Calixarene-based receptors for molecular recognition

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Abstract: Calixarene-based molecular receptors have been a widely developing area in material science and technology for the last few decades. Due to their bowl-shaped geometry, calixarene macrocycles are used as hosts allowing organic and inorganic guests to coordinate/sorb onto their cavity. This work briefly reviews the recent development of calixarenes.

Key words: Calixarene, receptor, host-guest, drugs, chiral, lipase

1. Introduction

There is considerable interest in developing efficient artificial receptors for molecular recognition and sensing as they have important functional roles in biological, medical, environmental, and chemical sciences.[1−8] There has been significant progress in exploring artificial receptors for sensing, particularly for metal ion sensing over the past 2 decades[9−11]; however, the synthesis and design of artificial receptors that indicate high binding affinity, selectivity, and sensitivity to a targeted molecule or anion still pose a great challenge to the scientific community. The design of complementary structural units that show recognition properties require building in relatively strong and directional attractive forces such as electrostatic interactions, and metal–ligand and hydrogen bonding. A strong binding interaction often provides promise for high sensitivity. Consequently, functional groups such as amides,[12−15] ureas,[16,17] thioureas,[18−22] amidoureas,[23−26] crown ethers,[27,28] carboxylic acids, azacrown ethers,[29−31] ester,[32−35] and positively charged groups[36,37] have been widely used to affix onto artificial receptors for recognizing neutral molecules and ions via noncovalent interactions.

Supramolecular chemistry has supplied solutions in the search for molecular structures that can serve as building blocks for the production of various receptors for charged species or neutral molecules. A relatively new class of synthetic macrocyclic building blocks has recently emerged among molecular receptors of numerous types, capable of binding specific substrates with high efficiency and selectivity. The calix[n]arenes with n = 4, 6, and 8 (Figure 1) are a class of supramolecular building blocks or platforms that are readily synthesized by one-pot procedures. They are synthesized by the easy condensation reaction of formaldehyde with phenol. The highly ordered structures of calixarenes offer not only boundless possibilities for chemical modification, but also make them extremely useful in the study of molecular recognition and supramolecular processes.[38−44]

The aim of this paper is to review the literature so as to provide useful information about complexation between organic molecules and calixarenes and their derivatives. This review will only consider calix[4]arene,

calix[6]arene, and calix[8]arene and especially their derivatives, which are initially derivatized at the lower or upper rim.
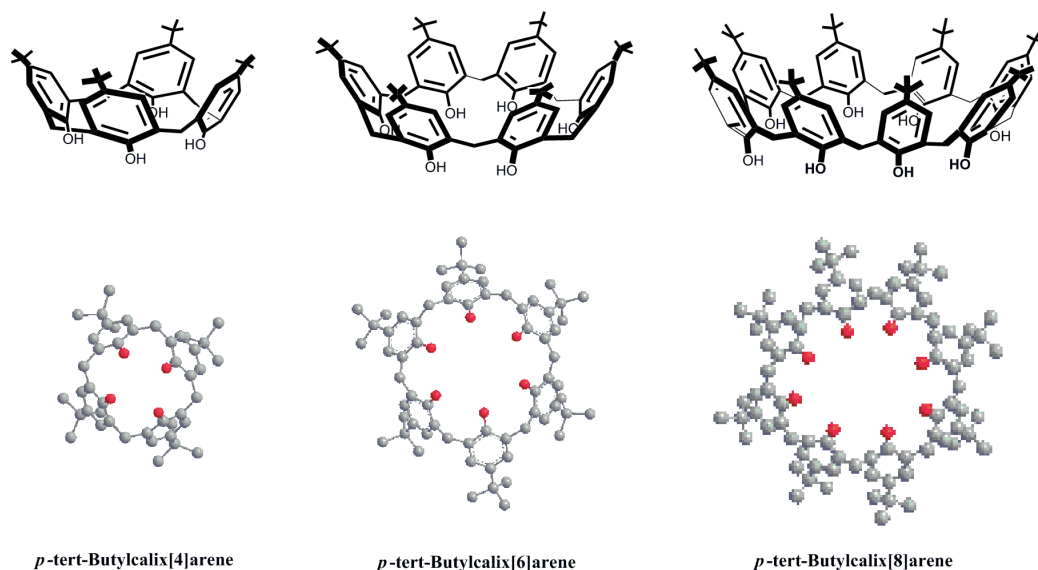

Figure 1. Structures of *p*-tert-butylcalix[n]arenes.

2. Calixarenes for drugs molecules

Modern drug discovery techniques produce numerous drug candidates possessing favorable properties for optimum biological activity, such as chemical structure, biological target affinity, and selectivity. However, their poor aqueous solubility often hampers their full development into a marketable drug product. Solubilization of poorly soluble physiologically active compounds continues to be one of the main stumbling blocks in the formulation of new chemical entities. The problem is traditionally solved by means of various solubilizing additives, such as salts, polymers, and other excipients, whose action is governed by, for example, salting-in effects, charge transfer, and inclusion "guest–host" complex formation.

The highly interesting organizational and carrier properties of calixarenes have been modestly investigated in the medicinal field; only a very few reports, essentially patents, have been devoted to their use as therapeutic agents.[45−51] In order to develop calixarene-based podands shaped as potent drug carriers and dispensers, the calixarene compounds derivatized at the lower or upper rim have recently been reported.
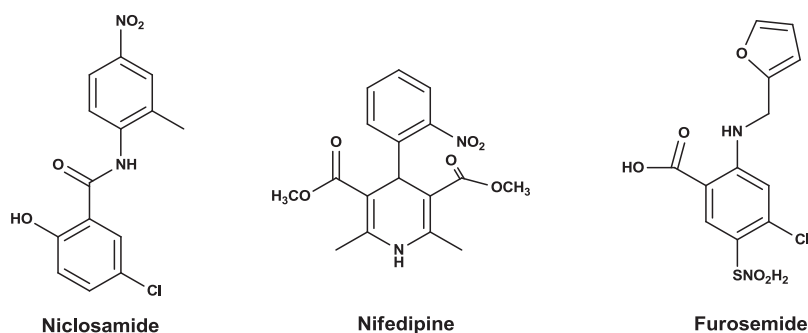

Figure 2. Poorly water-soluble drug molecules.

Niclosamide 5-chloro-N-2-chloro-4-nitrophenyl-2-hydroxybenzamide, nifedipine 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, and furosemide 5-(aminosulfonyl)-4-chloro-2-[(2-furanyl methyl) amino] benzoic acid (Figure 2) are poorly water-soluble drug molecules that are used as anthelmintics, calcium channel blockers, and loop diuretics, respectively.[52,53] The main problem with these molecules is their poor aqueous solubility. A commonly used technique to increase the solubility of poorly water soluble drugs is supramolecular complexation. Bayrakci et al.[54] have reported the extraction of poorly soluble drug molecules given above from the organic phase to the aqueous phase by water-soluble p-phosphonate calix[n]arene receptors via a liquid–liquid phase extraction process. In that study, as host molecules, tetrakis-O-(diethoxyphosphoryl)-p-tert-butylcalix[4]arene (**1**), tetrakis-O-(diethoxyphosphoryl)-calix[4]arene (**2**), bis-O-(diethoxyphosphoryl)-p-tert-butylcalix[4]arene (**3**), bis-O-(diethoxyphosphoryl)-calix[4]arene (**4**), and octakis-O(diethoxyphosphoryl)-p-tertbutylcalix[8]arene (**5**) (Figure 3) were synthesized, and the obtained results showed that the molecular size or the concentration of the calixarenes significantly influenced an increase in the solubility of drug molecules. Moreover, phase solubility profiles of drugs revealed that O-phosphorylated calixarene receptors **1** to **5** might be useful host molecules as drug-solubilizing agents toward niclosamide, furosemide, and nifedipine.
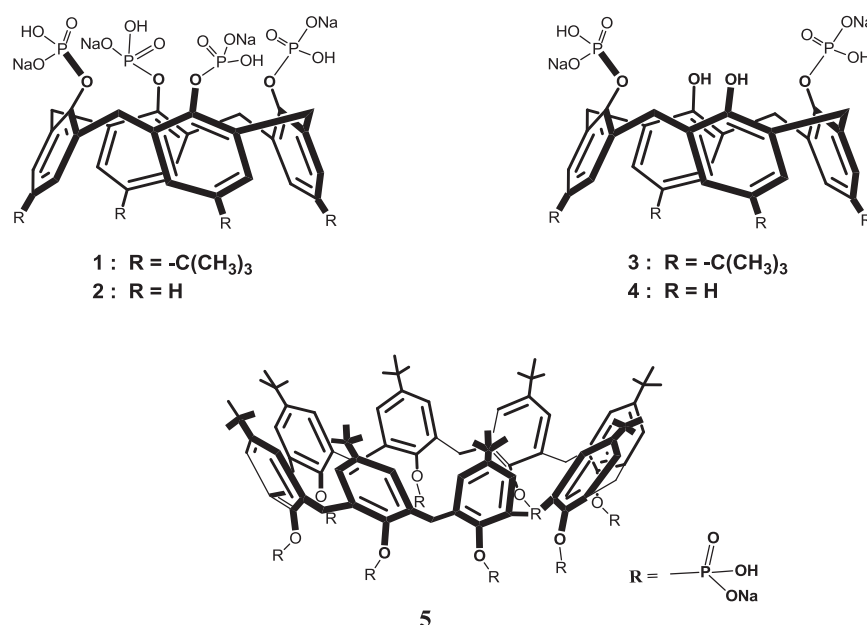

Figure 3. O-phosphorylated calix[4]arene and calix[8]arene receptors.

In another study, p-phosphonate calix[n]arenes **6a–c, 7**, and **8** (Figure 4) were prepared to increase the solubility of poorly water soluble drugs by Bayrakci et al.[55] These water-soluble calixarene derivatives were easily prepared from the reaction between their corresponding chloromethylated derivatives and trimethyl phosphite. The complexation studies showed that compounds **6a–c**, **7**, and **8** were effective receptors for niclosamide, furosemide, and nifedipine drug molecules. It could be concluded that the complexation of drug molecules depends on the structural properties of the water soluble p-phosphonate calix[n]arene such as hydrophobic cavity diameters, hydrogen binding ability, and stability or rigidity. It also depends on electrostatic interaction or ion-dipole attraction between drug molecules and p-phosphonate calix[n]arene.

6a R$_1$,R$_2$,R$_3$,R$_4$ = -POOHO⁻Na⁺
6b R$_1$,R$_3$ = -C(CH$_3$)$_3$, R$_2$,R$_4$ = -POOHO⁻Na⁺
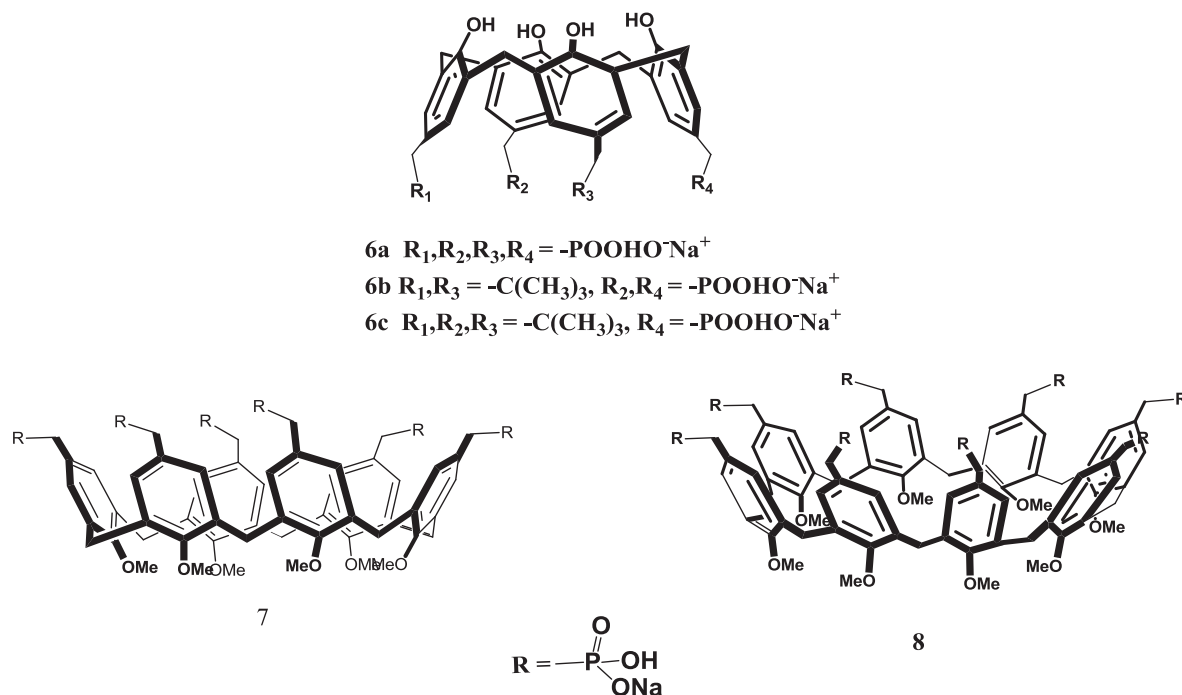**6c** R$_1$,R$_2$,R$_3$ = -C(CH$_3$)$_3$, R$_4$ = -POOHO⁻Na⁺

Figure 4. *p*-Phosphonate calix[n]arene receptors (n = 4, 6, 8).

