CHEMICAL MODIFICATIONS OF CALIXARENES AND THEIR ANALYTICAL APPLICATIONS

S. K. Menon[*] and Madhu Sewani

Department of Chemistry, School of Sciences, Gujarat University,
Ahmedabad - 380 009, India.
e.mail: menonsobhana@yahoo.com

Calix[*n*]arenes have emerged as very attractive building blocks for supramolecular chemistry because of their easy large-scale preparation, distinctive concave molecular architecture, tuneable size of inner cavity, excellent capability of derivatisation and wide range of applications. This review covers the various recent chemical modifications of calixarenes viz. the upper rim and the lower rim funtionalizations, substitution and replacement of methylene bridges, modification of the aromatic "walls" of the calix cavity and the extension of the calix[*n*]arene cavity. Calix[n]arenes have been used for a multitude of applications. However, the most promising applications are based on their chemical sensing properties i.e. their binding for anions, cations and neutral molecules, their applications in liquid liquid extraction, membrane transport and their use as ion selective electrodes, which will be discussed in detail.

I. INTRODUCTION

Reversible encapsulation is one of the more recent forms of molecular recognition. Small molecule targets are completely surrounded by larger molecular assemblies and steric barriers keep the guest from escaping the host. Calixarenes make useful modules for capsule construction. Calixarenes are widely used modules in supramolecular chemistry. Because of their easy large-scale preparation, distinctive concave molecular architecture, tuneable size of inner cavity, excellent capability of derivatisation and wide range of applications, calix[*n*]arenes have emerged as very attractive building blocks

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[*] Corresponding author

for supramolecular chemistry. There are a good number of superbly capable research groups busy with these molecules. Their work has generated hundreds of original journal articles, whole monographs [1]and extensive literature reviews.[2-8]

Historically, calixarene can be traced back to the discovery of phenol-formaldehyde resins investigated by Von Bayer in the 1970s. The polycondensation of phenol and formaldehyde in acid or base proceeds through the ortho and para positions, leading ultimately to the highly cross-linked matrix, such as bakelite. When para position is blocked with an alkyl substituents, condensation is restricted to a liner progression and this aspect of phenol -formaldehyde chemistry, led in the 1940s to the discovery of Calixarenes. The pioneering work of C. David Gutsche[9] in the late 1970s led to a renewed interest in the chemistry of phenol-formaldehyde products. Derived from the Greek word *calix* meaning vase, and *arene* indicating the presence of aromatic rings, calixarenes exist in a 'cup' like shape with a defined upper-rim, lower-rim and central annulus (Fig. 1).

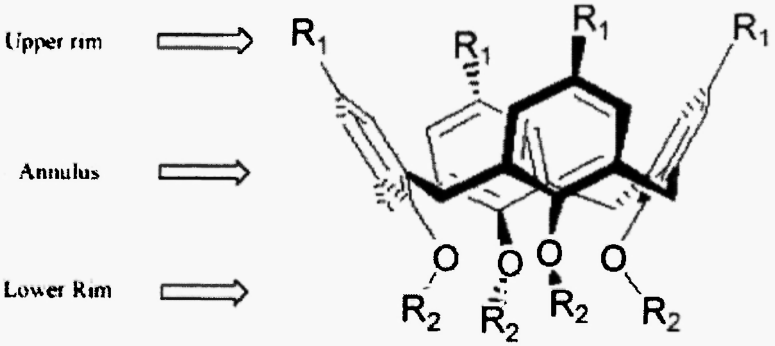


Fig. 1: Cone conformation of a typical calix[4]arene.

Calixarenes have found widespread use as complexation hosts for highly selective ion complexation and as frameworks for the construction of more complex structures due to rugged skeletons amenable to diverse funtionalizations. Central to these applications is their ready availability in various ring sizes and their protean capacity for assuming a wide variety of shapes. Calixarenes containing four, six, and eight aryl units (the "major" calixarenes) can be easily prepared in good to excellent yields and high states of purity and in any amount, ranging from milligrams to kilograms. Those containing five and seven aryl units (the "minor" calixarenes), although obtainable only in lower yields, are also useful starting materials for further structural elaboration. Calixarenes containing more than eight aryl units (the "large" calixarenes), on the other hand, are far less readily available and for many years were thought not to be present in the reaction mixtures. However, it is now known that calixarenes containing as many as 20 aryl units can, indeed, be formed in the condensation of *p-tert*-butylphenol and formaldehyde.[9]

II. FUNCTIONALIZATION OF CALIXARENES

In the past four decades, considerable attention has been devoted to the chemical modification of calixarenes, which has been used to profoundly alter the chemical and supramolecular properties of the parent macrocycles.[1]

The transformations are usually performed by:

(i) the functionalization at the *para* positions of the aromatic rings i.e. ***The upper rim.***

(ii) the functionalization at the phenolic hydroxyls i.e. ***The lower rim***.

(iii) Substitution and replacement of ***methylene bridges*** by Si, S, SO_2, -CH_2-O-CH_2- and -CH_2-N(R)-CH_2- groups significantly changing the physical and chemical properties of the parent compound.

(iv) the less investigated modification of the ***aromatic*** "***walls***" of the calix cavity[10] and

(v) Extension of the calix[*n*]arene ***cavity***

The calixarene platform provides unique possibilities to organize several binding sites in an array complementary to a potential guest.

i. Upper Rim Modification

A survey of the literature from the last five years reveals that various upper rim functionalizations with different groups have been reported. Although functionalization of lower rim calixarene hydroxyls is relatively well understood, upper rim derivatization requires careful selection of reagents and experimental conditions.

Novel "cone conformation" calix[4]arene derivatives, carrying either one or two cyclen (1,4,7,10-tetra-azacyclododecane) moieties at the upper rim (Fig. 2), have been synthesized.[11]

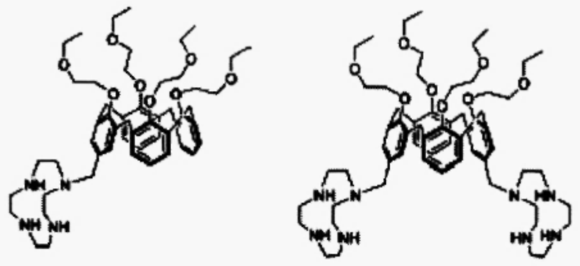
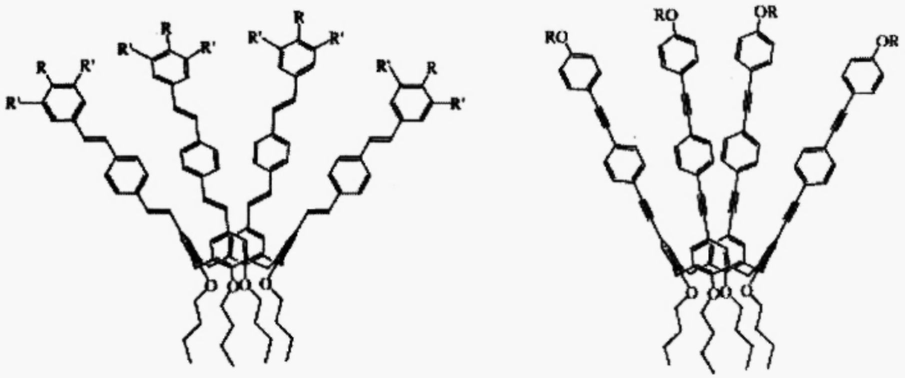


