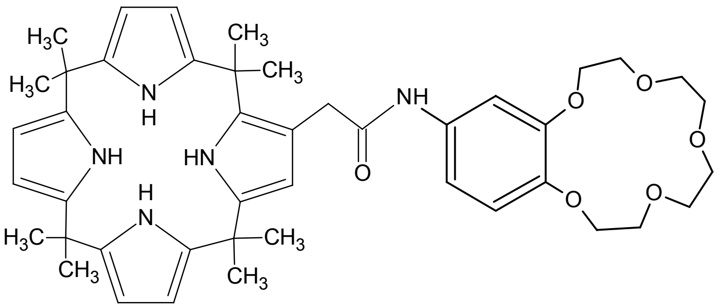
Figure-22 Molecular structures of *meso*-tetra(methyloctyl)calix[4]pyrrole (MTP) and *meso*-octaethylcalix[4]pyrrole (MOP).

8.9 Anion/cation Binding Properties of Dimeric-calixpyrrole System

The increase in range of functionalized calix[4]pyrroles, tempts the researchers to think seriously about applying them to real world of applications. One set of these applications involves functionalizing the calixpyrrole skeleton with other small molecules that would modify their properties and response. With this view, Gale *et al.*[82] synthesized “hooked” calixpyrroles, to create a ditopic receptor capable of binding a cation and anion simultaneously. By pursuing this approach they hoped to increase the apparent binding constants for anion recognition (or anion-cation pair) by calixpyrroles.

They synthesized calix[4]pyrrole-crown ether conjugate system[82] **95 (Figure-23)** and this approach served the dual purpose of adding a solubilizing crown ether groups augmenting solubility in both to aqueous and organic media and adding a cationic host site that would allow for the possibility of cooperative binding effects to be explored.

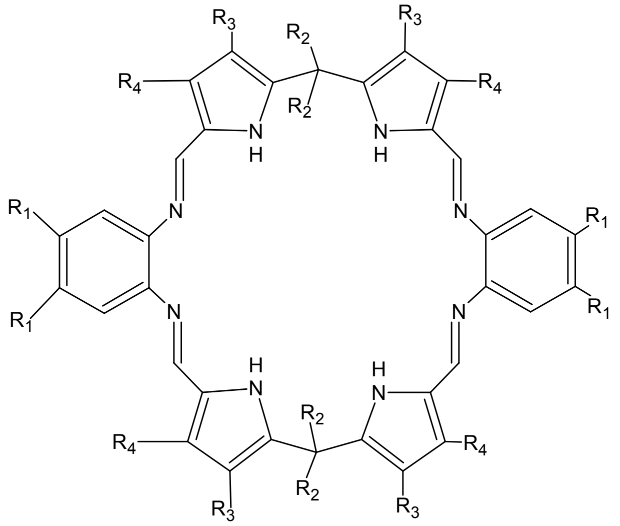
Preliminary ^{1}H NMR spectroscopic studies, carried out in CD_2Cl_2, revealed that system **95** bound both the tetrabutylammonium salts of Cl^- and Br^- roughly 15 times more effectively than parent calix[4]pyrrole molecule **1**. This result was interpreted in terms of the crown ether acting to assist with the coordination of the tetrabutylammonium cation, thereby contributing as additional electrostatic component to halide binding.[83]



95

Figure-23 Synthetic scheme for the formation of calix[4]pyrrole/crown-ether conjugate system.

Additionally, the synthesis, characterization and anion binding properties of three new member of calixpyrrole macrocycles, octa-azacalix[4]pyrrole Schiff-base[84] **96-99 (Figure-24)**. These new macrocycles had binding cavities that, on the basis of modeling studies, appeared big enough to accommodate at least two metal centers. The large core size and ability of these macrocycles to bind multiple anions led the authors to consider that compounds **96-98** could have a role to play as binucleating ligands for metal cations.