To investigate the effects of different calixarene derivatives as drug solubilizing agents, new water-soluble phosphonate calix(aza)crowns **9a–c** were synthesized by Bayrakci et al.[56] Liquid–liquid phase extraction and phase solubility studies with poorly water-soluble drug molecules such as niclosamide, furosemide, and nifedipine were performed to assess their binding properties. Among these drugs, furosemide was the drug most effectively dissolved by *p*-phosphonato calix[4](aza)crown ethers **9a–c** in water (Figure 5). The inclusion complexation of the drugs with the water-soluble calixarenes enables one to modify different characteristics of the active molecule to improve stability, crystallize amorphous drugs, prevent polymorphism, and increase solubility. The biopharmaceutical application of water-soluble calixarenes by their complexation can be expected to be of great importance in the future.
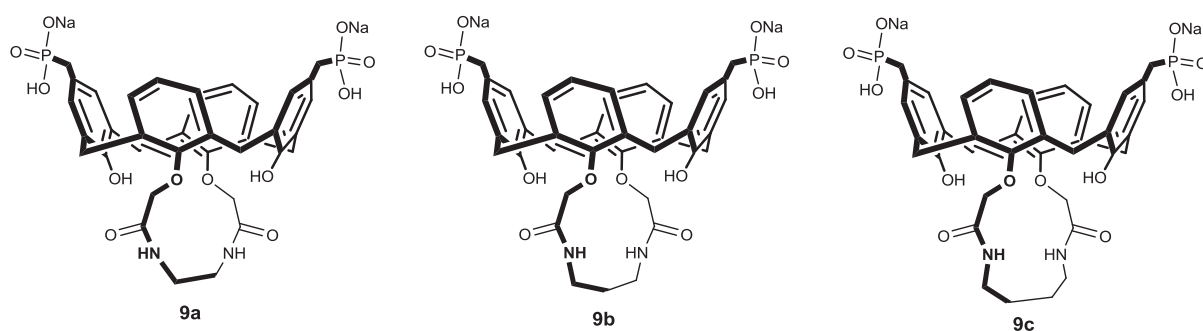


Figure 5. Water-soluble phosphonate calixazacrowns.

Drug toxicity in humans and animals is a major concern and the search for detoxificant agents is a challenge. Pyrolizidine-producing forages are a threat not only to livestock, but also to humans as a consequence of food contamination. Supramolecular systems are promising as detoxificant agents by decreasing the bioavailability of toxic compounds in biological environments. Silva et al.[57] have observed the interactions

between p-sulfonic acid calix[6]arene **10** and retronecine, a toxic pyrrolizidine alkaloid, by NMR techniques. NMR results showed that a strong association between retronecine and **10** was observed as a result of interactions established between the amine and/or hydroxyl groups of the alkaloid retronecine and the SO_3H group of compound **10** (Figure 6).
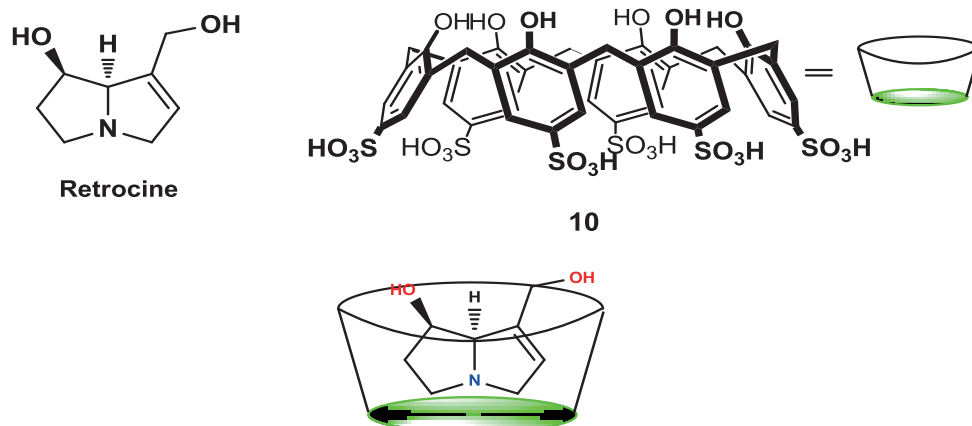

Figure 6. p-Sulfonic acid calix[6]arene and its complex with retrocine.

Wheate et al.[58] have examined the utility of p-sulphonatocalix[4]arene **11** as a drug delivery vehicle for multinuclear platinum anticancer agents, using trans[{PtCl(NH$_3$)$_2$}$_2$l-dpzm]$^{2+}$ (di-Pt; where dpzm = 4,4-dipyrazolylmethane) as a model complex (Figure 7). The side-on binding of the macrocycle to the metal complex, its low binding constant, and its inability to provide steric hindrance to attack of the metal complex by guanosine indicate that **11** may not be a suitable drug delivery vehicle for multinuclear anticancer drugs.
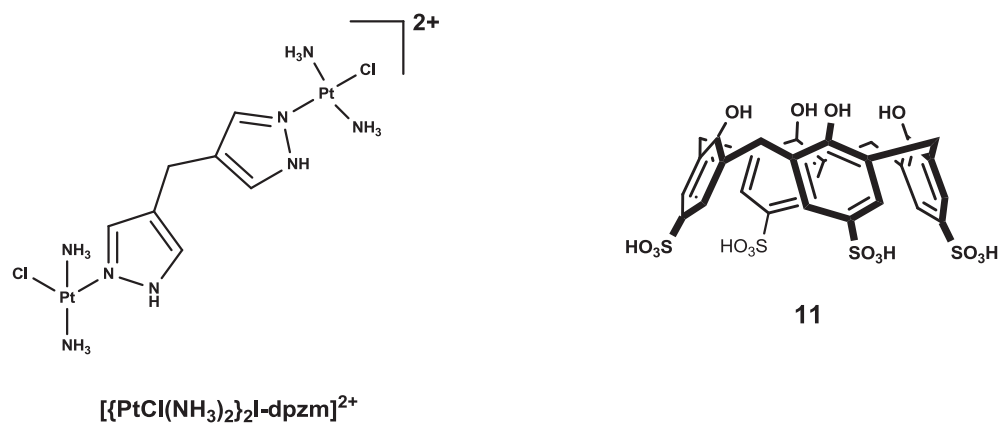

Figure 7. Structures of p-sulfonic acid calix[4]arene and [{PtCl(NH$_3$)$_2$}$_2$l-dpzm]$^{2+}$.

Xue et al.[59] have reported synthesis of amphoteric calix[8]arene **12** with a negatively charged upper rim and a positively charged lower rim based on water-soluble p-sulfonato-calix[8]arene. In view of the potential application of antibacterial drug loaded complexes formed by such calix[8]arenes as drug carriers or for hygiene paper products, they selected a hydrophobic antimicrobical drug of ciprofloxacin (CPF) as a model drug and investigated the pH-sensitive complexation of amphoteric calix[8]arenes in detail (Figure 8). The pH-sensitive amphoteric calix[8]arenes exhibit not only a good hydrophobic drug loading capacity but also pH-triggered drug releasing behavior.
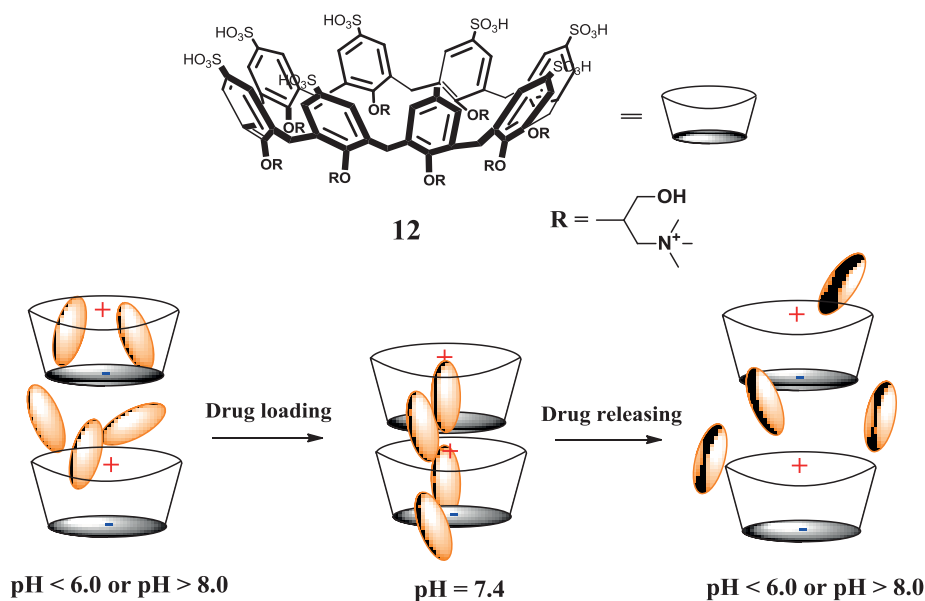
Figure 8. Amphoteric calix[8]arene and model of pH-triggered drug loading and releasing procedure.
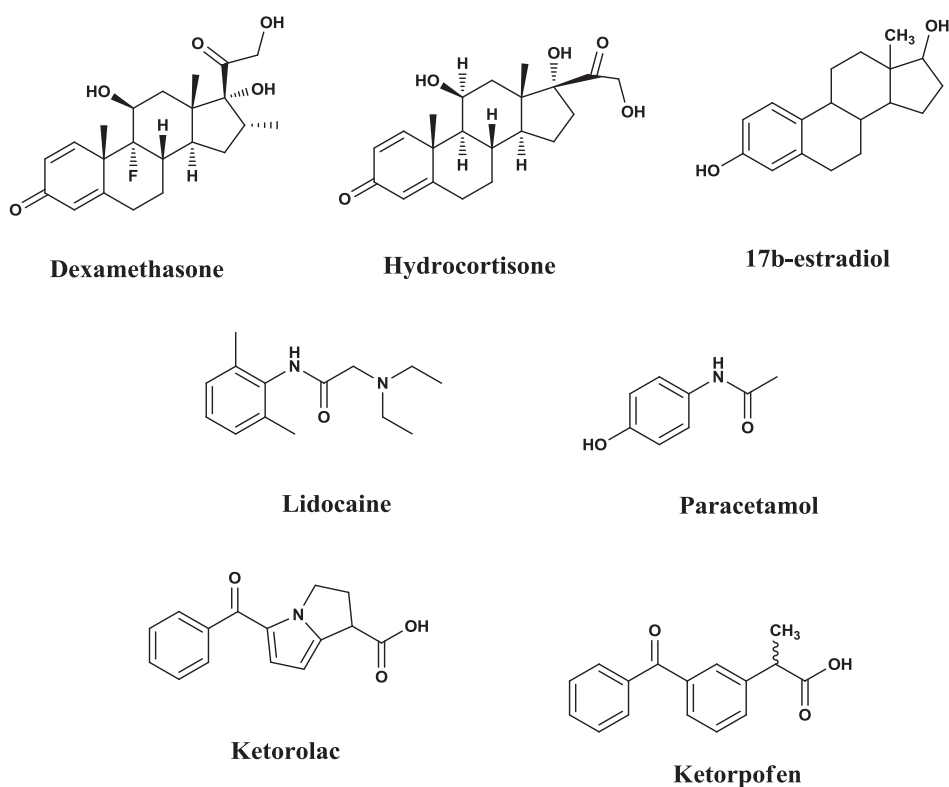
Figure 9. Chemical structures of the drugs used.

