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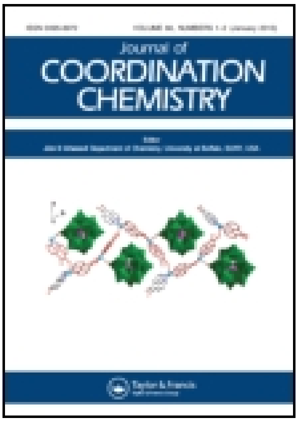

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Molecule and ion recognition of nano-baskets of calixarenes since 2005

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REVIEW

Molecule and ion recognition of nano-baskets of calixarenes since 2005

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The objective of this article is to introduce calixarene platforms in medical analysis for recognition of biomolecular compounds and ionic species with emphasis on publications in the last 6 years. Nano-baskets of calixarenes with specific recognition abilities play vital roles in maintaining life. Such molecules have attracted and motivated scientists to design artificial receptors, to recognize and to determine medical biomolecules and ionic species in biological studies. Efforts have been made to the synthesis, development, and evaluation of these receptors to determine biomolecules and drugs. The 3-D arrangements of functional groups in calixarene derivatives interact with guest biomolecules and ions at multiple points to construct a specific binding unit; this is the main concept of recent studies. In this review, medical biological applications of calixarenes are summarized in 13 main fields, including the analysis recognition of drug carriers, drugs, heparin and dopamine, amino acids, antigens and antibodies, hormones, enzymes, proteins and steroids, vitamins, alcohols, amines, aromatic species, polyaromatic hydrocarbons, pesticides, caffeine and other molecular compounds, lithium, sodium, potassium, cesium, calcium, strontium, chromium, iron, cobalt, nickel, copper, silver, zinc, cadmium, mercury, aluminum, thallium, lead, fluoride, chloride, iodide, acetate, hydrogen phosphate, and organic ions. For this purpose, the objectives of about 250 references (after 2005) have been reviewed.

Keywords: Medical application; Calixarene; Molecule recognition; Drug; Biological compounds; Cation; Anion

1. Introduction

Recognition and determination of biological compounds in medical sciences require the development of new methods. Analysis of molecular species by synthesized complexes [1–3], ligands [4], macrocycles [5], and crown ethers and cryptands [6] has been reported.

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General applications of complexes in medical, industrial, analytical, and biological research have been reviewed in many papers. Mendez-Rojas *et al.* [7] reviewed the medical applications of technetium (Tc) complexes. The development and design of Tc complexes for imaging of different organic tissues, of special interest for their medical applications, were discussed. Jones [8] reported *in vitro* and *in vivo* applications of therapeutic complexes to remove intracellular metal deposits.

Analysis and measurement of drugs and their metabolites, biologically active compounds, and related molecular species using spectroscopic techniques, electroanalytic methods, and chromatographic procedures as well as electrophoresis, have been reported in biological journals. Spectroscopic methods include determination of lamotrigine in pharmaceutical dosage forms and urine samples [9], and identification of anhydro-simvastatin and simvastatin dimer (two main impurities in the fermentation broth as well as in the final product of simvastatin that is a hypolipidemic drug) using ion-trap mass spectrometry [10]. Bende *et al.* [11] developed a simple and sensitive UV spectrophotometric method for the determination of imatinib mesylate in bulk and pharmaceutical formulations such as tablets and nanoparticles.

Chromatographic methods (such as HPLC) can be summarized as quantification of forskolin (a weight loss multi-herbal product) [12] and quantitative determination of oleanolic acid [13]. Analytical measurements in the field of electroanalysis techniques are widely used, such as determination of clopidogrel bisulfate, an antithrombotic drug, using cyclic voltammetry and differential pulse voltammetry (DPV) [14], and determination of valsartan using stripping voltammetry [15]. Electrophoretic measurements are useful to determine biomolecular compounds as well as ionic species. Enantioselective determination of amlodipine in commercial tablets using capillary zone electrophoresis coupled with diode array detector [16] and enantioseparation of cefotaxime by capillary zone electrophoresis using cyclodextrin as a chiral selector [17] was done in this bioanalytical field.