96 R_1=H, R_2=CH_3, R_3=H, R_4=H

97 R_1=OCH_3, R_2=CH_3, R_3=H, R_4=H

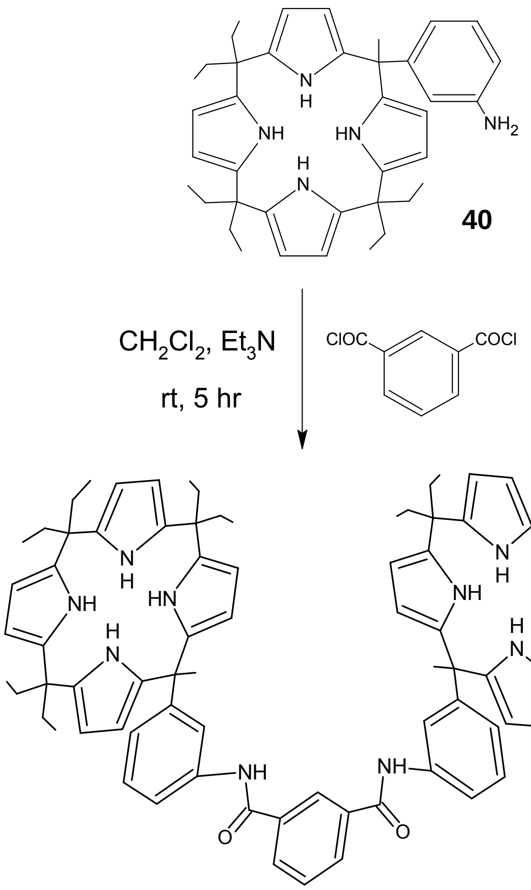
98 R_1=H, R_2=H, R_3=CH_2CH_3, R_4=CH_3

99 R_1=H,R_2=$CH_2CH_2CH_3$, R_3=H, R_4=H

Figure-24 Octa-azacalix[4]pyrrole Schiff-base **96-99**.

Pyrrolic ligands have a history as metal complexing ligands and, indeed, in limited instances have been used to support the formation of binuclear complexes. In fact, Schroder and Love reported that analogues of macrocycles **96-98** could be used to stabilize a bis-Pd (II) complex.[85] The synthesis of a new dipropyl-calix[4]pyrrole schiff-base macrocycle, compound **99**, and its Fe(III) coordinated complex has been also reported.[86]

In 2005, Saki and Akkaya[87] developed a strategy to the synthesis of dimeric system. They synthesized a novel dimeric calixpyrrole **100**, which was synthesized by mono-aminocalix[4]pyrrole **40** coupled with *iso*-phthaloyl in dichloromethane in presence of Et_3N **(Scheme-24)**.

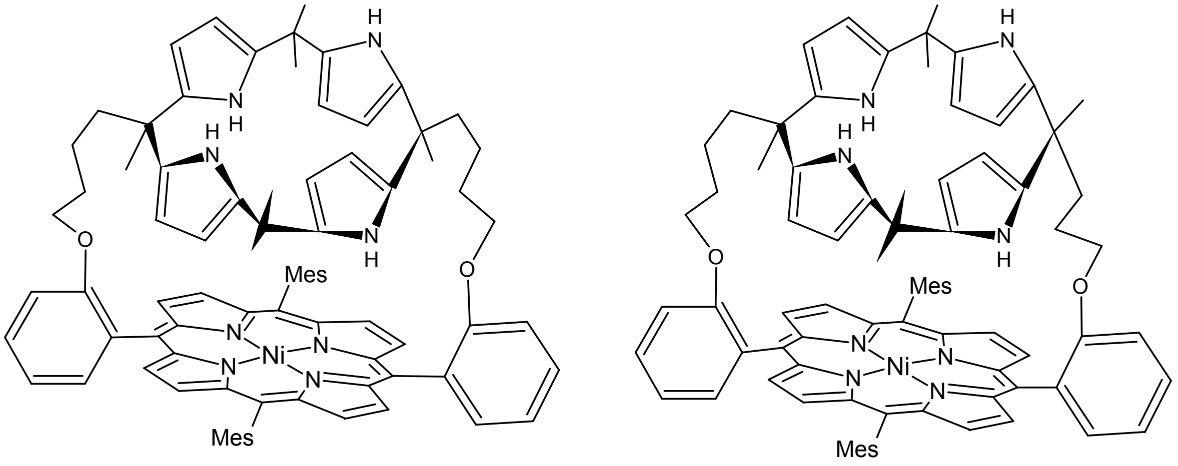


100

Scheme-24 Novel calix[4]pyrrole dimer.