Fig. 2

Heck and Sonogashira cross-coupling reactions have been used for the functionalization of the upper rim of a tetraiodinated calix[4]arene. In this way, oligophenylenevinylene (OPV) and oligophenyleneethynylene (OPE) arrays have been constructed on the calix[4]arene core to produce covalent assemblies of p-conjugated chromophores. The preparation of compound (Fig. 3a) is based on the functionalization of the upper rim of tetraiodinated calix[4] arene with styrene derivatives .The synthetic approach to prepare the calix[4]OPE (Fig. 3b) derivative relies upon a cross-coupling reaction of a terminal alkyne derivative on the upper rim of tetraiodinated calix[4]arene.[12]



a R = $OC_{12}H_{25}$, R' = H **b** R = $C_{12}H_{25}$

Fig. 3

A method of direct C-C coupling of azahetarenes with calix[4]arene, based on the nucleophilic addition to unsubstituted carbon atom in azines, has been developed. Functionalization of calix[4]arene with 3-methylthio-1,2,4-

triazine, 3-amino-1,2,4-triazine and quinazoline gave rise to exhaustive heteroarylation of the upper rim of calixarene in moderate yields (Fig. 4).[13]

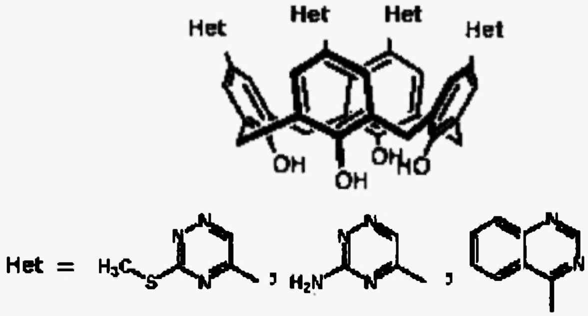
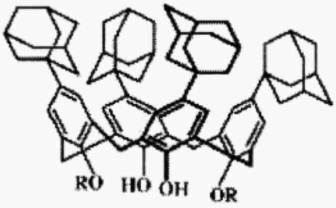


Fig. 4

Bithiophene groups substituted at the upper rim gave rise to a host-guest complex of tungsten oxo calixarene complex[14]. Napthalimido group has been introduced at the upper rim of calixarenes in varying proportions and a molecular capsule of two calixarenes is formed via perylene-bisimide spacer, and the compound is used for UV and fluorescence studies[15]. Two pyridyl groups are linked via amide linkage at the upper rim and the calix[4]arene bispyridyl amides formed complexes with aromatic and alkyl dicarboxylic acids[16]. 4-hydroxybenzyl groups introduced at the upper rim of the calix[4]arene act as anion binding groups[17]. Thiazolazo groups introduced at all the four positions of calix[4]arene were used to study for their recognition of heavy metal ions[18,20]. Calix-O-glycosides were synthesized by multiple glycosylation of upper rim of calix[4]arene polyols[19]. Heterocyclyl-methanamies attached at the upper rim of calix[4]arene act as a potential ligand for synthetic modelling of multinuclear metalloenzymes[21]. Semi-carbazone was attached at two positions of the upper rim of calix[4]arene, fixed on a resin and was studied for its sorption and separation studies of La(III), Ce(III), Th(IV) and U(VI)[22]. A convenient one-pot procedure for obtaining formyl substitution on upper rim of calix[n]arene via condensation with 1,1-dichloromethylmethylether is described.[23] Shokova *et al.* proposed a general procedure for selective upper rim adamantylation of calix[4]arenes, (Fig. 5) which is based on the difference in the reactivity of alkylated (or acylated) and free phenolic fragments in calix[4]arenes with respect to carbocationic adamantyl intermediates in trifluoroacetic acid. The reactions were carried out in excess TFA using chloroform as co-solvent. As starting compounds calix[4]arenes selectively alkylated or acylated at the lower rim were used. [24]



R= Alkyl or Acyl group

Fig. 5

ii. Lower Rim Modification

A survey of the literature on functionalized calixarenes shows that the attention of researchers has shifted from the upper rim to the lower rim. This is mainly due to the fact that, because of the expansion of the cavity after substitution, the increased lower rim diameter can facilitate the complexation and inclusion of bigger moieties like heavy metals and also relatively bulky organic molecules. The earliest reported work on the lower rim of calixarenes has been started with alkylation and acylation reactions.

Acylation and aroylation can be done on all the OH groups, or done selectively only on the desired OH function by selecting certain reaction conditions. An excess or limited amount of aroylating/acylating agent, the equivalents of reactants, the base, the solvent, all contribute to the arolated/acylated end product of substituted calix[n]arene.

Aroylation has been mainly reported with benzoyl chloride, p-nitro benzoyl chloride and 3, 5-di nitro benzoyl chloride, although a number of other types of calixarene esters are also known.

Acylation has been reported for calix[8]arene where reaction of p-tert-butylcalix[8]arene with di-ethyl dibromomalonate gave the tetra ester derivative with a cone conformation[25]. O-acylated derivative of octa-tert-butyl calix[8]arene was prepared in high yields, by treating it with dimethylacetamide in the presence of acetic anhydride to give 95.4% octa-O-acetyl-octa(tert-butyl)calix[8]arene[26].

Yilmazl *et al.* described the synthesis of a new monomeric dibenzonitrile derivative of p-tert-butylcalix[4]arene (Fig. 6) containing a polymerizable group at its lower rim. This monomer with an acryl amide group has been copolymerized with styrene yielding a linear polymer with pendant calixarene groups.[27]

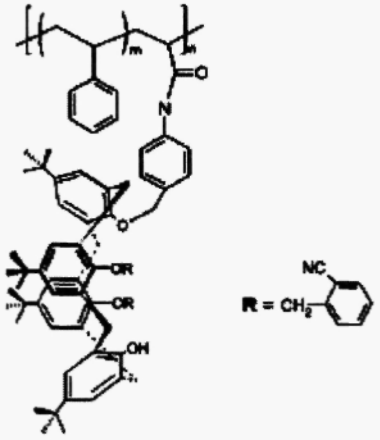


Fig. 6

Mono, 1-2 di, 1, 3-di, tri and tetra ethers of calix[4]arene have been reported. Mono benzylation of 1, 3-p-dinitrocalix[4]arene, with aluminum trichloride as the catalyst yields its respective derivatives, the aroylation occurring preferentially on the aryl residues not containing the p-nitro groups[28]. Distal dialkylation leading to 1, 3-diethers is generally much more easily achieved than proximal dialylation leading to 1, 2-diethers. Under conditions similar to those leading to mono ethers, but with an excess of the alkylating agent, 1, 3-diethers are produced, often in very high yields[29].