Not only complexes of enzymes [18], amino acids [19], hormones [20], pesticides [21], drugs [22–24], antitumor complexes [25], and carbohydrates [26], etc., have been studied in many papers, but also the importance of such complexes (especially with macrocycles) to determine and to recognize the molecular substances have been realized.

Calixarenes are obtained by oligomerization of phenol and formaldehyde. Their valency moieties can be easily varied at least from 1 to 8, while the stereochemical orientation of the ligating arms can be properly tuned by shaping. Depending upon the relative orientation of the *para* and phenolic sites, the tetramer (calix[4]arene) can adopt four different conformations [27]. Baldini *et al.* [28], in their review paper, illustrated these conformations including cone, partial cone, 1,2-alternate, and 1,3-alternate. Figure 1 presents the common structure of calixarenes. Various methods for functionalizing calixarenes have been developed and numerous calixarene derivatives have been synthesized during the past two decades.

Different complexing groups at the upper rim of calixarenes attract molecules with predefined selectivity. The lower rim functional groups of calixarenes are usually responsible for physical properties of calixarenes [29]. During the past three decades, calixarenic chromoionophores have been studied as specific molecule and ion indicators. Various types of chromogenic calix[4]arene derivatives have been synthesized, which have shown selective recognition and complexation with metal ions [30].

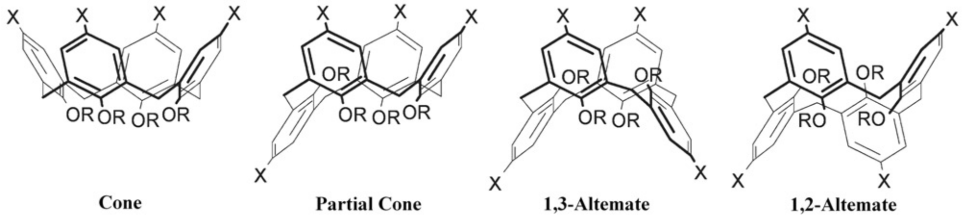


Figure 1. Illustration of four common conformations of calixarenes.

Calixarenes are, in fact, ideal "molecular platforms" for the introduction of specific ligating arms in a preorganized pattern. Therefore, depending on the nature of the ligating groups and on the dimension of the macrocyclic scaffold, these ligands become selective for certain ionic or molecular species. Although several ligands have been well studied in terms of chemical stability in acid conditions, their behavior under irradiation has been less explored [31]. Appropriately functionalized calix[4]arenes have been used as carriers in ion-selective membranes. Predominantly, calixarenes containing ester, ether, carboxylic acid, and carbamate have been reported as ion-selective electrodes (ISEs) for alkali metal ions [32]. Complexation and analyte recognition by macrocyclic compounds are the basis of research in medical studies [32]. Most of the research on calix[4]arenes as chromogenic ionophores involves modification of the lower rim with metal-chelating groups, such as acids, amides, esters, ketones, or any ligand that contains lone pair electrons, and then a fluorophore or chromophore is attached on the upper rim [33].

In this article, recent medical applications of recognition abilities of calixarenes and their derivatives are reviewed. Their applications in 13 main fields of drug carriers, drugs, heparin and dopamine, amino acids, antigens and antibodies, hormones, enzymes, proteins and steroids, vitamins, alcohols, amines, aromatic species, polyaromatic hydrocarbons (PAHs), pesticides, caffeine, and other compounds are discussed. Molecular recognition as well as 25 main fields of ion determination are also discussed. Applicability of calixarene derivatives in complexation, solvent extraction, liquid chromatography, membrane transport, potentiometry, voltammetry, conductometry, electrochemical and spectroscopic sensors, luminescence, and colorimetric techniques are reviewed using about 250 references, published after 2005.