They showed that the dimeric calixpyrrole receptor was a receptor of *p*-nitrophenolate ion. The displacement of *p*-nitrophenolate with various inorganic anions demonstrated that complex can be exploited in accordance with dye displacement strategy effectively signaling inorganic anion with a color change from nearly colorless to yellow-orange. They studied six different anions; the halides series, acetate and bisulfate. The dimer formed stable complexes with *p*-nitrophenolate ion with a concomitant reduction in extinction coefficient. Effective optical sensing of these anions was accomplished using the calixpyrrole dimer.[87]

A very different kind of ditopic receptor strapped calix[4]pyrrole-metalloporphyrin conjugates was synthesized and characterized as well as studied their preliminary anion binding ability[88] **(Figure-25)**. The condensation unexpectedly resulted in the formation of two conformational isomers of calix[4]pyrrole-capped porphyrins **101** and **102**.

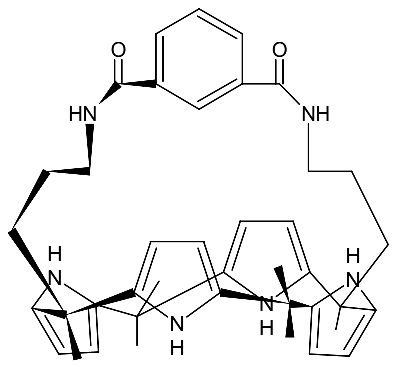


101 **102**

Figure-25 Calix[4]pyrrole-caped metalloporphyrins as ditopic receptor model.

They studied receptor **101**, bearing a connecting strap with a trans-junction relative to the porphyrin plane which was unique. Bearing two different kinds of binding elements (calix[4]pyrrole and porphyrin), compounds such as described in the reported paper could see utility in the design and synthesis of hetero-ditopic receptors, as well as Lewis acid assisted anion receptors. The anion binding studies revealed that only isomer **102** showed strong binding with fluoride anion in organic solvent, and neither isomer showed any appreciable binding with Cl^-, Br^- and I^-.

One of the newest approaches towards the problem of achieving anion selectivity had recently been put forward by the group of Sessler *et al.*[89] They synthesized strapped-calix[4]pyrrole **103** that contained amide functionality within the caplike strap, a trapped calix[4]pyrrole receptor, a flexible, m-phthalate-derived strap containing two amide groups which were chosen as the strapping element **(Figure-26)**.The presence of these amide groups was expected to provide additional hydrogen-bonding sites for anion-recognition.



103

Figure-26 *Cis*-strapped calix[4]pyrrole derivative **103**.

They showed that strapping a calix[4]pyrrole core with amide-containing linkers increases the binding affinity for halide anions in acetonitrile solution. The anion binding behavior of this receptor was investigated by ^{1}H NMR spectroscopy and isothermal titration calorimetry (ITC). A 2:1 binding stoichiometry was observed under the conditions of NMR analysis but not at the lower concentration regime used for ITC.[89]

Linear calix[4]pyrrole dimers[43] **27, 28, 29** are expected to show, (1) Increased association constants as a result of being able to bind anionic guests in a cooperative manner and (2) Increased selectivity vis-à-vis guests due to well-controlled distance and orientation effects.

The monomeric calix[4]pyrroles are known to bind phosphate and carboxylate anions.[43] While appropriately designed calix[4]pyrrole dimers can be regarded as the anion recognition elements and can selectively bind biologically important anions such as ATP and glutamate. Calix[4]pyrroles that contain two binding sites, such as compound **27**, could be used to bind polyanion substrates with fit geometry. Anion binding studies from ^{1}H NMR titration measurements revealed that compound **27** binds isophthalate in dichloromethane-d_2.

The anion binding affinities of halogen-bearing β-rim monosubstituted series calix[4]pyrroles[44] **31-34**, were then determined via standard ^{1}H NMR spectroscopic titrations. It was expected that the binding affinity of the series increases with increases in electronegativity of the halogen substituents in the case of chloride (as its TBA salt). Interestingly, for the case of dihydrogen phosphate, and to a lesser degree bromide anion, a change in selectivity is observed wherein the mono-chlorinated calix[4]pyrrole derivative was found to bind more strongly than its fluoride substituted congener.

NMR spectroscopic titration studies carried out in dichloromethane-d_2 revealed that pentapyrrolic calix[4]pyrrole[50] **49** shows enhanced affinities for several common anions of interest. When compared to compound **1**, compound **49** was found to exhibit affinities for Cl^-, Br^-, $H_2PO_4^-$ that are not substantially improved. However, it shows considerably higher affinities for benzoate and acetate. This behavior, as proposed by the authors, can be attributed to the coordination of both oxygen atoms of the carboxylate anion simultaneously by compound **49**, thus raising the affinity. By contrast, compound **1** coordinates only one oxygen atom of the carboxylate anion.