Ukhatskaya et al.[60] were interested in the evaluation of the solubilizing properties and estimation of the self-aggregation ability of positively charged 5,11,17,23 tetrakis(trimethylammoniomethyl)-25,26,27,28-tetrapropoxy-calix[4]arene tetrachloride (aminocalix) (**13**), including comparisons with a series of pharmaceutically relevant cyclodextrins. Phase-solubility measurements of some selected drugs (Dexamethasone, hydrocor-

tisone, 17β-estradiol, lidocaine, paracetamol, ketorolac, and ketorpofen) (Figure 9) with aminocalix and various cyclodextrins (CDs) (Figure 10) were carried out and aminocalix **13** showed a solubilizing ability that was comparable to the cyclodextrins. In general, aminocalix improved the aqueous solubility of lidocaine, paracetamol, and ketoprofen more efficiently than the CDs tested. However, maximum solubility enhancement was observed for steroidal drugs. Moreover, the experimental data showed that the mechanism of solubilization is based on a formation of aminocalix aggregates rather than by formation of drug/aminocalix inclusion complexes.
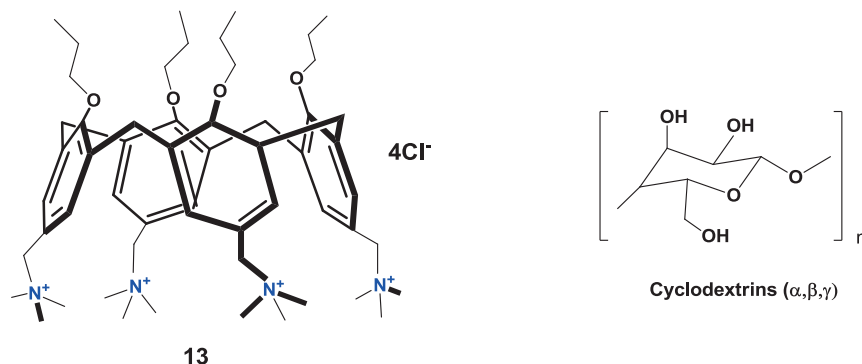

Figure 10. Structures of aminocalix **13** and cyclodextrins.

Yang et al.[61] have observed the solubilization of the poorly water-soluble drug nifedipine by water soluble 4-sulphonic calix[n]arenes. The experimental results indicated that the size of the 4-sulphonic calix[n]arenes, the pH of medium, and the concentration of the calix[n]arenes significantly changed the solubility of nifedipine. 4-Sulphonic calix[8]arene **14** improved the solubility of nifedipine the most, about 3 times, followed by 4-sulphonic calix[4]arene, about 1.5 times, while 4-sulphonic calix[6]arene decreased the solubility of nifedipine (Figure 11).
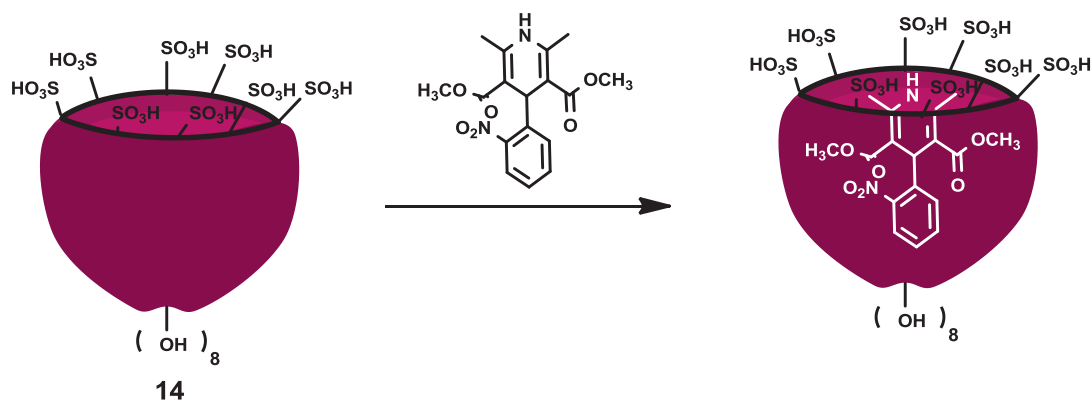

Figure 11. Complexation between 4-sulphonic calix[8]arene **14** and nifedipine.

3. Calixarenes in lipase immobilization

Immobilization of enzymes is key in expanding the applications of these natural catalysts by enabling easy separation and purification of products from reaction mixtures and efficient recovery of enzyme proteins. So far, most efforts have focused on immobilization, of which many approaches are known, involving adsorption of appropriate supports or covalent attachment to such materials as well as encapsulation in sol gel materials

or in polymers. Many crown ether activations of enzymes in organic media have been reported.[62] Crown ethers mainly form complexes with surface ammonium groups of lysine. Moreover, cyclodextrins (CDs), a class of compounds with a macrocyclic structure, have been successfully used to improve enzyme activity and to increase the reaction rate and enantioselectivity in enzyme-catalyzed reactions in organic solvents.[63,64] In the literature, calix[n]arene derivatives form complexes with cationic lysine.[65,66] Recently, in order to establish the role of calixarene binding sites on lipase activity, stability, and enantioselective hydrolysis reactions by different immobilization techniques, the effects of calixarene derivatives on lipase immobilization have been reported.

Erdemir et al.[67,68] have reported the synthesis of new calix[n]arene-based silica polymers **15a–c** as support and additive materials and the role of a calix[n]arene binding site on the lipase activity and stability with covalent immobilization of lipase (Figure 12). The results showed that the immobilized lipases have good stability, adaptability, and reusability in comparison with the free enzyme. On the other hand, they have used calix[n]arene-based silica polymers on sol-gel encapsulation procedures as additive materials, have observed the effects of calix[n]arene-based polymers **15a–c** in the enantioselective hydrolysis reaction of (R/S)-naproxen methyl ester, and compared covalently immobilized lipases with calix[n]arene-based polymers. The results indicated that the enantioselectivity and conversion effect of **15b** in enantioselective hydrolysis reaction proved significantly higher than those for the free lipase, other encapsulated lipases (**15a** and **15c**), and covalently immobilized lipases (Figure 13).
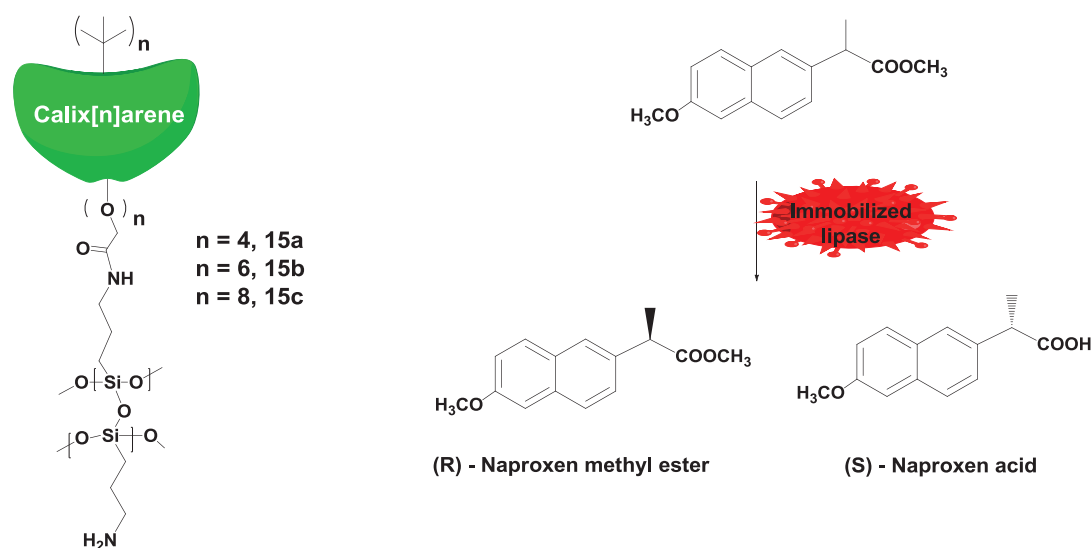

Figure 12. Structure of calix[n]arene-based silica polymers and enantioselective hydrolysis of (R,S)-naproxen methyl ester.

In another study, Erdemir et al.[69] have reported the synthesis of the glutaraldehyde derivatives calix[n]arene (n = 4, 6, 8) **16–18** (Figure 14) and using them as cross-linkers for immobilization of lipase. Activities of the obtained immobilized lipases were determined using p-nitrophenyl palmitate. It was found that, after immobilization, lipase activity decreased. However, thermal stability and reusability of the lipase increased. Multipoint covalent attachment of lipase on highly activated pre-existing supports via short spacer arms and involving many residues placed on the lipase surface promotes a rigidification of the lipase structure of the immobilized lipase. This should reduce any conformational change involved in lipase inactivation and should greatly increase the enzyme stability.
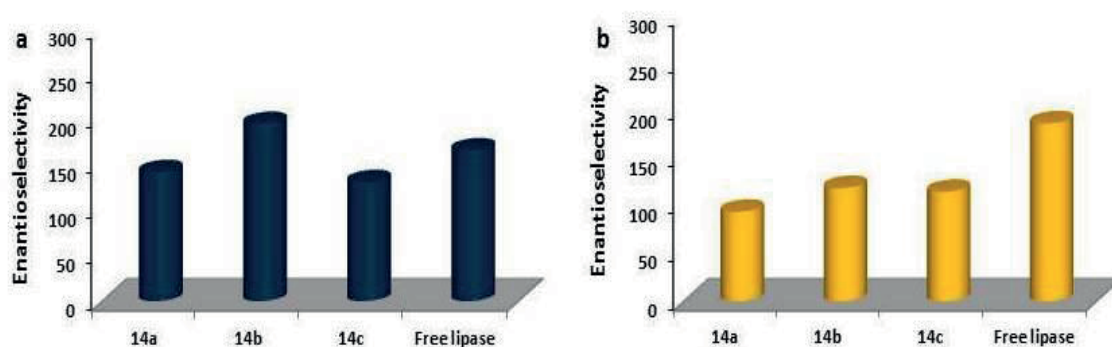
Figure 13. Enantioselectivities of encapsulated (a) and covalently immobilized lipases (b) in the enantioselective hydrolysis reaction of racemic naproxen methyl ester.
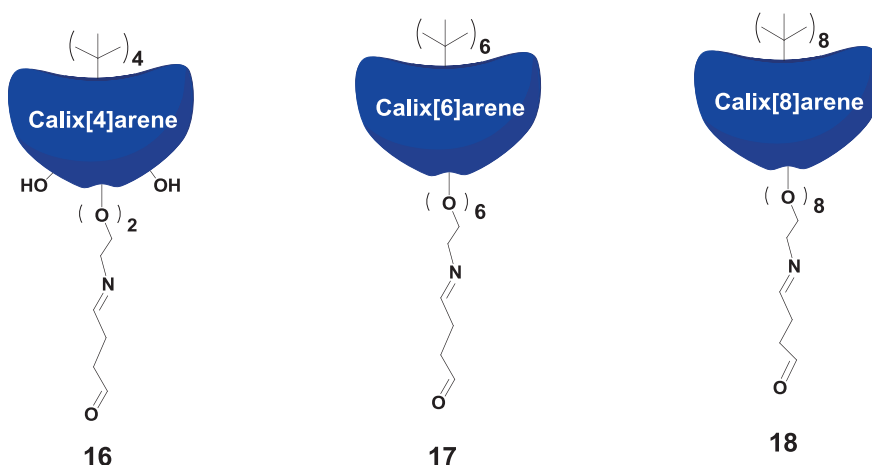
Figure 14. Aldehyde pointed calix[n]arene derivatives.