2. Recognition of drug carriers

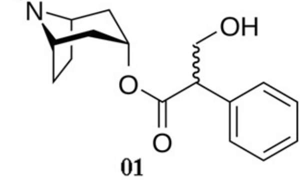
Australian chemists [34] synthesized tetrabromocalix[4]arene derivatives as inclusion hosts for nitrile guests and used them as pharmaceutical drug carriers to improve the bioavailability of medicines. Haino *et al.* [35] revealed that the syn isomer of a double calix[5]arene selectively captured higher fullerenes from fullerene mixtures and by elevation of the temperature to more than 100°C, its conformation was changed to the anti-isomer and liberated the captured fullerenes.

Kunsagi-Mate *et al.* [36] used photoluminescence and quantum chemical methods to study fullerene encapsulation with water-soluble calixarenes, thiacalix[4]arene-tetrasulfonate, and calix[6]arene-hexasulfonate. They reported that functionalization of calixarenes and fullerenes induced significant changes in molecular encapsulation processes. Bazylak *et al.* [37] determined the retention profiles in a series of oxadiazoles in narrow-bore HPLC systems, which can be useful in encapsulation optimization of 1,3,4-oxadiazolurea-type drugs with calixarenes.

3. Determination of drugs

Wang *et al.* [38] prepared inclusion complexes of topotecan with sulfonatocalixarene and investigated the stoichiometry, complex stability constants, and inclusion mode by means of 2-D NMR and ultraviolet-visible (UV-Vis) spectroscopy, determining that the dimethylaminomethyl group of topotecan and the quinoline ring were encapsulated in sulfonatocalixarene and the complex was more soluble than free topotecan.

Atropine (**01**) drug is administered *via* injection, eye drops, or in oral form to relax muscles by inhibiting nerve responses, used to dilate the pupils, and as an antispasmodic. Zareh and Malinowska [39] prepared an atropine selective membrane electrode using three calixarene derivatives: 37,40-*bis*-[(diethoxy-thiophosphoryl)oxy]-5,11,17,23,29,35-hexakis(1,1-dimethyl-ethyl)-calix[6]arene-8,39,41,42-tetrol; 37,38,39,40,41-pentakis-(diethoxythiophosphoryl)-oxy]-5,11,17,23,29,35-hexakis(1,1-dimethylethyl)-calix[6]-arene-42-ol; and 37-[(diethoxythiophosphoryl)oxy]-5,11,17,23,29,35-hexakis-(1,1-dimethylethyl)-calix[6]arene-38,39,40,41,42-pentol. Their practical linear ranges were 1.9×10^{-6} to 7.9×10^{-3}, 7.9×10^{-6} to 7.9×10^{-3}, and 6.3×10^{-6} to 7.9×10^{-3} mol L^{-1}, respectively. The recovery percentage and the relative standard deviation values were 97.5–99.1% and 0.39–0.72% for five determinations. The electrode was applied successfully for analyzing atropine sulfate in eye drops and injection solution.



01

Drug toxicity in humans and animals is a major concern. Hence, Brazilian chemists [40] investigated the complexation properties of detoxificant agents. They investigated the inclusion complexation of a toxic alkaloid (pyrrolizidine) and *p*-sulfonic acid calix[6]arene by NMR techniques.

American chemists [41] investigated the complexation between 4-sulphonato-calix[*n*]arenas (water-soluble calixarenes) and niclosamide (a poorly water-soluble anthelmintic drug) by phase solubility studies. Carbamazepine is a poorly water-soluble anticonvulsant drug. Indian chemists [42] studied the effect of *para*-sulfonated calix[4]arene and *para*-sulfonated calix[6]arene on aqueous solubility of carbamazepine by HPLC, DSC, PXRD, FT-IR, UV-Vis, and FT-Raman spectroscopy. Their results indicated the formation of 1 : 1 calix[6]arene : drug and 2 : 1 calix[4]arene : drug complexes. Drug dissolution rate of inclusion complex was more than physical mixture and more than drug alone.