Ghiasvand *et al.*[90] have proposed the method for the selective separation and preconcentration of Ag^+ and Tl^+ by liquid liquid extraction using tetraspirocyclohexyl-calix[4]pyrrole as a suitable selective complexing ligand.

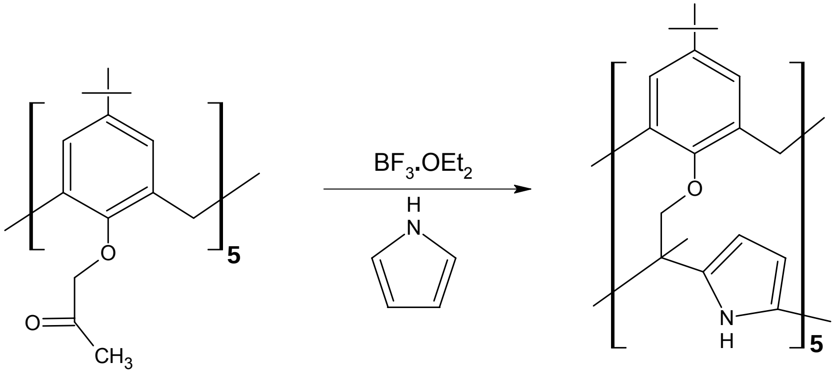
Recently, Chavasiri *et al.*[91] have synthesized and characterized few complexes of cobalt(II) calix[4]pyrrole ligands and developed a system of epoxidation of alkenes catalyst by Co(II) *meso*-tetrakis(4-methoxyphenyl)tetramethyl calix[4]pyrrole.

9. FORMATION OF HIGHER ORDER CALIXPYRROLES

Calix[4]pyrroles which are promising anion receptors, but due to the small size of their "cavities", calix[4]pyrroles 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.

- Calix[5]pyrrole-calix[5]arene conjugate: The first Expanded calix[n]pyrroles

Higher order systems cannot normally be isolated from "one-pot" preparations involving the condensation of pyrrole with acetone. Sessler's group have prepared a calix[5]pyrrole-calix[5]arene conjugate **105** *via* a templated process.[92] This system **104** was primed specifically, by using p-tetrt-butylcalix[5]arene pentaketone **104**, as both a reactant and template, it proved possible to prepare the calix[5]arene–calix[5]pyrrole pseudo-dimer **105** in 10% yield from pyrrole in the presence of $BF_3{\cdot}Et_2O$ as a catalyst **(Scheme-25)**.



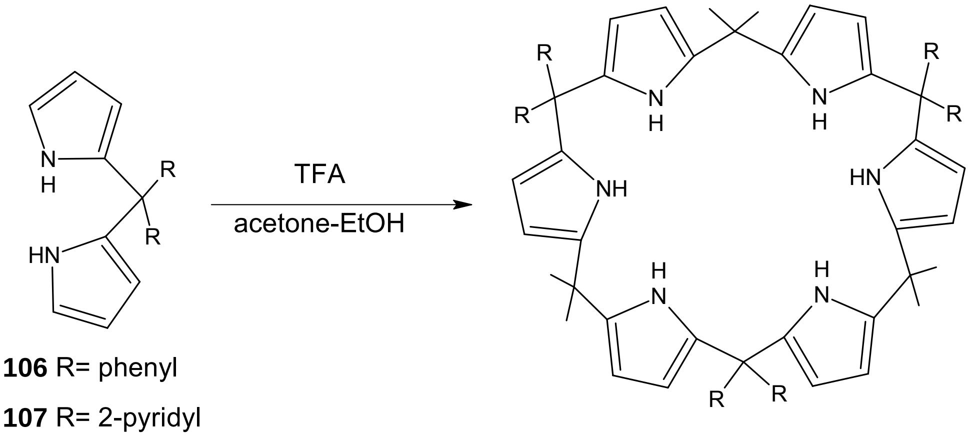
104 **105**

Scheme-25 Template synthesis of calix[4]pyrrole-calix[5]arene pseudo dimer **105**.