Trimethylation of the parent calix[4]arene can be accomplished with dimethylsulphate in DMF in the presence of BaO.Ba$(OH)_2$. Tetraalkylation of calix[4]arenes is generally carried out with an excess of the alkylating agent in the presence of the strong base sodium hydride The first instance of alkylation of the sulfide bridge, was achieved by the cyclocalkylation of p-tert-butylcalix[4]arene and p-tert-butylthiacalix[4]arene with various aliphatic glycols was achieved. This intra-bridging of the calix[4]arene afforded 1,2 and 1,3 bridged calixarenes with O, S- cyclization, which caused the formation of sulfonium phenoxide betaines as shown in Fig 7[30].

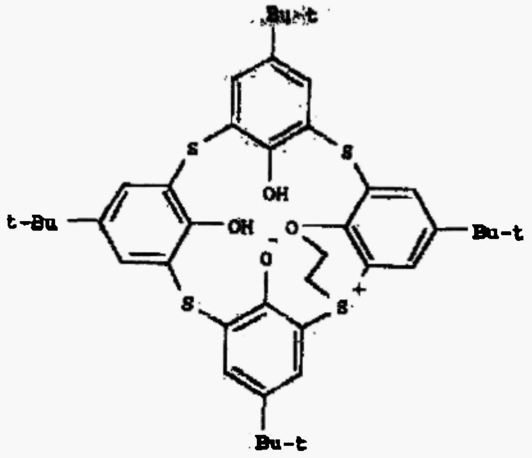


Fig. 7

p-tert-butylcalix[4]arene was reacted with p-and m-benzyl bromides in the presence of alkali metal carbonates and silylation of these derivatives gave their respective derivatives[31]. A series of six calix[4]arene derivatives bearing allyl groups and/or benzyl groups have been functionalized at the phenolic oxygen atoms[32]. p-t-butylcalix[4]arene diamides was synthesized in a stepwise method where it was first reacted with ethylbromoacetate, then the hydrolysis followed by the conversion to acid chloride and amidation gave the compound[33].

The first example of selectively functionalized calix[7]arenes was obtained by weak-base promoted O-alkylation or O-benzoylation of p-tert-butylcalix[7]arene. Mono,1,3- and 1,4-disubstituted calix[7]arenes have been obtained in workable yields, while the 1,2,4,6-tetra substitution was achieved with surprisingly high yield. Neri and coworkers have reported the first success in selective lower rim substitution, providing details for the preparation of 1, 3, 4, 6-tetra-O-arylmethyl ether of tert-butyl-calix[8]arene obtainable in yields of 20-41% using potassium carbonate as the base[34]. The direct methylation has been studied in considerable detail, and procedures have been worked out for generating some of the partially methylated compounds in isolable yields[35].

Alkylation with arylmethyl halides containing heteroatoms provides still another route for the introduction of functional groups onto the lower rim[36]. Methylthioethoxy and pyridyl 2 methyl oxy groups were introduced at the lower rim of calix[4]arene to give rise to bis derivatives of both types[37]. Sugar calixarenes were prepared by substitution of bisubstituted *p*-tert-butylcalix[4]arylethylamine calix[4]arenes at the lower rims with *O*-glycosyl groups. Calixarene derivatives with sugar residues in the lower rim constitute interesting hosts for the selective complexation of ionic species[38]. A few polymers containing calix[4]arene units with alkyl–nitrile functionalities at their lower rim have been reported, along with their ion extraction properties[39]. Polysiloxane derivatives of calix[4]arene were prepared in presence of chloroplatinic acid.[40] Proximal O, O' capped calix[4]arenes with a disiloxane bridge is synthesized using cesium carbonate as the base in THF, also providing an alternative of desilylation and thereafter alkylation using benzyl bromide with pottassium tert-butoxide as a base to give rise to unsymetric calix[4]arenes.[41] A new family of calix[4]arenes has been prepared by the incorporation of 2,2'-bithiazole units to azocalix[4]arene existing both in cone as well as in 1,3-alternate conformation[42].

Etherification in 1, 3 alternate conformation was carried out on calix[4]arene using $R=2\text{-}MeOC_6H_4OCH_2CH_2$ with considerable good yields[43]. Schiff base derivatives were synthesised using the amino ethoxy derivatives of calix[4]arene with the aromatic aldehydes in high yields[44]. Copolyethers and polyurethanes containing calix[4]arene units in the fixed cone conformation was prepared by reacting the bisphenol with the distal calix[4]arene diols[45].

iii. Substitution and replacement of methylene bridges

Replacement of methylene bridges and substitution at the methylene bridges can be used to attach various additional functionalities to calixarene skeleton, thus extending its utility as a building block for the construction of larger molecular assemblies and polymers.

Substitution on methylene bridges:

Calixarene derivatives with two distal methylene groups substituted in a trans fashion by phenyl or mesityl groups were synthesized (Fig. 8).[46]

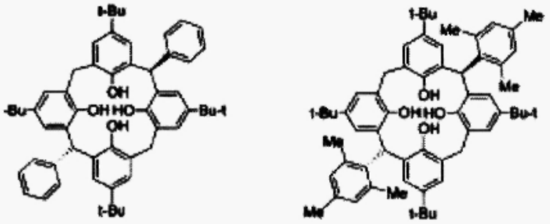


Fig. 8

The introduction of new functionalized arms at the methylene bridges of calix(n)arene bearing aryl,[47-48] and methyl, ethyl, isopropyl, tertbutyl, p-tolyl ,p-nitrophenyl has been synthesised by heat induced [3+2] condensation of linear trimer with the corresponding bishydroxy methylated alkanediyl diphenols in boiling xylene.[49] The first method for the direct regio- and stereo selective functionalization[50] of both axial and equatorial carboxamide groups at the methylene bridges is via a homologous anionic Ortho-Fries rearrangement to give corresponding calixarenes.[51]

Replacement of methylene bridges by Si, S, SO_2.