Inazumi *et al*. [43] studied the inclusion complexation of *p*-sulfonatocalix[6]arene with three kinds of phenothiazine dyes spectrophotometrically in a mixture of ionic liquid and ethanol and determined their association constants under external static pressure of up to 767 bar. The results revealed that with increasing external pressure, the inclusion equilibrium was shifted to the dissociation side in the alcohol–water mixtures; while, it was shifted to the association side in the ionic liquid mixture.

Japanese chemists [44] examined the effects of solvent polarity and pressure on the inclusion complexation of *p*-sulfonatocalix[8]arene with phenothiazine dyes. Depending on the bulkiness of the guest dyes, solvent polarity and external pressures increase the inclusion equilibrium constants. They also established the structures of the inclusion complexes using ^{1}H-NMR measurements.

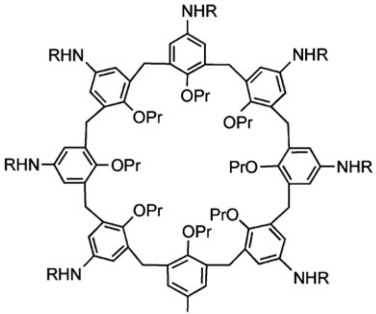
Methylene blue is structurally similar to chlorpromazine and typical antipsychotics. It is the base compound from which chlorpromazine and many other antipsychotics are made. In medicine, methylene blue is a monoamine oxidase inhibitor and if infused intravenously at doses exceeding 5 mg kg^{-1}, may cause serious serotonin toxicity, serotonin syndrome, if combined with any serotonin reuptake inhibitor such as sibutramine, duloxetine, or venlafaxine. In biology, methylene blue is used as a dye for a number of different staining procedures, such as Jenner's stain and Wright's stain. Since it is a temporary staining technique, methylene blue can also be used to examine DNA or RNA under the microscope or in a gel.

Inazumi and Sueishi [45] determined the equilibrium constants for the inclusion complexation of octaethyl-*p*-*tert*-butylcalix[8]arene octaacetate with methylene blue and characterized the structure of the inclusion complex by 2-D ROESY-NMR measurements. They found that calix[8]arene derivative forms a 1 : 1 inclusion complex with methylene blue in the upper main cavity. In Brazil, complexation of the local anesthetic tetracaine with *p*-sulphonic acid calix[6]arene was investigated using ^{1}H-NMR experiments [46].

Hashem and Jira [47] studied the effects of different chromatographic conditions on the separation of nine tricyclic neuroleptics and the effect of structural differences of analytes by a new HPLC stationary phase with calixarenes. They showed that chemical structure and pK_a of neuroleptics influenced their separation on the calix[8]arene stationary phase. Hashem *et al*. [48] used another method for extraction and quantification of celecoxib in tablets with a detection limit of 0.122 μg mL^{-1}. Strong binding of berberine, a clinically important isoquinoline alkaloid, to 4-sulfonatocalix[8]arene leads to considerable fluorescence quantum yield increase at pH = 2, utilized in the development of a fluorescent probe. Megyesi and Biczok [49] investigated the effects of cavity size of sulfonatocalixarenes and pH on the stability and fluorescent properties of the complexes. Based upon their research in Hungary, the stability of macrocycle complex diminished when sulfocalixarenes of smaller ring size served as host compounds but the pH affected the association strength to a much lesser extent.

4. Determination of heparin and dopamine

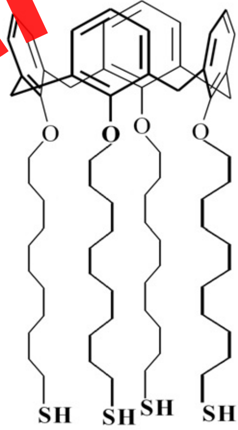
Heparin recognition of calix[8]arene polycations (**02–05**) was compared with two other heparin antagonists, protamine and polylysine. Experiments confirmed that calixarene derivatives have a higher specificity and affinity than other antagonists toward heparin neutralization as in an aqueous solution such as blood [50].