Preliminary ^{1}H NMR spectroscopic studies revealed that, like the corresponding calix[4]arene-calix[4]pyrrole pseudodimer, an internal hydrogen bonding array, involving NH (pyrrolic)-O (phenolic) interactions in **105** served to reduce the ability of this larger system to act as an anion receptor.

- Eichen's Synthesis of *meso*-Hexaarylcalix[6]pyrrole

The first example of a stand alone higher order calix[n]pyrrole was calix[6]pyrrole. It was produced as a result of a stepwise procedure developed by Eichen *et al.*[93] This synthesis was based on the use of the dipyrromethane building blocks **106** and **107**. In particular, reaction of **106** or **107** in a mixture of dry acetone and ethanol (1:1 v/v) in the presence of trifluoroacetic acid gave rise to *meso*-hexaphenylcalix[5]pyrrole **108** and *meso*-hexa(2-pyrridyl)calix[6]pyrrole **109**, respectively **(Scheme-26)**.



106 R= phenyl
107 R= 2-pyridyl

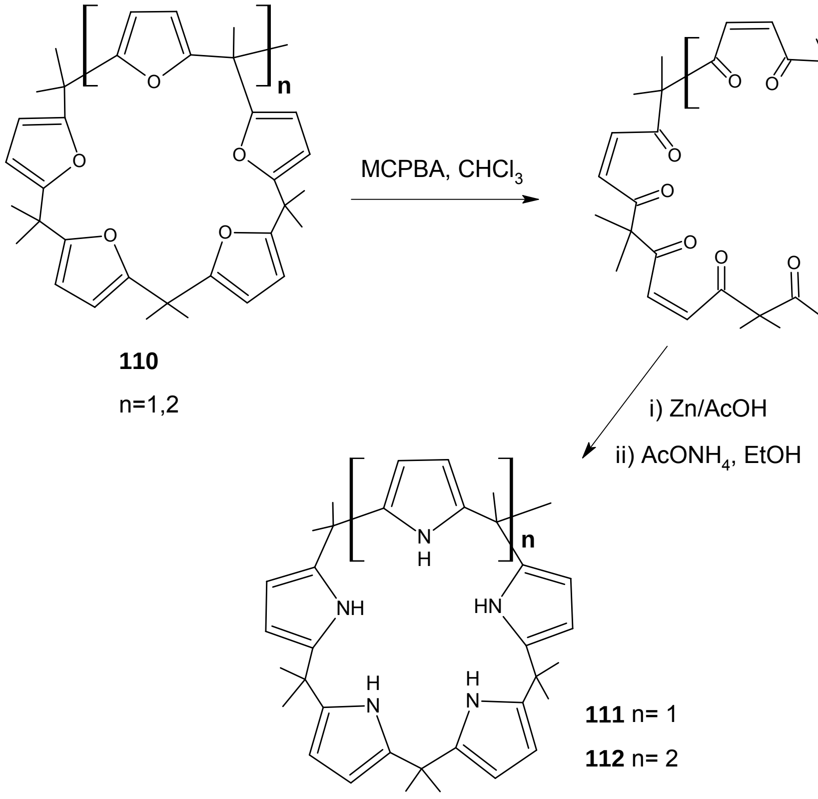
108 R= phenyl
109 R= 2-pyridyl

Scheme-26 Stepwise synthesis of the first calix[6]pyrroles **108** and **109**.

Investigating into the role of the acid catalyst in the synthesis of **108** 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.[94] A more generalized finding was that trihalogenated compounds and not just the acid, act as effective and selective templates in the template-assisted synthesis of **108**. NMR-based anion binding studies in acetonitrile-chloroform (1:9) revealed that compared to parent molecule calix[4]pyrrole **1**, **108** binds larger anions such as I^-, BF_4^-, and $CF_3CO_2^-$ quite effectively.[95,96] By contrast, this expanded system shows relatively reduced affinities for smaller anions, such as F^-, Cl^-, Br^-, and SCN^-.

- Kohnke's Synthesis of calix[n]pyrroles (n = 5,6)

In a procedure that differs completely from the two above methods. Kohnke *et al.*[97,98] discovered a conversion-based method for the synthesis of calix[5]pyrrole **111** and calix[6]pyrrole **112**. In this procedure, readily accessible calix[*n*]furans **110** (n = 1, 2) were converted into the corresponding eneketones by oxidative ring-opening of the furan units with *m*-chloroperoxybenzoic acid (MCPBA). After selective reduction of the olefinic double bonds using zinc in acetic acid, a multiketones intermediate was obtained. Treatment of species, decaketone and dodecaketone, with excess ammonium acetate in ethanol at reflux, gave **111** and **112 (Scheme-27)**.