In the sol-gel encapsulation method, the crown ether derivatives and cyclodextrins have generally been used as macrocyclic compounds. Calixarenes for lipase immobilization by the sol-gel method were first used by Yilmaz et al. They thought that it might be interesting. Yilmaz et al.[70] have investigated the use of the calix[n]arenes and their derivatives (carboxyl and amine) (Figure 15) as additives on lipase immobilization by the sol-gel process and the effect of calix[n]arene derivatives in the enantioselective hydrolysis reaction of (R,S)–naproxen methyl ester. *Candida rugosa* lipase was encapsulated within a chemically inert sol-gel support prepared by polycondensation by tetraetoxysilane (TEOS) and octyltrietoxysilane (OTES) in the presence and absence of calix[n]arene **19a–c**, calix[n]-NH$_2$ **20a–c**, and calix[n]-COOH **21a–c** (n = 4, 6, 8) compounds as additives. The catalytic activity of the encapsulated lipases was evaluated in model reactions, i.e. the hydrolysis of p-nitrophenylpalmitate (p–NPP), and the enantioselective hydrolysis of racemic naproxen methyl ester that was studied in an aqueous buffer solution/isooctane reaction system. The results indicated that the **20a**, **20b**, and **21b** based encapsulated lipases in particular had a higher conversion and enantioselectivity compared with the sol-gel free lipase.
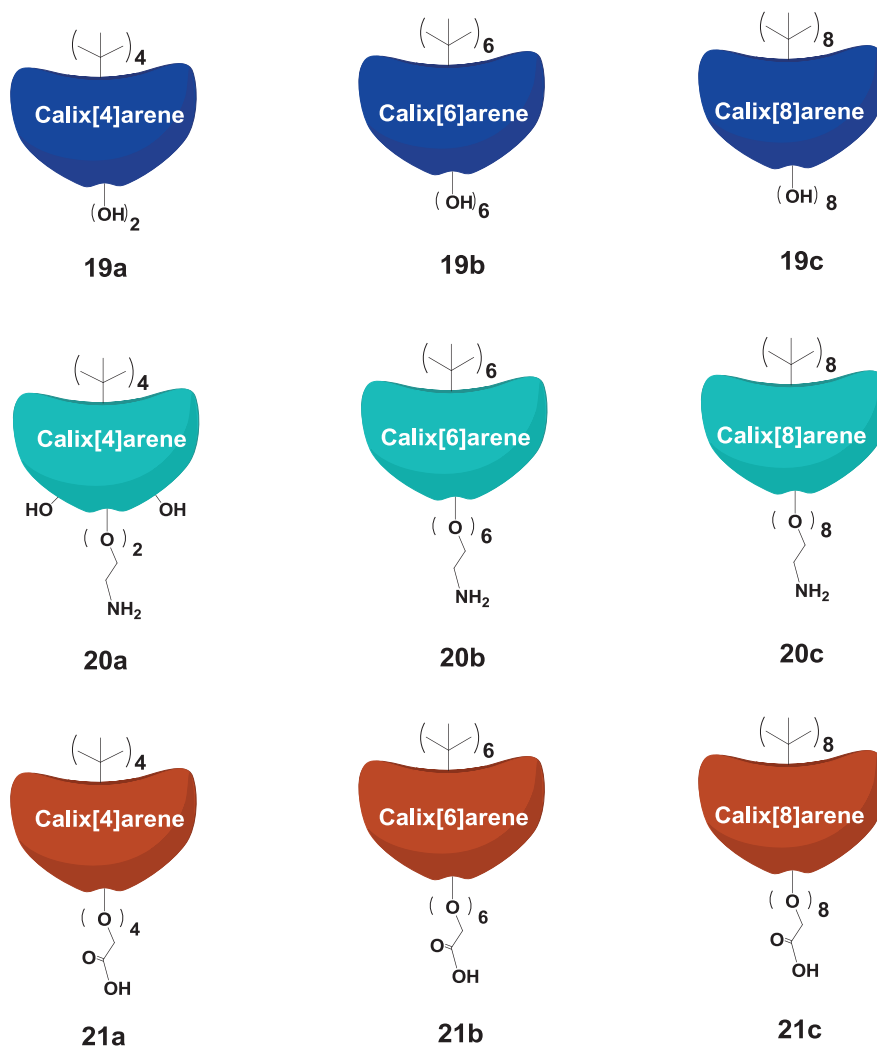
Figure 15. Calix[n]arenes and its derivatives used in the sol-gel process.

To improve the catalytic activity of lipase from via sol-gel encapsulation, the same group[71] has synthesized calix(aza)crown compounds **22**–**24** as new additives (Figure 16). The catalytic activity of the encapsulated
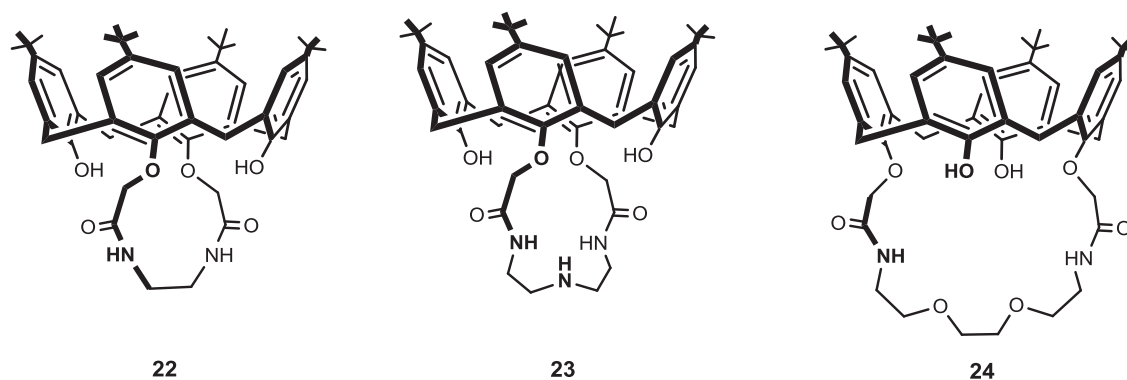

Figure 16. Calix(aza)crown derivatives.

lipases was evaluated both in the hydrolysis of p-nitrophenyl palmitate (p–NPP) and the enantioselective hydrolysis of racemic naproxen methyl ester. It was found that the percent activity yields of the calix(aza)-crown-based encapsulated lipases were higher than that of the free lipase. Moreover, the encapsulated lipases still retained about 18% of their conversion ratios after the sixth reuse in the enantioselective reaction.
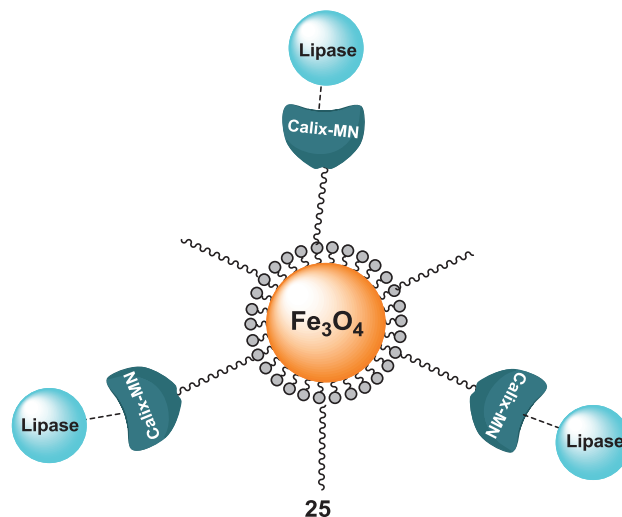
Figure 17. Proposed structure between calixarene-based magnetic nanoparticles and lipase.

By introducing magnetic properties to organic or biomolecules, separation and reusable processes become easy tasks due to magnetic speciation. Sayin et al.[72] have reported the stability and enzymatic activity of *Candida rugosa* lipase immobilized on N-methylglucamine based on calix[4]arene magnetic nanoparticles **25** (Figure 17). The results show that the magnetic calix[4]arene-based encapsulated lipase **25** has shown particularly high conversion and enantioselectivity. It has also been noted that the magnetic calix[4]arene-based encapsulated lipase has excellent enantioselectivity (E = 460) compared to the free enzyme (E = 166). In addition, the recovery and reusability of encapsulated lipase nanoparticles **25** is also important for economical use of the enzyme, which may very easily be due to its magnetic properties. Reusability studies in the hydrolysis of racemic naproxen methyl ester show that the immobilized lipases still retained 28% of their conversion ratios for 24 h after the 5th reuse cycle.

4. Calixarenes for azo dyes and aromatic amines

The disposal of liquid effluents from various industries, viz. textiles, paper, plastics, leather, foods, cosmetics, etc., poses a common problem faced by many countries since the effluents contain a number of contaminants including acids, bases, dissolved solids, toxic compounds, and color. For industrial liquid effluents, color is the first contaminant to be recognized because of its visibility; even small quantities of dyes can color large bodies of water. These industrial effluents can be toxic to aquatic life, and can interfere in the transmission of sunlight, thus reducing the action of photosynthesis.[73]

Recent studies related to sorption of toxic compounds indicate that there is widespread concern about the synthesis of adsorbent resins able to eliminate organic pollutants. Different chemical and physical processes as well as solid phase extraction are currently in use. Solid phase extraction is one of the most efficient and well-established procedures in the field of separation science; it finds application in various fields such as industrial, environmental, clinical, food, and pharmaceutical chemistry. Solid phase extraction is usually

conducted using a column or cartridge containing an appropriate sorbent. The sorbents may be of organic origin or mineral. Among these sorbents, modified silicas (C8 and C18), ion exchangers,[74] graphitized carbon black,[75] various polymeric sorbents such as polystyrene–divinyl benzene (PS–DVB),[76] immunosorbents,[77] molecularly imprinted polymers,[78] conductive polymers,[79] porous polymers,[80] and polysaccharides such as chitin,[81,82] starch,[83,84] and chitosan,[85,86] are reported. In this respect, supramolecular chemistry has been a much better tool to search for molecular structures that can serve as building blocks for the production of enhanced molecules by anchoring functional groups oriented in such a way that they supply an appropriate binding site. This was accomplished by the development of macrocyclic molecules such as synthetic crown ethers, cryptands, spherands,[87] cyclodextrins,[88,89] and calixarenes.[44, 90−94]
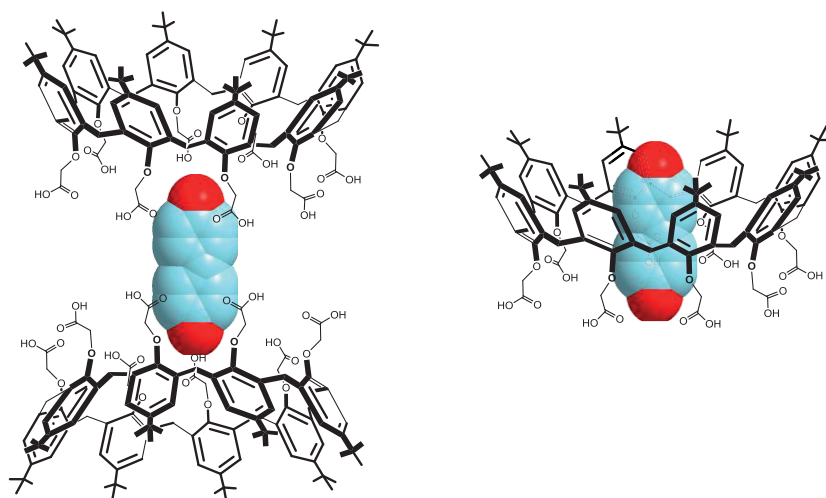
**Figure 18.** Complexation models between compound **26** and benzidine.

In this connection, different calixarenes or their polymers have been prepared and used in the removal of toxic molecules. For example, Yilmaz et al.[95] investigated the extraction abilities of *p-tert*-butylcalix[n]arenes (n = 6, 8) and their ester and carboxylic acid derivatives for some selected carcinogenic aromatic amines. The concentration of aromatic amines in water phase was determined using high-performance liquid chromatography (HPLC). HPLC results indicate that *p-tert*-butylcalix[8]arene-octacarboxylic acid **26** showed a better affinity than other compounds towards all aromatic amine species at almost all pHs. The sorption of aromatic amines by carboxylic acid derivatives of *p-tert*-butylcalix[*n*]arene shows that carboxyl groups have a major role in the formation of hydrogen bonds and electrostatic interactions between aromatic amines and sorbent (Figure 18).

In another study by Yilmaz et al.,[96] the Mannich base **27** was synthesized by the reaction of calix[4]arene with a cyclic secondary amine (1,4-dioxa-8-azaspiro-[4,5]decane) and formaldehyde. Then compound **27** was treated with dibromoxylene to give calix[4]arene-based copolymer **28** (Figure 19). In batch sorption experiments, **27** and **28** were found to be better sorbents for azo dyes than for the aromatic amines. The maximum percent sorption of azo dyes was 95%–99% for **27** and 83%–97% for **28** when the pH of the dye solution was in the range of 2.0–8.0. The sorption of azo dyes and aromatic amines with calix[4]arene-based compounds shows that amino groups have a major role in the formation of hydrogen bonds and electrostatic interactions.
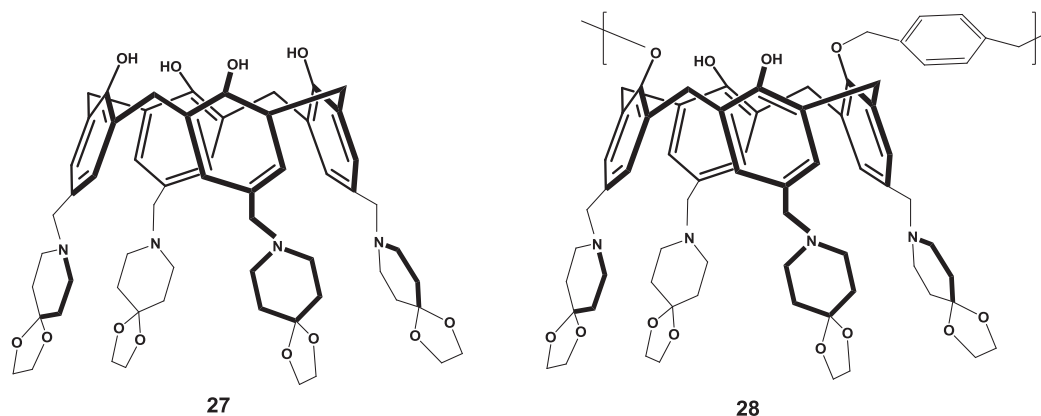
Figure 19. A Mannich base of calix[4]arene and its copolymer.