R = L- Lys
R = CO(CH$_2$)$_6$NH$_2$
R = L- Lys
R = CO(CH$_2$)$_6$NH$_2$

02–05

Silva *et al.* [51] investigated the antithrombotic activity of water-soluble *p*-sulfonato-calix[*n*]arenes and six *O*-monosubstituted derivatives (like heparin) and proposed a mechanism for the anticoagulant effect of those calixarenes. Lai *et al.* [52] determined dopamine using a calix[4]arene crown-4 ether film modified glassy carbon electrode with a dynamic range of 2.0×10^{-5} to 1.0×10^{-3} mol L^{-1} and detection limit of 4×10^{-7} mol L^{-1}. Recently, Slovakian chemists [53] synthesized 25,26,27,28-tetrakis(11-sulfanylundecyloxy)calix[4]arene (**06**) and used that in a mixture with 1-dodecanethiols or hexadecanethiols to form self-assembled monolayers (SAMs) as a sensor for dopamine with a detection limit of 50 pmol L^{-1} discrimination ability between dopamine and epinephrine. They used cyclic voltammetry in the presence of redox probe [Fe(CN)$_6$]$^{3-/4-}$ to evaluate the SAMs.



06

5. Determination of amino acids

Nau *et al.* [54] investigated an enzymatic reaction including the hydrolysis of arginine to ornithine catalyzed by arginase. 1-Aminomethyl-2,3-diazabicyclo[2.2.2]oct-2-ene and *p*-sulfonatocalix[4]arene were used as the fluorescent dye and the macrocycle, respectively. *p*-Sulfonatocalix[4]arene displayed binding constants of 6400 $(\mathrm{mol\,L^{-1}})^{-1}$ with arginine, 550 $(\mathrm{mol\,L^{-1}})^{-1}$ with ornithine, and 60,000 $(\mathrm{mol\,L^{-1}})^{-1}$ with the selected fluorescent dye. Depletion of the substrate allowed the fluorescent dye to enter the macrocycle and led to the desired fluorescence response.

Hassen *et al.* [55] studied the complexation of calix[4]arenes and two amino acids (arginine and lysine) using faradic electrochemical impedance spectroscopy. They used three calix[4]arene coatings including a calixarene modified by carboxylic acid groups, a benzyl-modified calixarene, and a calixarene with sulphonated long chain. Limits of detection for the first calix[4]arene coating were $1 \times 10^{-3}\,\mathrm{mol\,L^{-1}}$ and $6 \times 10^{-3}\,\mathrm{mol\,L^{-1}}$ for arginine and lysine, respectively.

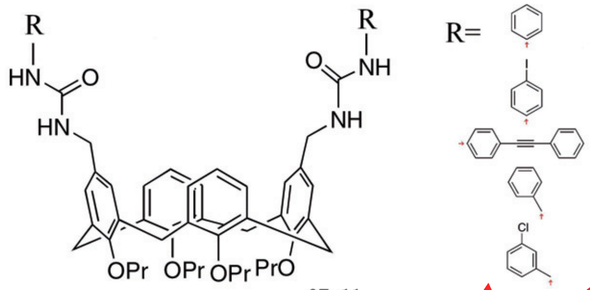
Mutihac and Mutihac [56] investigated the transport through the liquid membrane of L-tryptophan methylester and L-tyrosine methylester using *p*-*tert*-butylcalix[6,8]arene as carrier. The transport depended on the pH, the structure of calixarenes, the structure of amino acids, and the nature of anion used as ion pair for cation–receptor complexes. The properties of solvent involved in liquid membrane played an important role in selecting membrane systems and also in membrane stability. Mutihac [57] and Mutihac *et al.* [58] studied the ability of functionalized calix[*n*]arenes as carriers in transport through liquid membranes of different biological amine compounds including ammonium ion, amines, amino acids, and peptides. They presented the effect of factors that influence the separation of the above compounds by transport through liquid membranes using the calix[*n*]arenes.