Koning *et al.* synthesised p-tert butyl silacalix(4)arene tetramethyl ether in which the methyl bridges [-CH_2-] are replaced by $Si(CH_3)_2$, by stepwise reaction of p-tert butyl methoxybenzene and dichloromethyl silane followed by cyclization.[52] p-tert butyl thiacalix(4)arene in which the four methylene bridges [-CH_2-] of p-tert butyl calix(4)arene replaced by sulfide linkages [-S-] was conveniently synthesized in a one-pot process by heating a mixture of p-tertbutyl phenol, elemental sulfur S_8 , and NaOH in tetraethylene glycol dimethylether with removal of H_2S[53] and homothiacalixarenes were prepared from the reaction of bis(chloromethyl)phenol-formadehyde trimer with alkanedithols in good yield.[54] Sulfur bridges in the molecule cause some differences in the chemical and physical properties compared to the common p-tert butyl calix(n)arene. For example, p-tert butyl thiacalix(4)arene was found to bind transition metal ions very well[55] without the introduction of supplementary ligating groups.

Oxidation of bridging sulfur afforded sulfinyl- and sulfonyl calix(4)arene which shows intrinsic metal-ion selectivity determined by hardness and softness of the ions.[56-57]

Replacement of methylene bridges by -CH_2-O-CH_2- and -CH_2-N(R)-CH_2- groups

Homooxacalix(n)arene and homoazacalix(n)arene are cyclic tetramers or trimers where -CH_2-O-CH_2- and -CH_2-N(R)-CH_2- linkages(groups) replace the methylene bridges, respectively. They have a cavity size that stands between the respective calix(n = 4, 5)arene and a conformational mobility somewhat higher than that of conventional tetramers.[58]

Recently, N-hydroxyprazine bearing homotrioxa calix(3)arene was a new artificial receptor which exhibited cooperative molecular recognition with Ga^{+3}-ion towards ammonium cations in CH_2Cl_2[59] and uranyl complex with homooxacalix(n)arene, [60] Yb^{+3}; Nd^{+3} complexes and alkali-metal binding properties of homoazacalix(n)arene have been reported.[61-63]

iv. Substitution on aromatic "walls" of the calixarene

Modification of the aromatic "walls" of the calix cavity have been relatively less studied, including their hydrogenation to cyclohexane-based derivatives or their oxidation to quinone[64] or dienone[65] compounds. In this regard, it can be envisaged that the introduction of oxygenated functions into the calix walls would give rise to polar derivatives with novel and interesting supramolecular properties. One way to introduce these functions in a 2, 4, 6-trisubstituted phenol ring is the direct addition of molecular oxygen (oxygenation) to the corresponding phenoxide anion to give epoxy-*o*-quinol or epoxy-*p*-quinol derivatives,[66] which are amenable of further synthetic elaboration. Neri *et al* reported the oxygenation of calixarene phenol rings to give the first examples of epoxy-*p*-quinol and diepoxy-*p*-quinol calixarene derivatives[67]as shown in Fig. 9:

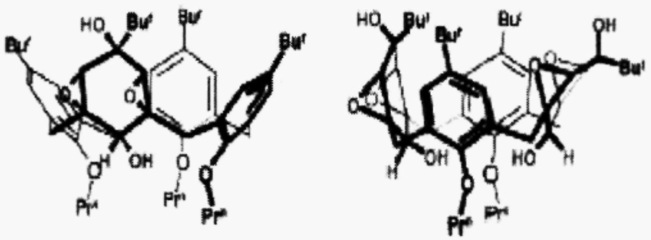


Fig. 9

v. Extension of the calix[*n*]arene cavity

Reinhoudt *et al.* carried out much work in the linking of medium-sized building blocks to calix[*n*]arene systems. The combination of upper rim 1, 3-functionalised calix[4]arenes with bridged and di-bridged resorcin[*n*]arenes yields both 1 : 1 and 2 : 1 calix-resorcin[*n*]arenes.[68] This has provided the synthetic methodology for a new class of potential receptor molecules with large concave surfaces. Indeed, one such receptor composed of two calix[4]arene fragments and one bridging cavitand, has been shown to complex the steroid prednisolone- 21-acetate in apolar solvents.[69] Synthesis of receptor molecules *via* a combination of calix[4]- and calix[6]arenes with other medium-sized building blocks, including cyclodextrins (Fig. 10), porphyrins and cyclotriveratrylene, has also been described.[70-71] The combination of 1,2-crown[6]cavitands with calix[4]arenes or resorcin[4]arenes resulted in potential receptor molecules with large hydrophobic surfaces. Calix[4]arenes diametrically substituted at the upper rim with two melamine units (Fig. 11) spontaneously form well-defined box-like assemblies in the presence of two equivalents of 5,5-diethylbarbituric acid. These molecular box assemblies consist of nine different components and are held together by 36 hydrogen bonds.

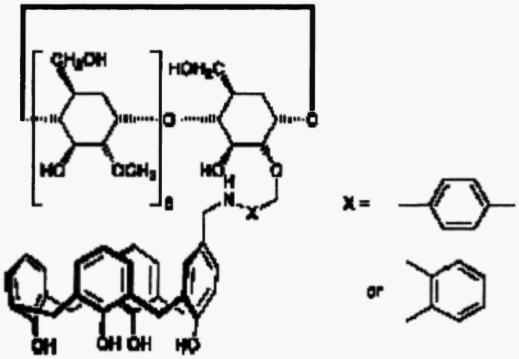


Fig. 10

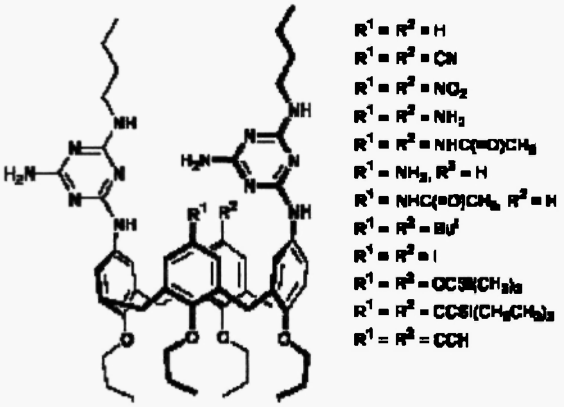


Fig. 11

III. APPLICATIONS OF CALIXARENES

A survey of the literature reveals that calix[n]arenes have been used for a multitude of applications, e.g., in liquid liquid extraction, in liquid membrane transport, as ion selective electrode, for anion as well as cation binding and/or sensing, in sensors for neutral molecules, in catalysis,[72-73] as solid lipid nanoparticles,[74] in binding biological substrates,[75], as enzyme mimics, as chromogenic sensors,[76] as optical sensors,[77] as chiral recognition devices, in chromatographic stationary phases,[78] in molecular inclusion, as field effect transistors,[79] as NLO active materials, for antibody labeling, and recently for the generation of combinatorial libraries[80].