The higher level of dye removal by **28** suggests that a Coulomb interaction exists between the amino groups incalix[4]arene and the sulfonate groups in azo dyes (Figure 20).
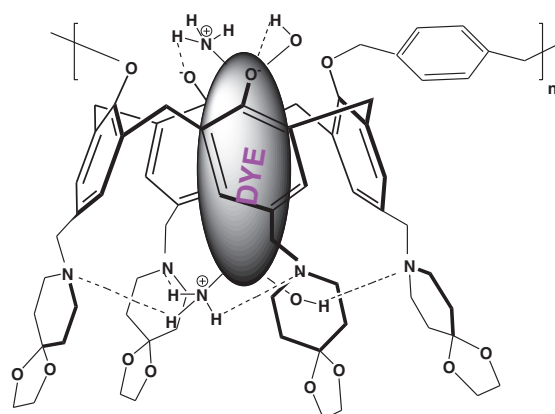

Figure 20. Proposed interaction of azo dye with **28**.

The conversion of calix[4]arene derivative **27** into its polymeric form (**28**) significantly improves the aromatic amine sorption capability. This can be explained by the fact that the calixarene derivative in the polymeric matrix may have gained a more rigid and appropriate structure, which supports the sorption of amine in the SPE system. It is possible that the polymer has a role in which it folds into conformations that place functional groups from multiple calix[4]arene units in the polymer into a preferred conformation where they can associate with the aromatic amines.

Aromatic amines were expected to form inclusion complexes with insoluble calix[4]arene derivative **27** and its polymer **28**. Solid–liquid batch sorption experiments were used to assess their ability to remove the aromatic amines from an aqueous solution. The separation and quantification of aromatic amines were realized by means of HPLC. It was observed that **27** has a little affinity for selected aromatic amines. However, when it was converted to a rigid structure by anchoring it in a polymeric backbone it showed remarkable extraction ability.

Ozmen et al.[97] have reported the synthesis of different calix[n]arene derivatives (**29–34**) with different internal cavity sizes (Figure 21) and observed the capacities of these sorbents to remove carcinogenic direct azo dyes from water using the SPE process. The results obtained were compared with those of unsubstituted calix[n]arenes.
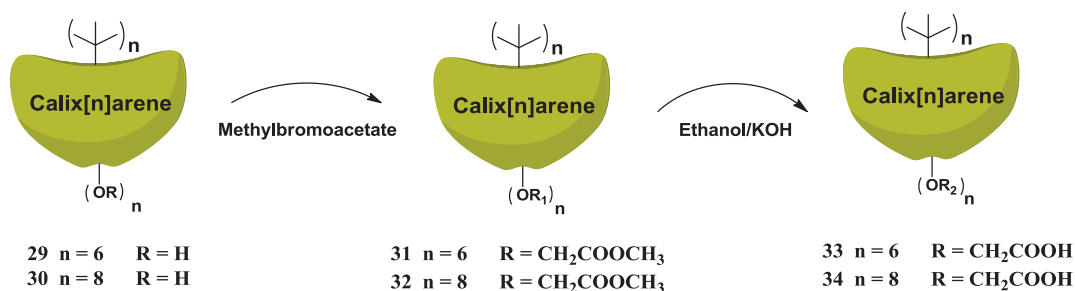
Figure 21. Synthetic roots for calix[n]arene derivatives.

However, it was found that the parent calixarenes **29** and **30** have less affinity towards azo dyes (i.e. Evans Blue [EB], Direct Blue [DB15], and Chicago Sky Blue [CSB]). The ester derivatives of calix[6,8]arenes **31** and **32** resulted in a remarkable improvement in their sorption capabilities towards all azo dyes. Here, it should be noted that the *p-tert*-butylcalix[n]arene ester derivatives demonstrate binding abilities towards sodium cations.[98,99] The pronounced Na^+ binding suggests an ion-pair extraction mechanism in which Na^+ coordinates with the ester binding site, while the azo dye anion inserts into the hydrophobic calixarene cavity.

In the aqueous solution, the acid dye is first dissolved; consequently, the sulfonate groups of the acid dye (dye–SO_3Na) are dissociated and converted to dye anions. The direct dye is a relatively large molecule and is negatively charged at most of the pH ranges (>5.0).

$$Dye - SO_3Na \longrightarrow Dye - SO_3^- + Na^+$$
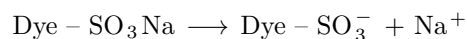
The higher levels of dye removal by calix[n]arene carboxyl acid derivatives **33** and **34** compared with the other calix[n]arene sorbents **29**–**32** suggest that a Coulomb interaction exists between the carboxylic acid groups of calix[n]arenes and the sulfonate groups of azo dyes (Figure 22).
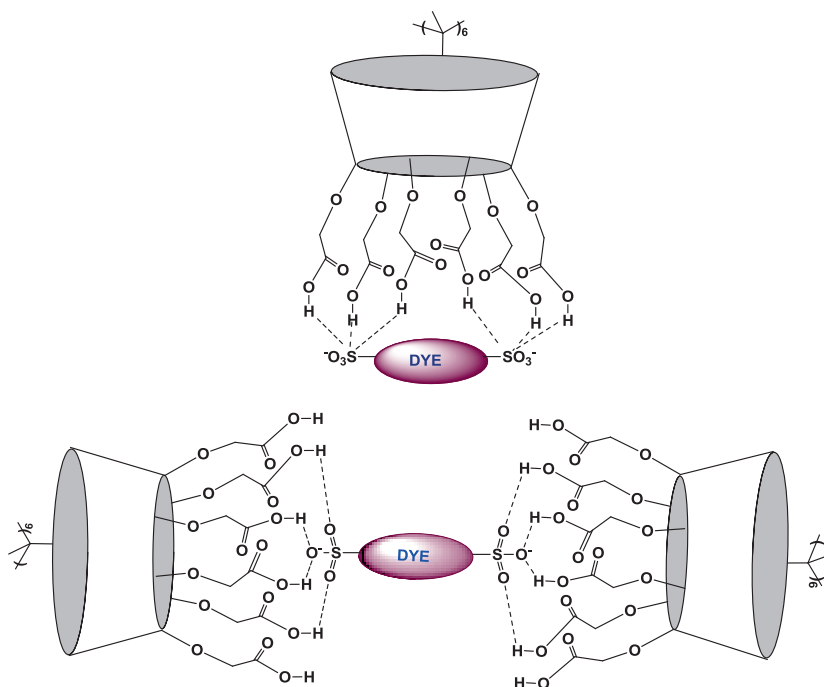

**Figure 22.** Proposed interaction of calix-sorbent **33** with azo dye.

The substitution patterns of EB and CSB are similar to each other, whereas DB 15 contains sulfonate groups at different positions on the naphthalene rings, which might cause lower sorption rates of DB 15. Carboxyl groups of calix[n]arenes **33** and **34** produce intermolecular hydrogen bonds with these sulfonate groups. Thus, the cavity size, cyclic structure, and functional groups of calixarene derivatives were found to be the most important factors for sorption of azo dyes.

Yilmaz et al.[100,101] have reported that calix[4]arene-based oligomer **35** (Figure 23) is synthesized by the condensation of *p-tert*-butylcalix[4]arene with hexamethylene diiso-cyanate and utilized to sorb water-soluble azo dyes (i.e. Titanium Yellow [TY], Direct Violet 51 [DV51], Tropaeolin 000 [TP], Methylene Orange [MO], and Direct Blue 71 [DB71]). The sorption studies of selected azo dyes have been evaluated and the polymer **35** was found to be a good azo dye sorbent.

Kamboh et al.[102] describe a novel synthetic method for the immobilization of calix[4]arene on the surface of modified Amberlite XAD-4 resin (Figure 24) that does not require the derivatization of calixarene moiety. The novel resin bearing calix[4]arene **36** was used as sorbent for the removal of azo dyes. A batch-wise sorption study was realized and it was found that the resin **36** is more effective as compared to calix[4]arene as well as pure Amberlite XAD-4 resin in removing the selected dyes (i.e. Reactive Black-5 [RB-5], Reactive Red-45 [RR-45], and Congo Red [CR]). The effect of sorbent dosage and pH on % sorption was also studied. During the extraction process, various kinds of interactions such as deprotonation of the hydroxyl groups of resin **36,** electrostatic repulsion, dissociation of reactive dyes into anions/cations, and structural variations were monitored and it was found that they are highly pH-dependent.
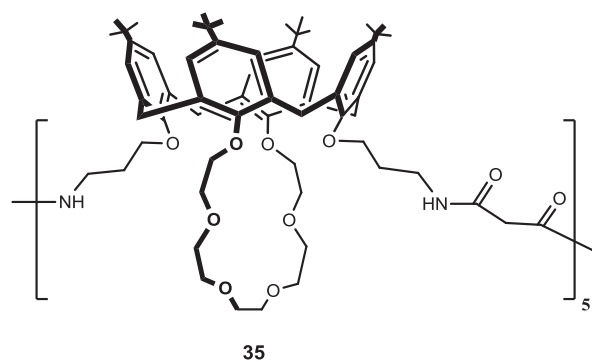

Figure 23. Calix[4]arene-based oligomer **35**.
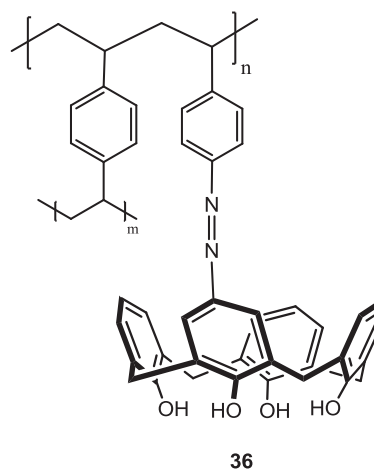
Figure 24. The novel calix[4]arene-based resin **36**.

The sorption and desorption properties of the starch grafted *p-tert*-butyl-calix[n]arene-SGCn (SGC4, SGC6, SGC8) for butyl Rhodamine B **37** solution (Figure 25) have been investigated by Chen et al.[103] Static adsorption behavior was studied using SGC8 **38** as sorbent, and butyl rhodamine B (BRB) solution as simulation dye wastewater. The adsorbent may be easily regenerated using ethanol solution as a desorption agent to extract dye from SGC8. It was found that the rate of desorption of BRB is dependent on the concentration of ethanol and the temperature. SGC8 demonstrates excellent adsorption and desorption behaviors toward dye molecule. The new-style adsorbent of SGC8 is regarded as a potential adsorbent to deal with dye or organic wastewater.
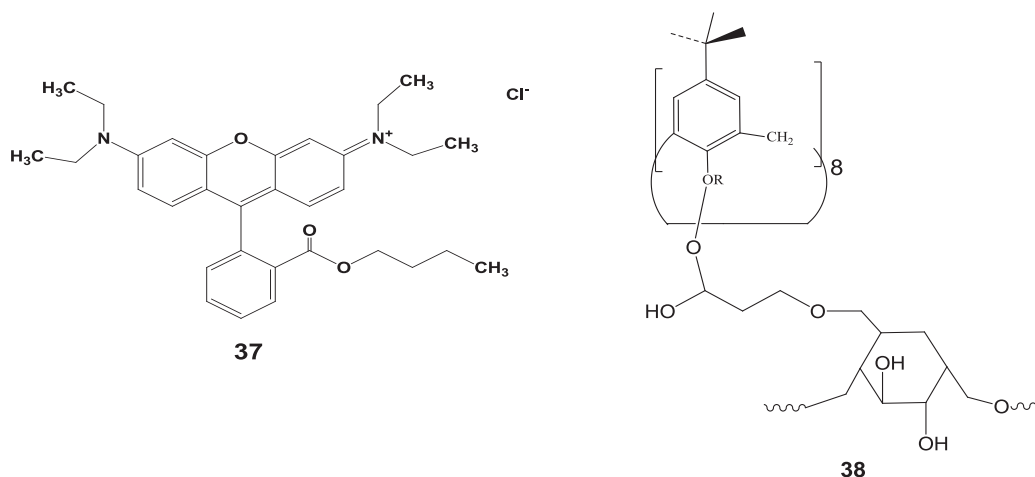
Figure 25. The structures of *p-tert*-butyl-calix[8]arene-SGC8 and butyl Rhodamine B.

The same group[104] has presented the characteristics of host–guest complexation between water-soluble calix[n]arene sulfonates (CnS, n = 4, 6, 8) and BRB by fluorescence spectrometry. The complex stability constant monotonically increased with the number of phenolic units in the calixarene molecule. The inclusion complexes of CnS with BRB were driven by the favorable enthalpic changes, accompanying negative entropy changes. The molecular recognition mechanism indicated that the hydrogen bonding and electrostatic interaction played 2 effective roles in the formation of inclusion complexes, as well as the hydrophobic interaction and van der Waals forces.