Chinese researchers [59] synthesized 1,3-*bis*-arylformyl-hydrazone substituted thiacalix[4]arene derivatives and 1,3-*bis*-acyl hydrazone-bridged calix[4]arene derivatives to study their extraction ability toward α-amino acids. They showed similar binding properties with high extraction percentage but low extracting selectivities. Hydrazone-bridged biscalixarene with calix[4]arene and thiacalix[4]arene subunits exhibited not only high extracting abilities but also good extracting selectivities toward α-amino acids. Turkish researchers [60] reported extraction properties of chiral calix[4]arene diamide derivatives toward some selected α-amino acid methylesters. A chiral *p*-*tert*-butylcalix[4]arene bearing phenylethylamine was synthesized and its liquid phase extraction properties toward some chiral α-amines and α-amino acid methylesters were reported [61].

Hamdi *et al.* [62] synthesized cone calixarenes bearing acid or amido moieties and used them in the extraction of native amino acids and amino acid esters. Researchers studied calixarene carboxylic acid derivatives as powerful extractants for biologically important amino compounds. Based upon their work, the larger macrocycles calix[6]arene and calix[8]arene carboxylic acid derivatives were more effective for the adsorption of amino acid derivatives on the impregnated resin than the calix[4]arene derivative [63]. Shimojo and Goto [64] used a calix[6]arene carboxylic acid derivative incorporating *tert*-octyl groups at the upper rim. In isooctane neither calix[6]arene nor D2EHPA were effective at nucleobase extraction, but the addition of D2EHPA along with calix[6]arene drastically enhanced the efficiency of adenine and cytosine extraction and one nucleobase forms a stable complex with one calix[6]arene and two D2EHPA molecules.

Dziemidowicz *et al.* [65] synthesized calix[4]arene phosphonic acids with various substituents at the lower rim and studied their complexing properties toward methyl esters of six amino acids using ^{1}H-NMR spectroscopy. They observed mixed 2 : 1 and

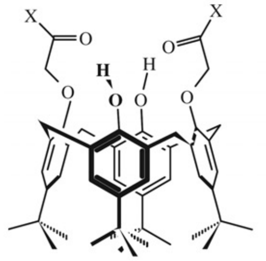
1 : 2 (host–guest) complexes with all amino acid methyl esters. Bew *et al.* [66] reported the ability of five *bis*-1,3-urea calix[4]arene derivatives (**07–11**) to complex 14 *N*-protected α-amino acids including *N*-Boc glycine, *N*-acetyl-(*S*)-phenylalanine, *N*-Cbz-proline, *N*-Fmoc-(*S*)-valine, *N*-Fmoc-glycine, *N*-Fmoc-(*S*)-proline, *N*-Fmoc-(*S*)-phenylalanine, *N*-Fmoc-(*S*)-tryptophan, *N*-Fmoc-(*S*)-arginine, *N*-Fmoc-(*S*)-histidine, *N*-Fmoc-(*S*)-histidine-Trt, *N*-Fmoc-(*S*)-phenylglycine, *N*-Fmoc-(*S*)-*t*-butoxityrosine, and *N*-Fmoc-(*S*)-3,5-diiodotyrosine.



07–11

Polish and Ukrainian chemists [67] studied the host–guest complexes (1 : 1) of calix[4]arene *bis*-hydroxymethylphosphous acid with glycine, L-leucine, L-alanine, L-valine, and L-isoleucine residues in methanol solution with the aid of the titration experiments followed by ^{1}H-NMR and UV spectroscopic methods. The stability constants for macrocycle and aliphatic L-amino acids were determined and the results indicated that host–guest complexation was under the control of the direct electrostatic interaction between amino acid residue NH_3^+ and negatively charged calixarene phosphoryl group. They correlated the stability of the inclusion complexes with the size of the aliphatic amino acid's side chain.