However, the most promising applications are based on their chemical sensing properties i.e. their binding for anions, cations and neutral molecules, their applications in liquid liquid extraction, membrane transport and their use as ion selective electrodes, which will be covered in detail.

i. Calixarenes as Chemical Sensors

With the aim of building biomimetic receptors, the host-guest chemistry of calixarenes has been widely explored in the past.[81] Calixarenes have been widely used as three-dimensional building blocks for the construction of artificial molecular receptors[82] capable of recognizing neutral molecules,[83] cations[84] and more recently anions.[85-90] In particular, the lower or upper rim of the calix[n]arene unit can be modified to achieve more sophisticated structures to bind specific guest species. All studies showed that, whereas calix[4]arenes suffer from the smallness of their cavity, the larger calix[6]arenes are too flexible to provide a good receptor. As a result, the former has been used only as a platform for the preorganization of a binding site, whereas the cavity of the latter could not be exploited, unless their flexibility was restricted. Di- or polytopic receptors are constructed with two or more binding subunits within the same macrocycle structure. Once recognition of each binding subunit has been identified, the ability of multiple recognition and mutual effects of binding subunit occupation provide entries to higher forms of molecular behavior such as cooperativity, allostery and regulation, as well as communication or metal transfer.[91]

a. Calixarenes as Cation receptors

Calix[n]arenes represent an interesting class of preorganized aromatic hosts exhibiting an enhanced ability for cation-π interaction. In many biological systems, metal cation-π interactions play an important role in molecular recognition. Interest has focused on the interaction between organic cations in both natural and synthetic receptors. Systematic studies of a series of related structures of artificial receptor molecules have revealed the role played by cation-π interactions. Calixarenes and related skeletons are a widely used platform in order to study cation-π interactions.

Recent results obtained with the complexation of various calix[n]arenes and five structural types of organic cations, namely ammonium ions, quaternary ammonium ions, phosphonium ions, iminium ions and tropylium ions are reviewed.[92] The influence of both the guest structure and the shape and flexibility of the hosts on the complex stability in the gas phase and in solution is considered.

The three-step synthesis of a calix[6]arene capped with a TAC (TAC:1,3,5-triazacyclohexane) unit (Fig. 12) is presented. The novel *C3v* symmetrical calix[6](aza)cryptand displayed an exceptionally high affinity for small ammoniums.[93]

Fig.12

Arnaud-Neu *et al.* have reported the synthesis of two pentamethyl ester derivatives of the *p*-benzyl- and *p-tert*-octylcalix[5]arenas (Fig. 13).[94]

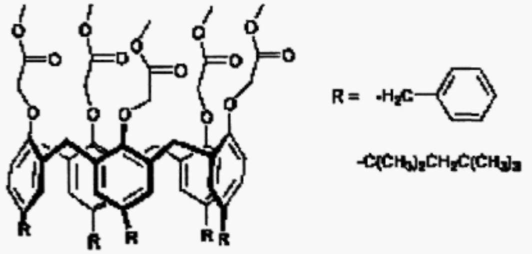


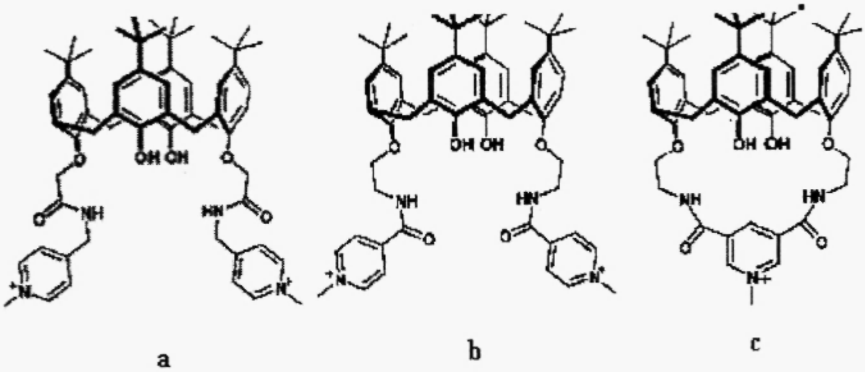
Fig. 13

Liquid–liquid extraction studies have shown that these ligands display high selectivity within the alkali metal cation series.

b. Calixarenes as Anion receptors

The molecular recognition of anionic guest species by positively charged or electron deficient neutral abiotic receptor molecules is an area of intense current interest. The importance of favorable amide or protonated imine hydrogen bonding interactions for anion binding has recently been exploited in the design of calixarene anion receptors which are still relatively rare.[95] Several excellent studies on anion coordination have been reported using calixarene based chelating units. Synthetic receptors containing two individual recognition sites for a cation and anion have potential application in metal controlled anion sensing devices. In designing complexants for these particular guest anions a number of structural features can be incorporated in to the host molecule that may be important in achieving selective binding.

For such a molecule to be effective as a host it is necessary that its structural features are compatible with those of the guest anion. The vast majority of calix[*n*]arene anion receptors have relied upon functionalizing the upper or lower rims with cationic moieties. Beer and co-workers have prepared lower rim substituted calix[4]arene bis-pyridinium receptors and a novel lower rim bridged calix[4]arene pyridinium receptor (Fig. 14).[96]



a b c

Fig. 14

The bis-pyridinium species, 14a and 14b, complex H_2PO_4, Cl^-, $Br^-$and HSO_4^- anions with L : $2X^-$stoichiometry, with 16a showing a preference for $H_2PO_4^-$. Conversely, 14c forms 1: 1 stoichiometric complexes with Cl^- and Br^-.

c. Calixarenes as receptors of neutral molecules

In order to make calixarenes capable of binding large organic guest molecules, considerable effort has been expended in extending the length of the calixarenes cavity, and several deep-cavity calixarenes have been synthesized by derivatisation at the 'upper rim'. However, the chemistry of deep-cavity calixarenes has been slow to develop because of the lack of high-yield synthetic pathways to such compounds. Therefore the design of new calixarene derivatives and the exploration of new synthetic methods are of obvious interest. The complexation and catalytic properties of calixarenes and their derivatives have been extensively studied. It has been well established that calixarenes can include small molecules in the solid state. Unambiguous evidence for inclusion complexes of calixarenes in solution has also been reported. These studies mainly involved aqueous solutions and hydrophobic binding of nonpolar substrate groups into the relatively nonpolar calixarene cavity. There are only a few examples of the complexation of neutral molecules in non-aqueous solutions. It seems that some calixarene derivatives should also be able to bind nonpolar substrates in a polar non-aqueous medium and in this case the driving force for the complexation is lipophobic interactions. Tung *et al.* reported the synthesis of *p*-[1-(4-hydroxyphenyl)-1-methylethyl]calix[8]arene (Fig. 15) for the first time, and solubilization, fluorescence and photochemical probe studies demonstrated that this calixarene can form inclusion complexes with a variety of aromatic compounds in polar non-aqueous solutions[97].