For adsorption of some azo dyes (reactive black-5 [RB-5] and reactive red-45 [RR-45]), Kamboh et al.[105] prepared *p-tert*-butylcalix[4]arene-based silica resin **39** (Figure 26). They carried out a batch-wise adsorption study to optimize various experimental parameters such as the effect of pH, adsorbent dosage, electrolyte, contact time, temperature, and dye concentration. The maximum adsorption of RB-5 and RR-45 was achieved at pH 9.0 and pH 3.0, respectively. As a result, the prepared resin **39** proved to be highly effective for the removal of selected azo dyes.
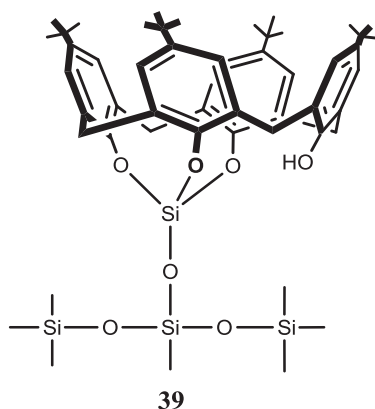
Figure 26. *p-tert*-Butyl-calix[4]arene-based silica resin **39**.

The new water-soluble calix[4,6]arene appended magnetic nanoparticles **40** and **41** (Figure 27) were used as sorbents in removing selected carcinogenic aromatic amines from aqueous solutions by Yilmaz's group.[106] The magnetic feature of sorbents provides rapid and easy separation and recovery from the reaction medium in

an external magnetic field (Figure 28). The separation and quantification of aromatic amines were performed by HPLC. From the chromatographic data, it was concluded that the sorption of aromatic amines by **40** and **41** sorbents shows that amino and sulfonic acid groups are responsible for the formation of hydrogen bonds and electrostatic interactions.
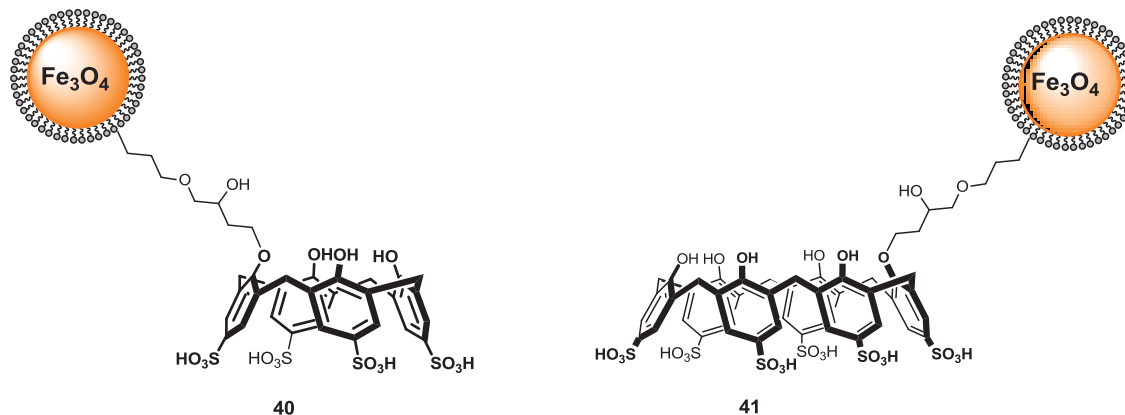
Figure 27. The water soluble calix[4,6]arene appended magnetic nanoparticles.

Figure 28. Schematic illustration of magnetic separation of azo dyes from aqueous solution.

Figure 29. *p*-Sulfonatocalix[6]arene-modified gold NPs and isomeric diaminobenzenes.

As selective colorimetric probes for the determination of isomeric diaminobenzenes, the water-soluble *p*-sulfonatocalix[6]arene-modified gold NPs **42** (Figure 29) were synthesized by Han et al. [107] The *p*SC6-Au NPs **42**

were employed as colorimetric probes to detect diaminobenzene (DAB) isomers. Moreover, in order to investigate the molecular r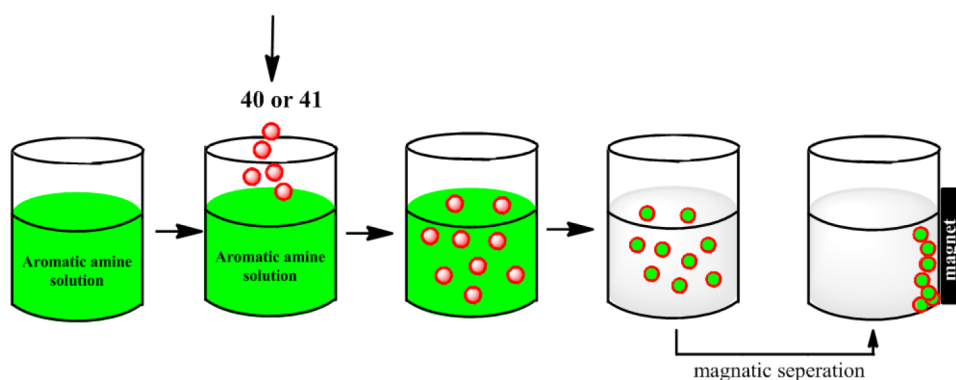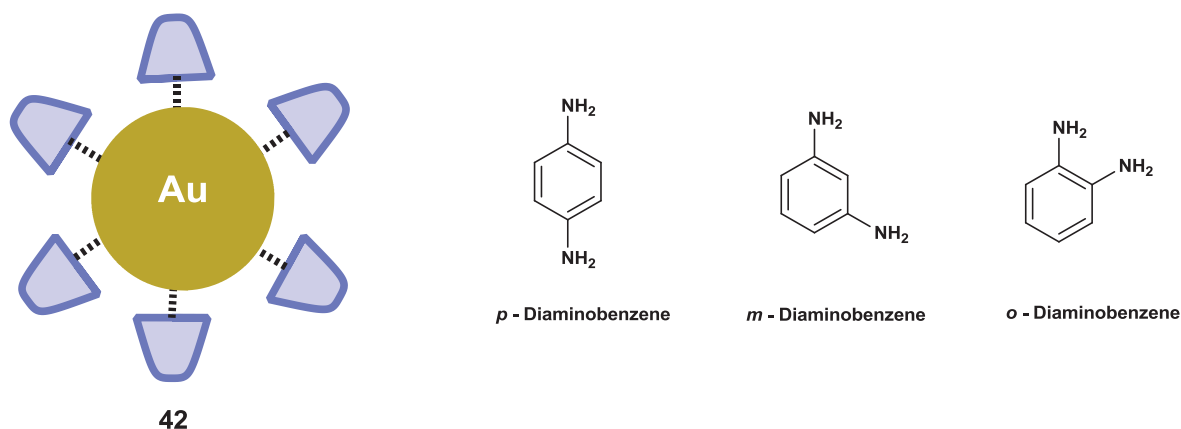ecognition ability of $p-$ SC6-Au NPs, different aqueous ethanol solutions of aromatic amines were used. However, the sensitivity of pSC6-Au NPs towards other amines, including o-diaminobenzene, o-toluidine, m-toluidine, p-toluidine, o-chloroaniline, p-chloroaniline, o-nitroaniline, m-nitroaniline, p-nitroaniline, and aniline, is negligible.

5. Calixarenes for chiral recognition

Chiral recognition, the process in which an enantiomerically pure host molecule selectively binds one of the enantiomers, is one of the most essential reaction processes occurring in living systems. Hence, chiral calixarenes have attracted increasing attention owing to their capacities in enantio-discrimination processes. Chiral calixarenes can be prepared by attaching chiral moieties at one of the upper or lower rims of calixarene by synthesizing inherently chiral derivatives in which an asymmetric substitution of the macrocycle is associated with its intrinsic 3-dimensional nature. From a practical point of view, the first approach appears to be preferable in that inherent chirality always needs a difficult resolution on an appropriate scale.[108] Thus, a large number of chiral calixarenes have been synthesized by using chiral units,[109] such as single amino acids,[110] peptides,[111] amino alcohols,[112]
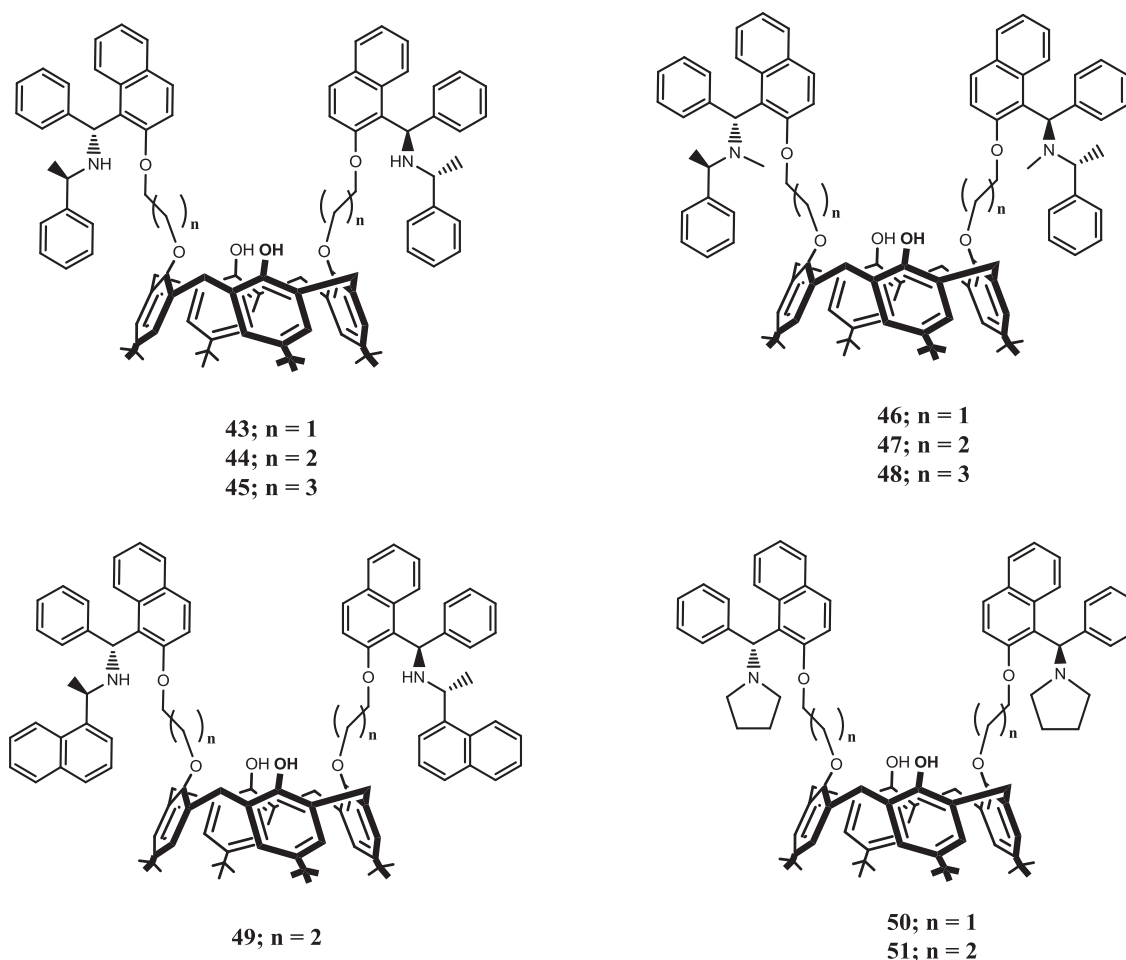


Figure 30. Chiral calix[4]arenes bearing aminonaphthol units.

sugars,[113] tartaric acid esters,[114] binaphthyl,[115] glycidyl,[116] menthone,[117] and guanidinium groups.[118]

Durmaz et al.[119] have reported the synthesis of 2 armed chiral calix[4]arenes **43–51** functionalized at the lower rim with chiral aminonaphthol units (Figure 30) and the enantioselective recognition properties of these receptors with various carboxylic acids (Figure 31). The receptors indicated different chiral recognition abilities towards the enantiomers of racemic materials and formed 1:1 or 2:1 complexes between host and guest. From the NMR experiments, it was concluded that the chiral calix[4]arenes **44** and **51** could be used as chiral NMR solvating agents to determine the enantiomeric purity of mandelic acid at ambient temperature.
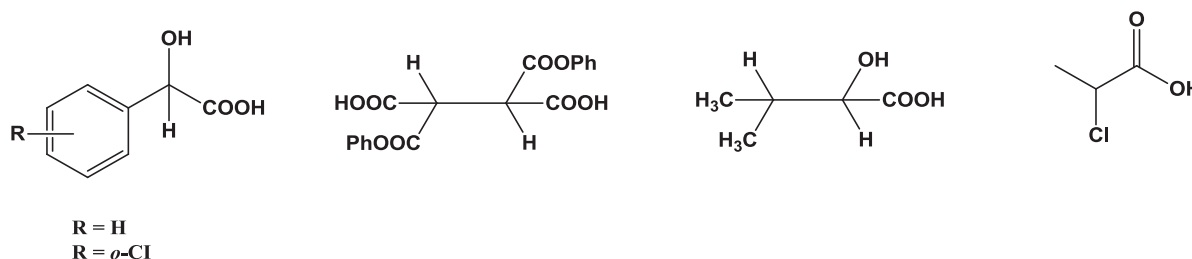

Figure 31. Chemical structures of carboxylic acid used.