Kim *et al.* [68] used a series of calix[4]arenes (**12–16**) substituted by acid and amido functions, glycolic chains, and hydroxyl groups as carriers in liquid membranes. Transport of aromatic amino acid methylesters (**17–19**) through liquid membrane (from the aqueous source phase to the aqueous receiving phase) was assisted by the pH gradient. They discussed the influence of calixarene and amino acid structures upon transport through liquid membranes.

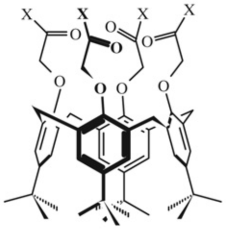


X = OH

X = $NHCH(CH_2OH)_2$

X = $NHC(CH_2OH)_3$

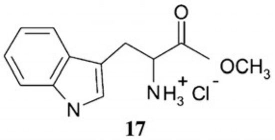
12–14



X = OH

X = NH(CH$_2$)$_2$O(CH$_2$)$_2$OH

15 and 16



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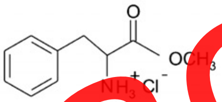

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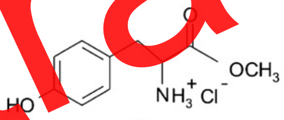
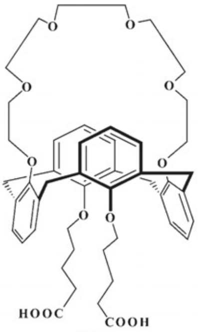


19

Sosovska *et al.* [69] made conductometric chemosensors based on *c*-benzylresorcinolcalixarene for the determination of amines and amino acids, which exhibited a better affinity toward amine species than other macrocycles. Ijeri *et al.* [70] designed a sensor to determine amino acids that are neither electroactive nor with strong UV-Vis absorption. The sensor was based on capacitive sensing of amino acids using different calixarene derivatives (**20**–**23**) immobilized on silicon transducers.



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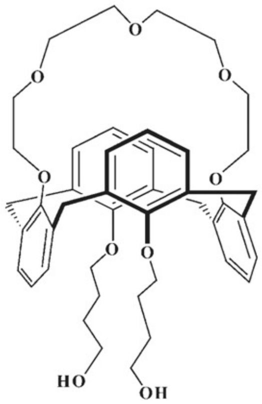

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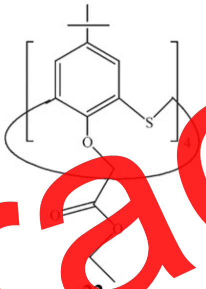

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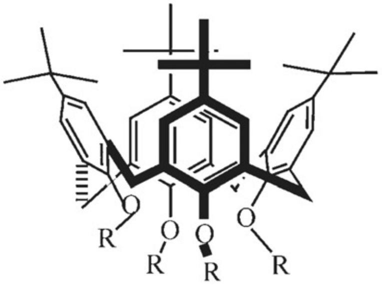


$R = CH_2COOCH_2CH_3$

23

6. Determination of antigens and antibodies

Chen *et al.* [71] investigated the antibody surface coverage, the layer thickness, adsorption, and orientation on a calix[4]crown utilizing surface plasmon resonance on a well-known protein artificial receptor molecule (ProLinker^{TM}). The immunoactivity of immobilized antibodies was compared using two different methods. In ^{1}H-NMR, chiral shift reagents achieve rapid determination of the enantiomeric excesses of chiral compounds. Lanthanide complexes, cyclodextrins, crown ethers, porphyrins, and macrocycles are a variety of chiral shift reagents.