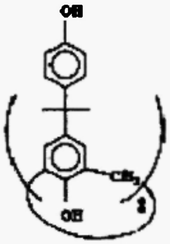


Fig. 15

A crystal of an inclusion compound between a calix[16]arene and molecules of acetonitrile and dichloromethane, used as solvents, has been obtained and its X-ray structure studied.[98]

Silva *et al.* presented a study of the complexation properties of *p*-sulphonato-calix[4]arene, *p*-sulphonato- calix[6] arene and *p*-sulphonato-calix[8]arene (Fig.16) towards three steroids: progesterone, testosterone and oestradiol.[99]

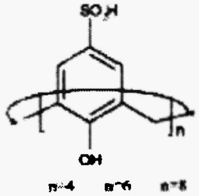


Fig. 16

ii. Calixarenes in Liquid-liquid extraction

Liquid-liquid extraction coupled with spectroscopy owes its broad development to its practically unlimited scope for controlling chemical process in geochemistry, biochemistry, soil sciences, metallurgy and other fields and still there is a growing demand for more specific procedures. Extraction coupled with ICP-AES offers the best selectivity and sensitivity to an analytical separation process.

The efficiency and selectivity of complexones and extractants based on calixarenes are determined by the efficiency of all noncovalent interactions realized in the system ion metal–calixarene. Extracting and transporting properties of calixarenes, unlike their noncyclic analogs, depend not only on the efficiency of the inner-sphere coordination of the metal ion, but also on the cooperative effect of other noncovalent interactions, particularly van der Waals interactions. The counterion effect, which is well known in the extraction chemistry, appears in a specific way in the extraction systems based on calixarenes. The main reason for the above peculiarities lies in the so-called cooperative nature of interaction that brings about the additional stabilization of the metal complex based on calixarene due to interactions with the counterion. Therefore, when calixarene derivatives are used as extractants and carriers of the metal ions, the effect of calixarene matrix on the extracting properties of calixarene derivatives toward the metal ions is determined by both preorganization of the donor groups, which results in the efficient multicenter coordination of ions with the relevant size, and in the possibility of the additional cooperative interactions, for example, with ions of the supporting salt. This, in turn, makes it possible to monitor the selectivity and efficiency of the extraction process by changing the concentration conditions.

Some new classes of complexones based on functionalized thiacalix[4]arenes, calix[4]resorcin- and pyrogallolarenes were synthesized and their ionophore properties were studied toward alkali and some *d* and metal cations. Calixarenes, unlike their noncyclic analogs, were shown to exhibit a cooperative effect of different noncovalent interactions due to preorganization of donor groups on calixarene matrix.[100]

Bohmer *et al.* have reported calix[4]arene based extractants which incorporate CMPO{ octyl(phenyl)(*N*,*N*-diisobutylcarbamoylmethyl) phosphine oxide} moieties at either the wide or narrow rim. Such pre-organisation of the chelating ligands leads to a 100-fold (or greater) increase in extraction efficiency combined with an enhanced selectivity for actinides and lighter lanthanides.[101]

A novel particulate system carrying CMPO ligands preorganised on a calixarene scaffold has been synthesised and demonstrated to extract Eu3+, Am3+ and Ce3+ at high efficiency from simulated nuclear waste streams.[102] A series of four azocalixarene derivatives bearing bipyridyl units and additional functional groups such as amide, ester and pyridine at the phenolic oxygen atoms were synthesized. Extraction properties towards different metals using liquid–liquid extraction by atomic absorption spectrometry have been studied and exhibit Ag^{+1} selectivity.[103]

Yilmaz *et al.* reported the synthesis and application in metals and dichromate ion extraction studies of a new dibenzonitrile derivative of p-tert-butylcalix[4]arene monomer and its copolymer.[104]

New thiacalix[4]arenes functionalized with biheterocyclic and azophenyl groups at the lower rim and the upper rim of the macrocycle, respectively, were synthesized and their extraction properties towards Cu2+, Ag+, Ni2+ and Pb2+ studied.[105]

A series of calixarene carboxylic acid derivatives were used as host molecules for the quantitative extraction of amino acids in a liquid-liquid extraction system.[104] The interaction between the ammonium cation of the amino acid and the oxygen atoms of the host molecule was the main driving force for the complexation and the extraction mechanism was established by slope analysis and the Job method.

Polymeric calix[*n*]arene derivatives have been synthesized and their selective extraction of transition metal cations has been studied.[106-107]

Several new nitrogen-containing calixarene derivatives (Fig. 17) have been synthesized and their ion-binding properties investigated by solvent extraction.[109] Extraction studies showed that these derivatives could efficiently extract Pb^{2+} (as picrate salts) from the aqueous phase into chloroform. The introduction of nitrogen donor atoms to the lower rim of calixarenes increases the complexation ability for lead ion appreciably. These results imply the nitrogen-containing calixarene derivatives are a kind of new good receptors and they have potential uses in extraction separation, phase transform, recovery of metal and exclusion of the toxic metal ions.

A series of calix[6]arenes substituted with phosphoryl functional groups (Fig. 18) were prepared by the Arbuzov reaction of hexakis(chloromethyl)calix[6]arene hexamethyl ether with isopropyl esters of trivalent phosphorus acids, followed by appropriate chemical transformations. The extractive power of these compounds with respect to americium and europium was studied.[110] Due to the cooperative binding of the metal cation with phosphoryl groups, the phosphorylated calixarenes are more effective extractants than their acylcic analogs and commercial organophosphorus extractants.

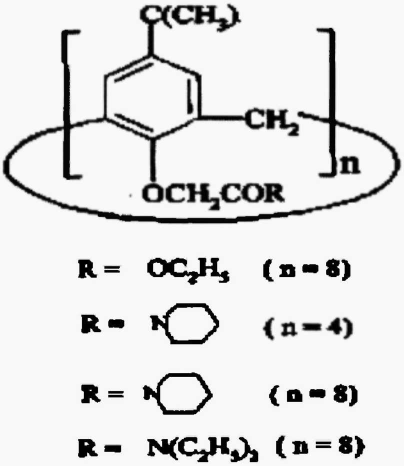
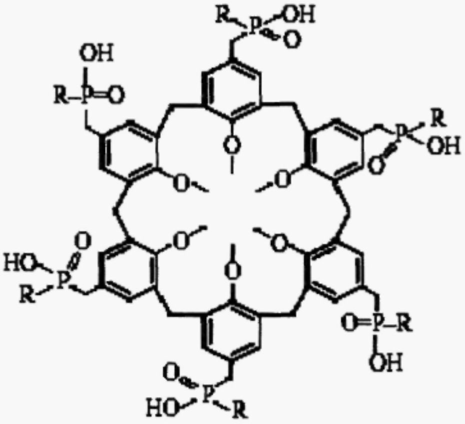