The same groups[120] have presented the transport of amino acid derivatives (phenylglycine, phenylalanine, and tryptophan methyl ester hydrochlorides) and mandelic acid through a bulk liquid membrane in the presence of chiral calix[4]arene derivatives given above and **52** as a new chiral calix[4]arene (Figure 32). The receptors with aromatic groups and hydrogen bonding sites indicated considerably higher transport rates and stereoselectivities.
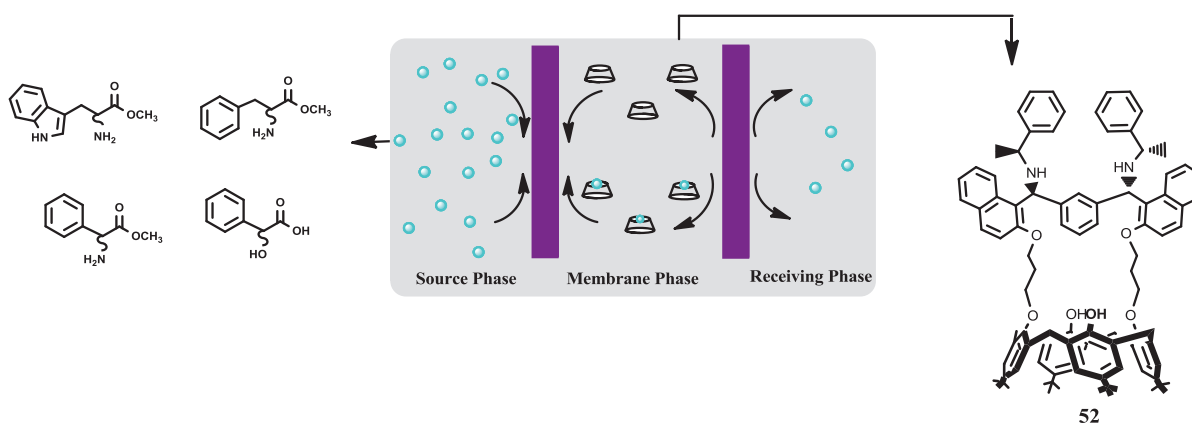
Figure 32. Transport mechanism of amino acid methyl esters and mandelic acid with chiral calix[4]arenes.

Chiral Schiff base and amino alcohol derivatives of calix[4]arene (Figure 33) were synthesized and their chiral recognition properties towards someselected amino acid methylesters and amino alcohols were investigated by Erdemir.[121] Even though the chiral calix[4]arene Schiff base and amino alcohol derivatives **53** and **54** were excellent extractants for all amino acid and amino alcohol species used, chiral discrimination between amino acid and amino alcohol molecules could not be achieved. It should be noted that the hydrophobic cavity of chiral calix[4]arenes and hydrogen bonding led to our recognizing amino acid methyl esters (D/L-alanine, D/L-phenyllanine, and D/L-tryptophan) and amino alcohols (D/L-phenylglycinol and R/S-5-(hydroxymethyl)-2-pyrolidinone) (Figure 34).
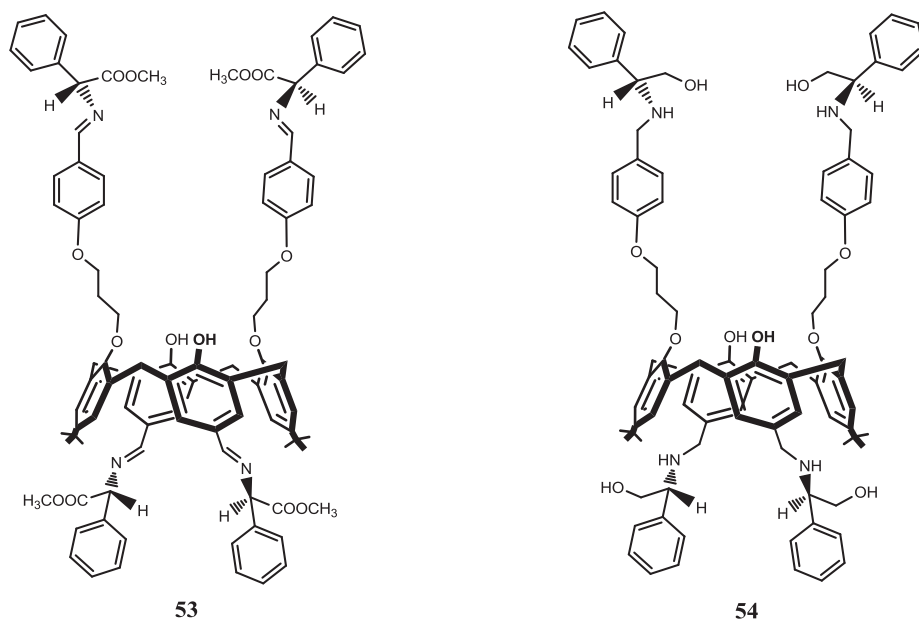
Figure 33. Chiral Schiff base and amino alcohol derivatives of calix[4]arene.
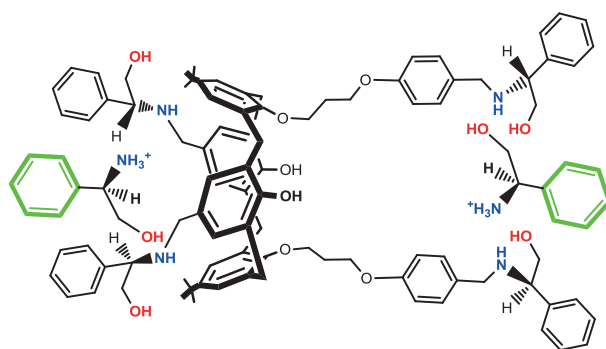
Figure 34. Proposed interaction model between **54** and L-pheglyglycinol.

Recently, Bozkurt et al.[122] have synthesized novel chiral calix[4]arene derivatives bearing amino alcohol moieties (**55–66**) (Figure 35) and studied the transport of amino acid esters (phenylglycine, phenylalanine, and tryptophan methyl esters hydrochloride) and mandelic acid through a chloroform bulk liquid membrane system using these chiral calix[4]arene derivatives **55–60**. Chiral receptors **55–60** showed different chiral recognition abilities towards the enantiomers of racemic guests. Chiral receptors having aromatic end groups indicated considerably higher transport rates and stereoselectivities. From the obtained data, it was concluded that the multiple hydrogen bonding, steric hindrance, structural rigidity or flexibility, and $\pi-\pi$ stacking between the aromatic groups may be responsible for the enantiomeric recognition.

Calix[4]azacrowns containing a calix[4]arene platform and an azacrown moiety in their framework have received much attention due to their special structures and good complexing properties toward anions and cations. Thus, Demirtas et al.[123] studied the synthesis of novel chiral calix[4]azacrown derivatives **61–64** (Figure 36) and their enantioselectivities towards some amino acid esters. Chiral recognition properties of these receptors were investigated using UV-vis spectroscopy. The experimental data showed that chiral receptors **61** and **63** have strong binding and some chiral recognition ability for the enantiomers of phenylalanine and alanine methyl ester hydrochlorides.
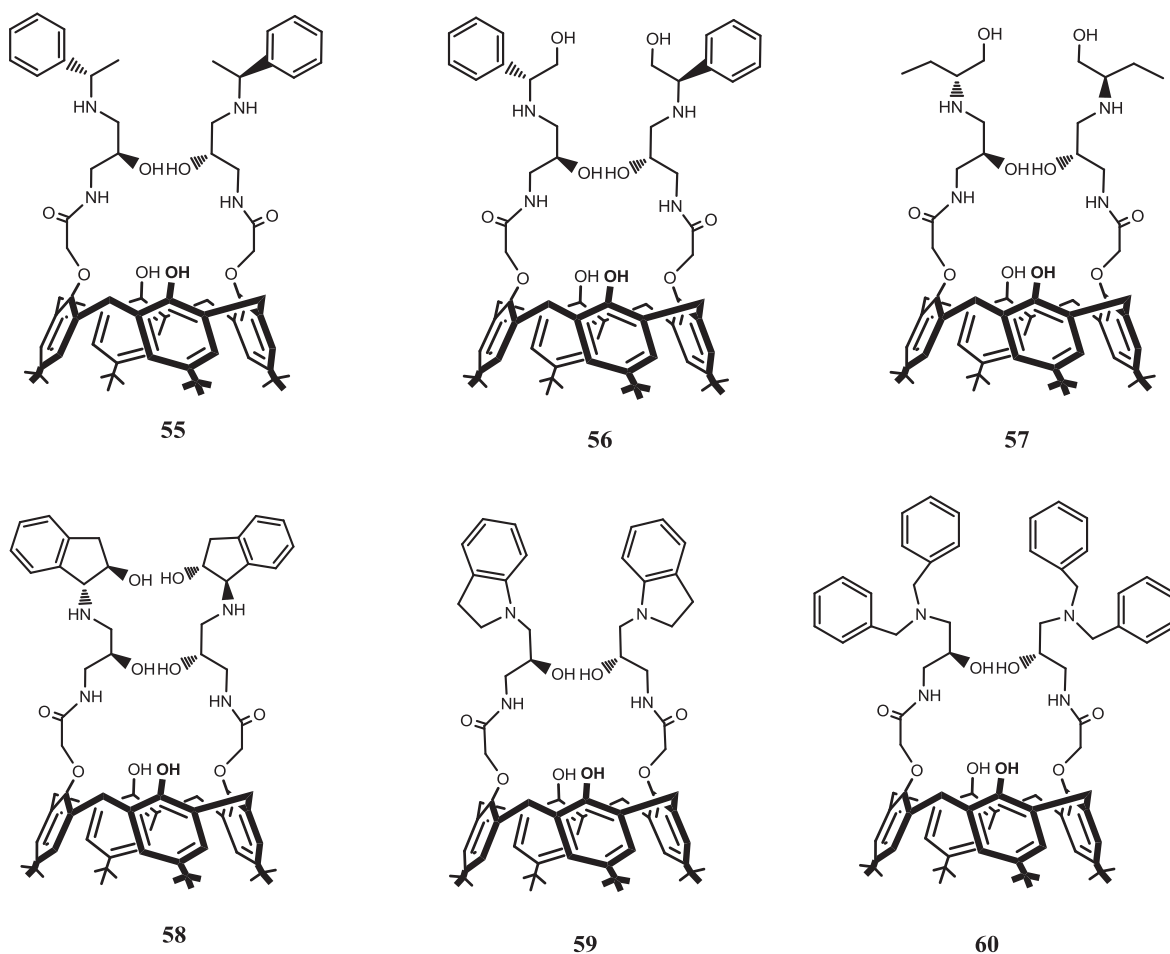
Figure 35. Chiral calix[4]arene derivatives bearing amino alcohol moieties.
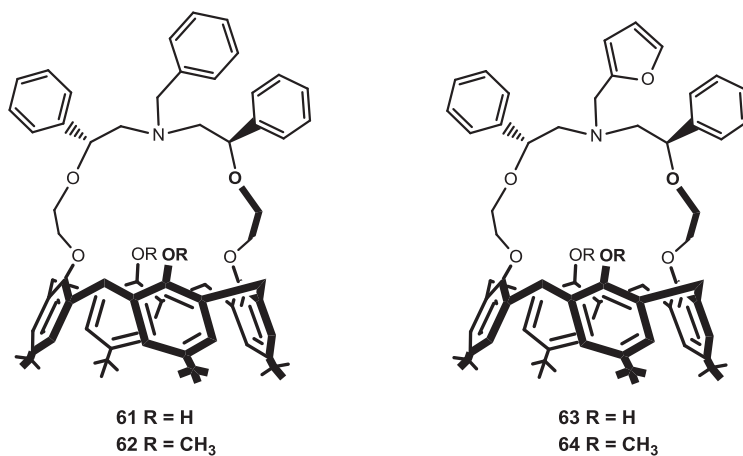

61 R = H
62 R = CH₃

63 R = H
64 R = CH₃

Figure 36. Chiral calix[4]azacrowns.