110
n=1,2

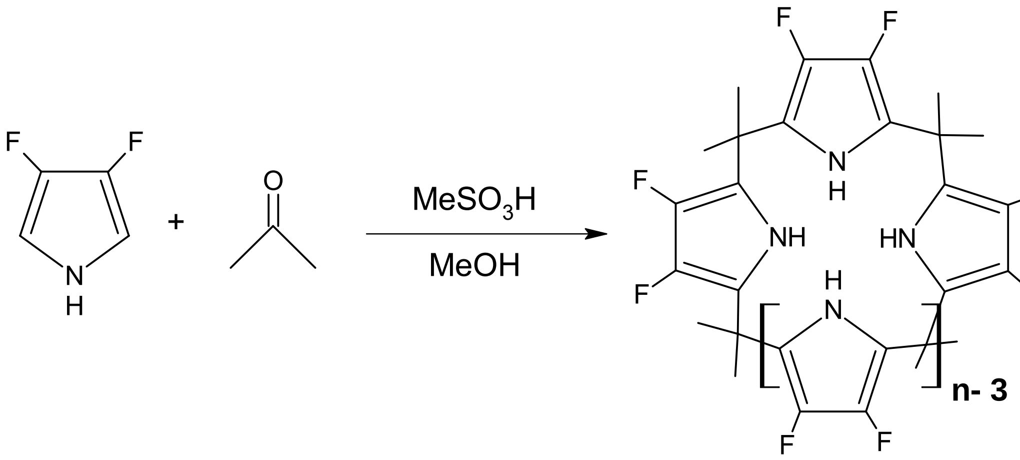
111 n= 1
112 n= 2

Scheme-27 Conversion synthesis of compounds **111** and **112**.

X-Ray crystal structures of the 1:1 complexes formed from mixtures of **112** and TBACl (tetrabutylammonium chloride) and TBABr (tetrabutylammonium bromide) revealed that the halide ions were encapsulated within the macrocycle cavity *via* six NH-X- hydrogen bonds.[99,100] They observed a weaker binding affinity for chloride anion with compound **111**.

➢ Sessler and Marquez's synthesis of Perfluorinated Calix[n]pyrroles (n = 5,6,8)

In the course of initial attempts to prepare β-octafluorocalix[4]pyrrole **113** *via* a one-pot condensation of 3,4-difluoropyrrole with acetone, two byproducts were seen in the reaction mixture in addition to the desired product.[101] These species, which were produced in isolable quantities, proved to be decafluorocalix[5]pyrrole **114** and hexadecafluorocalix[6]pyrrole **115**. On the other hand, appreciable quantities of dodecafluorocalix[6]pyrrole **116** were only obtained by using a templated approach. Specifically, at reduced temperature (-10ºC) and in the presence of TBA chloride, the one-pot condensation of 3,4-difluoropyrrole and acetone in methanol in the presence of methanesulfonic acid was found to afford **116** in 20% yield, along with other calixpyrrole products **(Scheme-28)**.



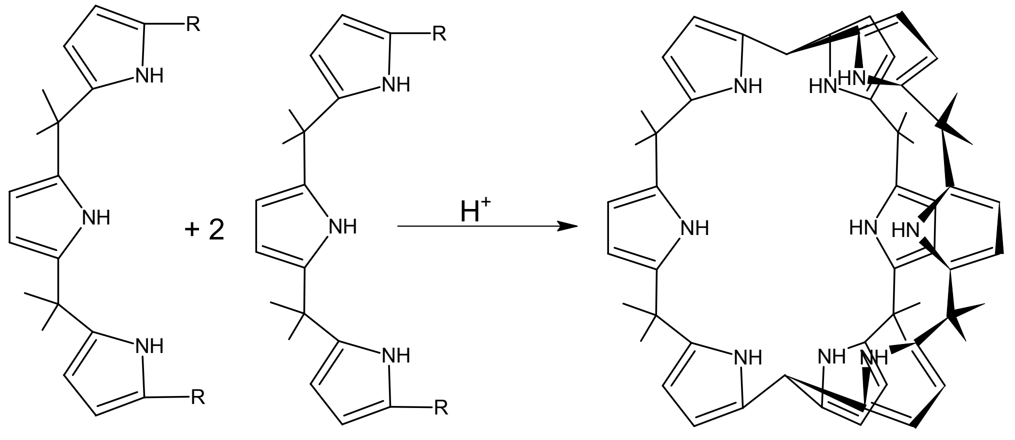
113 n=4 **114** n=5
115 n=8 **116** n=6

Scheme-28 One pot synthesis of compounds **113-116**.