Fig. 17

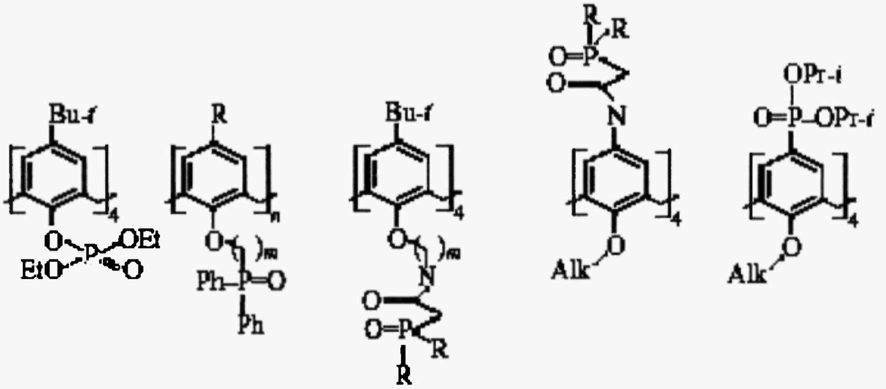


a, b

R = Ph (a), Bu (b).

Fig. 18

Calix[4]arenes **I**, **II**, **III**, and **IV** containing diethoxyphosphoryl, diphenylphosphine oxide, or carbamoylphosphine oxide groups (Fig. 19) at the upper or lower rim of the macrocycle exhibit high extractive power and selectivity with respect to lithium[111] silver ,transition metals ,and lanthanides and actinides.[112] Tetraphosphorylated calix[4]arenes **V** form host- guest complexes with benzene derivatives in solutions.[113]



I **II** **III** **IV** **V**

Fig. 19

iii. Calixarenes in Transport through liquid membrane

Vigorous development of chemistry of trans-membrane transport, which plays an important role in biological systems, has started quite recently. The appearance of the first synthetic receptor molecule[114] capable of selective binding of organic and inorganic substrates has given impetus to the development of a new interdisciplinary field of science, supramolecular chemistry. Together with recognition and catalysis, transport is an essential function of supramolecular systems, which belong to fundamental process of supramolecular chemistry.[115]

Selective permeability of membranes is provided by carrier molecules present in the liquid membrane and able to interact selectively with the compound to be transported. Carriers determine the nature of the substrate penetrating the membrane and the physicochemical characteristics of the mass transfer. Variation of the receptor architecture makes it possible to control the transport process and to analyze the influence of various structural factors on the thermodynamic and kinetic parameters of the transport.

Effective recognition of a substrate by a receptor can be attained by maximizing the area of interaction between them. This is possible in the case where a receptor can embrace a substrate from every site being linked to it by numerous non-covalent molecular interactions. Calixarenes satisfy these requirements. Indeed they have molecular cavities of appropriate size and incorporate a lot of reactive sites; this makes possible the design of structures with a complementary arrangement of binding sites.

A survey of the literature of the last five years shows that many calixarene derivatives have been used for liquid membrane transport of diverse molecular species. A series of calixarene carboxylic acid derivatives were used as host molecules for the quantitative extraction of amino acids in a liquid-liquid extraction system.[116] The interaction between the ammonium cation of the amino acid and the oxygen atoms of the host molecule was the main driving force for the complexation. Using calix[4]arene-based aminophosphonates as a carrier through membrane, the transport of zwitterionic amino acids have been realized.[117] The aminophosphonate groups were responsible for the transport efficiency and the order of the transport rate. The calix[4]arene with chiral pendant groups has been used for chiral recognition of some L-amino acid derivatives through liquid membrane.[118] On the study on the transport of the biogenic amines and aromatic amino acid methylesters in protonated form as ion pairs in the presence of picrate anion by using *p*- tert- butylcalix[n]arenes (n = 6, 8) as carries, Mutihac et al has shown that the above-mentioned calixarenes transport these amino acids through liquid membrane.[119] The results showed that the inclusion abilities of the investigated hosts were correlated with their conformational properties. The extraction abilities and the transport through chloroform liquid membrane of *p*-tertbutylcalix[n]arenes (n = 6, 8) upon some amino acid methylesters have been investigated. The experimental results suggested that amino acid methylesters are extracted into organic phase and transported by *p*-tert-butylcalix[n]arenes (n = 6, 8) in the presence of tropaeolin 00 ([4-(4_-anilinophenylazo)benzenesulphonic acid]) as counterion. The extractability and the transport have been proved to be essentially controlled by the structure of calixarene, the nature of amino acid and the nature of anion used as ion pair for cation-receptor complexes.[120] A series of novel 1,3-alternate calix[4]arene-azacrown ethers with 2-picolyl, 3-picolyl, and benzyl groups on the nitrogen atom were synthesized (Fig. 20). Based on two-phase extraction and bulk liquid membrane studies on this ligand–metal complexation, 2-picolyl-armed calixazacrown ether showed the highest selectivity for silver ion due to electrostatic interaction through effective three-dimensional encapsulation assisted by the nitrogen atom of the 2-picolyl group.[121]

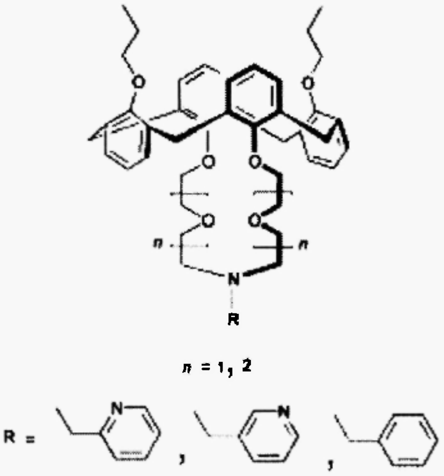


Fig. 20

iv. Calixarenes as Ion Selective Electrode

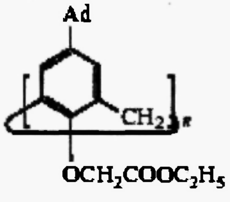
Molecular sensors are required for the efficient detection of charged and neutral pollutant species within organic and aqueous effluents. In the presence of the substrate molecule or ion the chemical sensor is designed to exhibit a physical response which can easily be detected.[22] In particular redox-active molecular receptors have been designed to sense target guest species *via* means of an electrochemical response.

Liquid membrane type ion-selective electrodes (ISEs) provide one of the most powerful sensing methods because they afford the ability to select various sensory elements according to the shape and size of the target ion. Liquid membrane type electrodes for inorganic cations are now commercially available. There are not many of these ISEs that respond strongly enough to discriminate among organic guests, and the selectivities of these electrodes are mostly controlled by the lipophilicity of the guest.