The complexation of chiral calix[4]azacrowns with α-amino acid esters possibly occurs through interaction of the nitrogen atom in the azacrown loop and the quaternary ammonium cation in the amino acid esters (Figure

37). Noncovalent interactions between the guests and hydrogen bonding sites defined by ethylene oxygens, furan oxygen, and phenolic oxygen contribute to the stabilization of these complexes as well as $\pi-\pi$ interactions.
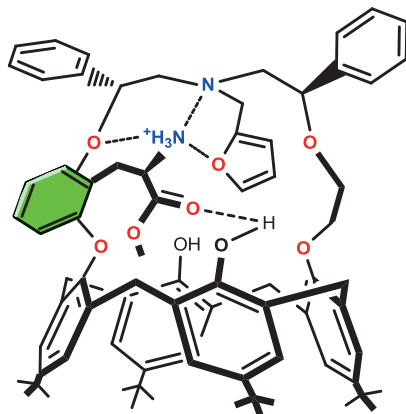
Figure 37. Proposed recognition mode of **63** toward a chiral amino acid methyl ester.

Miao et al.[124] have reported enantioselective recognition of mandelic acid with (R)-1,1-bi-2-naphthol-linked calix[4]arene via fluorescence and dynamic light scattering. For this, they prepared a chiral 1,1-bi-2-naphthol-derived calix[4]arene **65** via a click reaction (Figure 38). The results indicated that **65−Cu(II)** complex has excellent enantioselective recognition of mandelic acid with a fluorescence "turn on" mode. Moreover, significantly improved sensitivity of chiral discrimination of mandelic acid was achieved using a DLS technique, which may provide a novel and effective way of enhancing the sensitivity of enantioselective recognition for other analytes.

65   **65 - Cu²⁺**
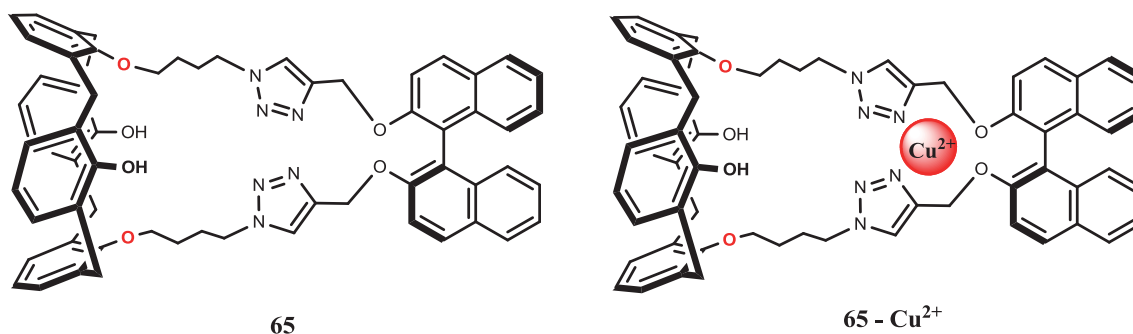
Figure 38. Chiral 1,1-bi-2-naphthol-derived calix[4]arene and its Cu^{2+} complex.

Qing et al.[125] have reported the synthesis of 2-armed chiral anion receptors **66** and **67** (Figure 39), calix[4]arenes bearing dansyl fluorophore, and (1R,2R)- or (1S,2S)-1,2-diphenylethylenediamine binding sites and their chiral amino acid anion binding abilities by fluorescence spectra. The receptors exhibited good fluorescent responses to various anions, and the association constants between the hosts and guests were calculated from the fluorescence quenchment changes. It was found that receptors **66** and **67** have good enantioselective recognition ability towards N-acetyl aspartate and form 1:1 complexes with the guests.
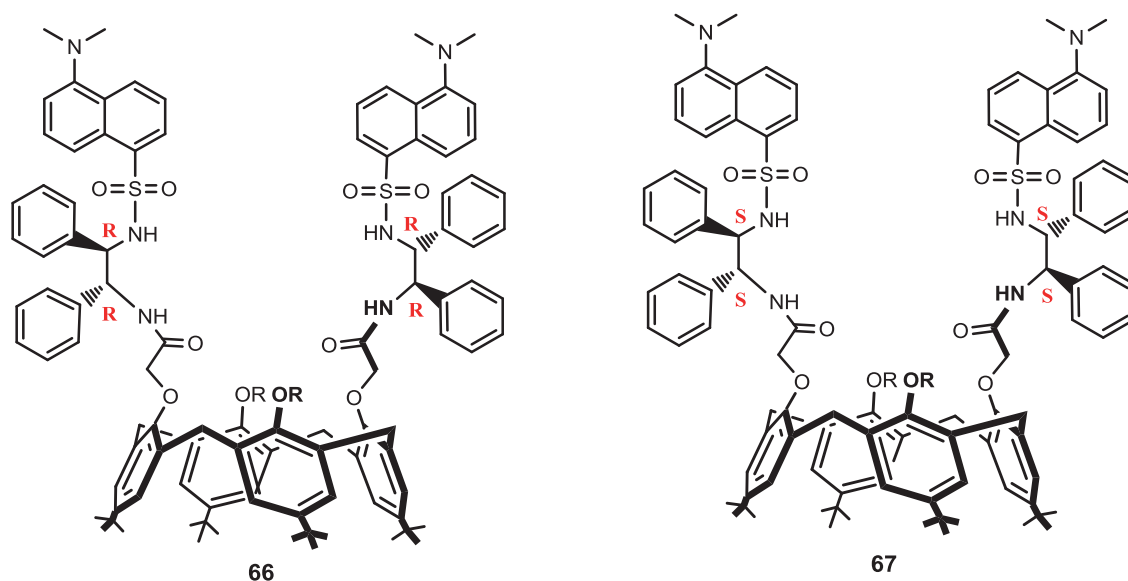
Figure 39. Chiral anion receptors **66** and **67**.
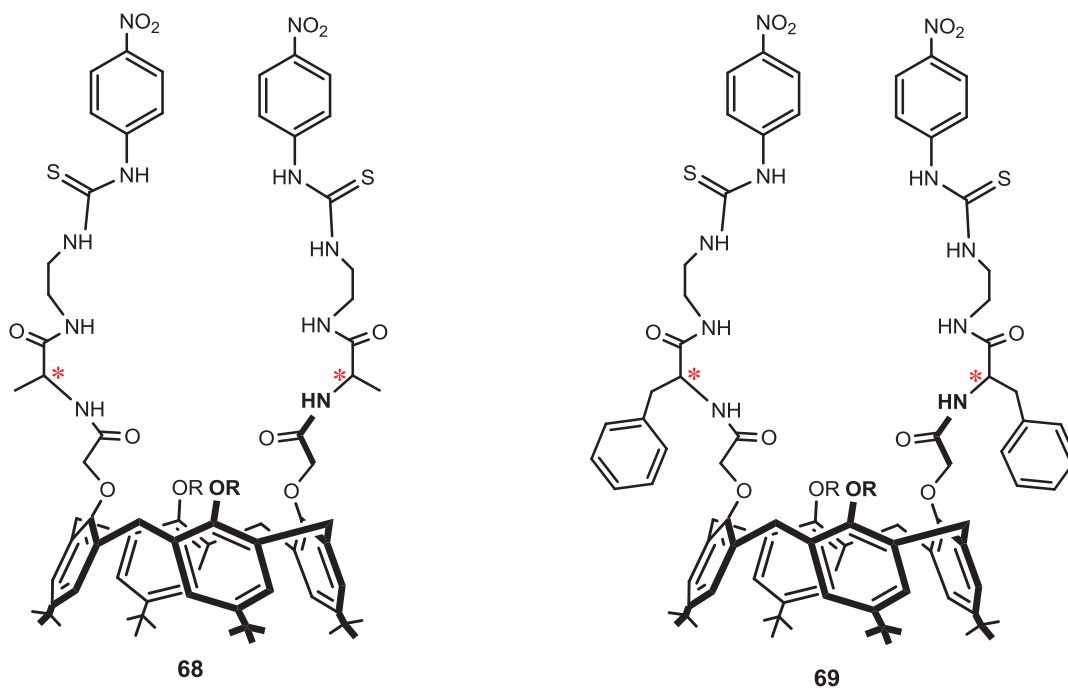
Figure 40. Calix[4]arene-based chromogenic chemosensor.

The same group[126] designed calix[4]arene-based chromogenic chemosensors (Figure 40) for the α-phenylglycine anion. Anion-binding abilities of these chiral receptors were investigated by UV-Vis absorption and ^{1}H NMR spectroscopy. The results showed that **68** and **69** form 1:1 stoichiometric complexes with the L- or D-α-phenylglycine anion by multiple hydrogen-bonding interactions and indicate good enantioselective recognition for the enantiomers of the α-phenylglycine anions. Furthermore, the good enantioselective recognition and obvious color change on complexation of **68** and the α-phenylglycine anion show that **68** could be used as a chiral chromogenic sensor for enantiomers of the α-phenylglycine anion.
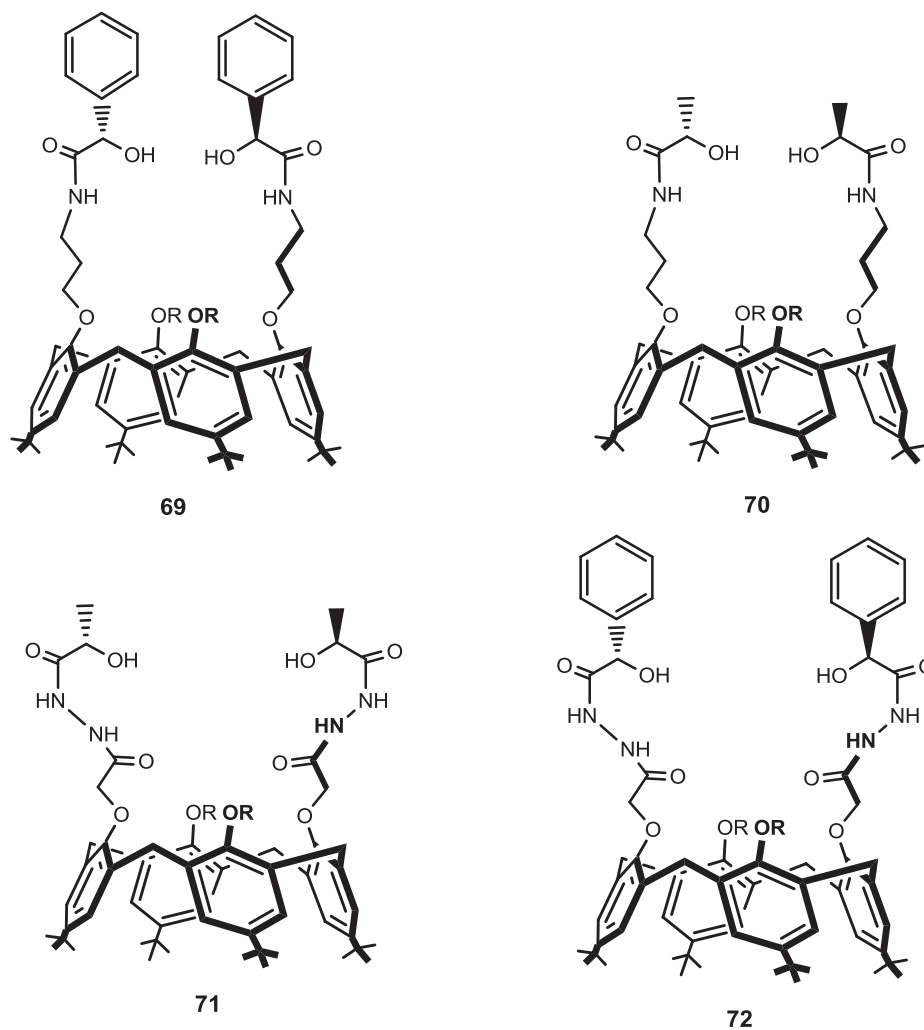
Figure 41. Chiral calix[4]arene derivatives **69–72**.

To observe the transport of amino acid methyl ester through bulk liquid membrane with different chiral calix[4]arenes, Durmaz prepared novel chiral calix[4]arene derivatives **69–72** functionalized at the lower rim as carriers (Figure 41). The receptors were found to act as carriers for the transport of aromatic amino acid methyl esters from the source phase to the receiving phase. The transport rate and L/D selectivity of amino acid esters depend strongly upon the structure of the chiral calix[4]arenes and guests. The best enantioselectivity was obtained in the case of phenylglycine methyl ester for all chiral carriers.

Acknowledgments

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