NMR spectral studies revealed that **114** displays a higher affinity for both the fluoride and chloride anions relative to the corresponding β-octafluorocalix[4]pyrrole **113**. Compound **115** was found to have a much weaker affinity for chloride anion; however, it was found to bind the pyrophosphate surprisingly well ITC titration studies carried out in dry acetonitrile revealed that **113** binds chloride anion with an affinity that is higher than those of **114** and **116**. On the other hand, among the three receptors **116** displays the highest bromide affinity.

- The first Cryptand-like Calixpyrrole

A final example of a novel calixpyrrole is the Cryptand-like calixpyrrole **119** reported by Bucher et al.[102] The key step in the preparation of this topologically non-planner system is a tetramethyldiformyltripyrane. It was prepared in low yield from the statistically controlled reaction of pyrrole with acetone. Although not obtained in very high yield and requiring precursors that are themselves monotonous to make, the synthesis of this system is remarkably simple from at least the intellectual perspective: all that is required is the mixing of the diformyl tripyrrane **117** with its corresponding α-free form **118** in the presence of an acid catalyst. The resulting condensation produces the Cryptand-like calixpyrrole **119** in 15% yields **(Scheme-29)**.



R= CHO
117

R= H
118

119

Scheme-29 First cryptand-like calixpyrrole-type molecule **119**.

X-Ray diffraction analysis discovered that the molecule adopts an in-in configuration wherein both *meso*-like bridging carbon atoms are pointing in toward the center of the molecule. The small size of the resulting cavity precludes compound **119** from acting as a so-called *endo* receptor. Still it binds a wide range of anions in CD_2Cl_2 with 1:1 (**119**: F^-), 1:2 (**119**:NO_3^-), and 2:1 (**119**: Cl^-) stoichiometries, as measured by ^{1}H NMR binding studies. It is thought that in all cases the binding was “calixpyrrole-like” and taking place on the outer surfaces of the cryptand.

Efforts are ongoing to expanded the size of the macrocycle, by modifying the structure of the parent calix[4]pyrrole skeleton, introducing heteroatom, and modulating the inherent anion selectivities.[103-109]

10. CONCLUSION

Calixpyrroles possess interesting properties which are often very different from those of classical calixarenes specially as anion sensors in both optical and electrochemical realms. We believe that the almost all the important results presented in this review will open up a potentially new chapter in the chemistry of calixpyrroles. The new nature of the calixpyrroles, deep cavity calixpyrroles, progress made in the synthetic strategies (eco-friendly), ease of synthesis and versatility in terms of modification and functionalization at *meso* and C-rim (β) position, may inspire a range of new and improved applications for calixpyrroles, as useful precursors for the next generation of supramolecules including their use as building blocks, as possible receptors for anion–cation extractions, chemical sensors for molecular recognition and optical devices. Although still in its modem era infancy, is ripe for further rapid development not only in size but also for unexplored interesting applications.

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Hiren Mandalia born in Lakhatar, Surendranagar, Gujarat as the last son of Nirmala and Chandrakant Mandalia on 4th October 1980. He graduated in Chemistry from Saurashtra University, 2001, post graduation in Analytical Chemistry, from Gujarat University, 2003 and joined research group of Dr. V. K. Jain to pursue his Doctorate degree, entitled *"Functionalized Macrocyclic Compounds and Their Analytical Applications"* . He has been awarded Research Assistantship in the project of GUJCOST (DST) Gujarat from December-2004 to March-2007. His dedication and untiring efforts resulted in synthesis of very complicated macrocyclic compounds particularly in hetero-calixarene category, calixpyrroles and further synthesizing their derivatives. These novel molecules would find application as ditopic receptors, detection and determination of toxic and trace metal ions, biological important molecules like amino acids, sugars in various natural and standard samples. After completion of his Ph.D. degree, he would like to take up challenges where he can display and implement his innovative ideas.