Ion-selective electrodes incorporating macrocyclic compounds as ionophore ligands are well established for many of the metal ions.[123] Potentiometric detectors based on ionselective electrodes are especially suited for fast, accurate, reproducible and selective determination of various metal ions. Such potentiometric detectors offer advantages such as selectivity, sensitivity, good precision, simplicity and so on. These methods allow direct on-line monitoring of concentration of selected species without any pretreatment. Calixarenes represent a family of oligophenols linked in macrocyclic arrays by methylene bridges and act as active agents for ion-selective electrodes because of very selective behaviour for some ions over the other. Functional groups modifications of calixarenes and changes in the cavity size and molecular conformation allowed the selectivity of corresponding electrodes to be controlled.

Recently, calixarenes have received considerable attention as an interesting class of ionic and molecular binding hosts and studies show that various functionalized calixarenes are selective host molecules for cations, [124] as well as anions.[125-126] The well-defined structure of the calixarene cavity could also be investigated for inclusion of organic guests. Calix[6]arene has a sufficiently large cavity so that it can accommodate organic guests, whereas the calix[4]arene cavity is too small for ordinary organic guests. Calixarenes have attracted the attention of researchers as prospective ionophores for ion-selective electrodes.

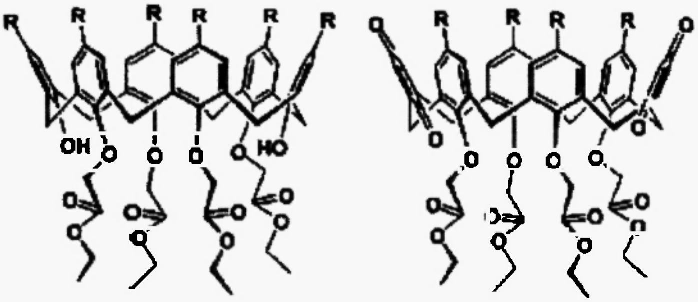
Calix[4,8]arenes bearing adamantyl substituents in the upper rim and ethoxycarbonylmethoxy groups in the lower rim of the macrocycle (Fig. 21) were proposed as ionophores in membranes of ion-selective electrodes (ISEs) for determining alkali cations. Depending on the number of phenolic fragments (*n*) in the calixarene molecule, ISEs respond to either sodium (n= 4) or cesium (n = 8) ions in the presence of other alkali metals. [127]



$n = 4, 8$

Fig. 21

The tetraester of calix[6]arene affords an excellent binding site for protonated primary amines, because the NH3+ moiety of these guests can bind strongly to the inward-directed ester carbonyl groups of the host by hydrogen bonds. Jeon *et al.* synthesized lipophilic tetraesters of calix[6]arene and calix- [6]diquinone (Fig. 22) and exploited them as the sensory element of a PVC matrix liquid membrane electrode for organic amines (protonated form). The potentiometric response properties were examined for octylamine, 1-methylheptylamine, 2-ethylhexylamine and *tert*octylamine as octylamine isomers and phenethylamine.[128]



R=H
R=*t*-Butyl

R=H
R=*t*-Butyl

Fig. 22

Di- and tetraamide *tert*-butylcalix[4]arenas (Fig. 23) were synthesized and described. Their ionophoric properties were studied in liquid membrane ion-selective electrodes. The correlation between the chemical structure and potentiometric ion-selectivity and complex formation constant has been studied. The PVC membrane electrodes based on tetraamides show high sodium selectivity, are stable and long lasting. Disubstituted amides are selective for larger and more lipophilic ions, as for example guanidinium ion.[129]

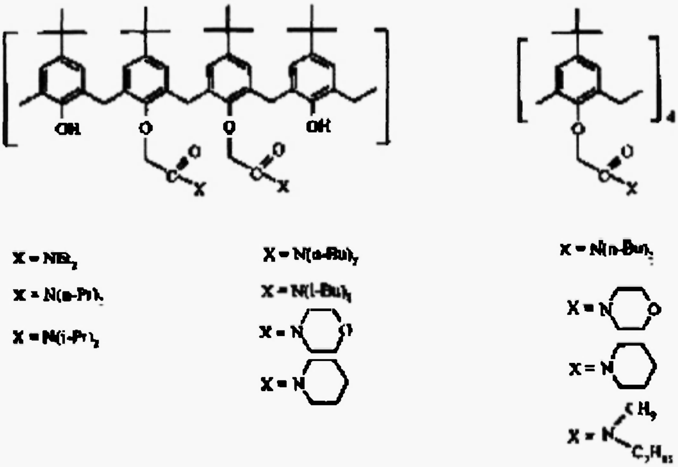


Fig. 23

A novel family of ferrocene-derivatised calix[4]arene ligands (Fig. 24) possessing ester amide and acid amide co-ordination groups has been prepared. Electrochemical studies show these redox-active ligands electrochemically recognise trivalent lanthanide ions *via* significant anodic perturbations of the ferrocene–ferrocenium redox couple. With a ferrocene-bridged calixarene dimer containing ester, amide and phenolic co-ordination functionalities, anodic shifts as large as 200 mV are observed on addition of one equivalent of lanthanide ion.[130]

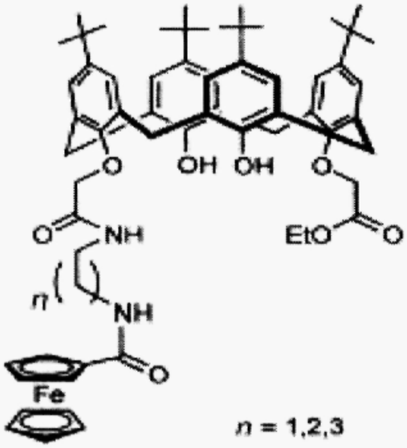


Fig. 24

Calixarene derivatives show selectivity towards Cs+, Cu2+, Cd2+, Pb2+.[131] Recently calixarene derivatives[132-134] have been exploited for the measurement of silver(I). Mahajan *et al.* reported the potentiometric response characteristics and selectivity properties of poly (vinylchloride) (PVC) matrix membrane ion-selective electrodes for silver (I) ion, based on Schiff base p-tert-butyl calix[4]arene derivatives (Fig.25) containing N and O as binding sites.[135]

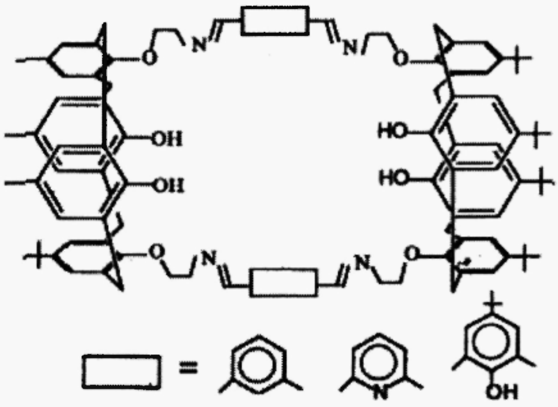


Fig. 25

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