Development of immunosensors is increasingly finding applications in clinical diagnostics and biological research. They consist of immobilization of antigens or antibodies on the surface of calixcrown and the direct electrochemistry of horseradish peroxidase. South Korean and Iranian chemists [72] used calixcrownchips and immobilized the alanine aminotransferase monoclonal antibody on a thiol derivative of calixcrown (1,3-dimethoxy,2,4-dithiol-calix[4]crown-5-ether) fixed to a gold surface. They claimed that the calixcrownchip immunosensor microarray provided much better technical performance than a comparable enzyme sensor.

7. Determination of hormones

Hashem and Jira [73] investigated the retention behavior of nine tricyclic neuroleptics on three different RP-HPLC columns. Based upon their experiments, two recently developed columns, calixarene bonded (CALTREX® AIII) and monolithic (Chromolith® Performance RP-18e), were compared with a conventional RP-C18 HPLC column (LiChrospher®). The results elucidated how the mobile phase conditions affect analyte retention on the columns. Under their laboratory conditions, a calixarene-bonded phase was the best for that separation, a monolithic phase gave comparable results, and the conventional RP column was the least effective.

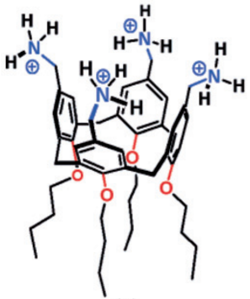
Zhang *et al.* [74] developed a selective electrochemical method for determination of norepinephrine using a calix[4]arene crown-4 ether film modified glassy carbon electrode. Liu *et al.* [75] used *p*-tetra-butyl calix[6]arene-L-histidine modified glassy carbon electrode for determination of epinephrine and serotonin by cyclic voltammetry and DPV in the presence of 1.0×10^{-3} mol L^{-1} ascorbic acid.

8. Determination of enzymes

Oshima *et al.* [76] used calix[6]arene carboxylic acid derivatives to extract lysozyme quantitatively. French researchers [77] used three water-soluble calix[*n*]arene derivatives including *para*-sulfonatocalix[4,6,8]arenes to investigate the effects on the activation of NADPH oxidase in neutrophils. They showed that all three molecules do not induce NADPH oxidase activation, and hence do not stimulate neutrophils and are not cytotoxic.

9. Determination of proteins and steroids

Oshima *et al.* [76] described quantitative extraction and recovery of cytochrome C using calix[6]arene carboxylic acid derivatives. Kolusheva *et al.* [78] embedded calixarene receptors (**24–26**) within vesicles comprising phospholipids and the chromatic polymer polydiacetylene for color detection of proteins. The colorimetric assay constitutes a generic platform for high-sensitivity detection of water-soluble proteins.



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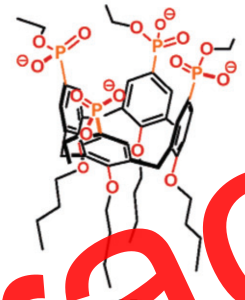

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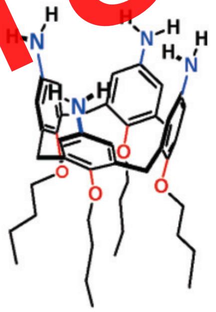

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Liu *et al*. [79] prepared four silica stationary phases including *β*-cyclodextrin, *p*-*tert*-butyl-calix[8]arene, chloropropyl, and ODS and applied them to separate steroids *via* chromatography. They showed that the retention mechanisms of the four stationary phases for steroids were obviously different, and excellent separation was achieved on *β*-cyclodextrin-bonded silica stationary phase. The retention process on *β*-cyclodextrin exhibited inclusion complexation, hydrogen bonding, and weak hydrophobic interaction, while for *p*-*tert*-butyl-calix[8]arene bonded silica stationary phase, π–π and hydrogen bonding besides hydrophobic interaction played an important role.

Baldini *et al*. [28] reviewed the fundamental aspects of multivalency and the properties of calixarene-based multivalent ligands in lectin binding and inhibition, protein surface recognition, DNA condensation and cell transfection, crystal engineering, self-assembly, and nanofabrication. Binding stoichiometries and association constants for parent *para*-sulfonatocalix[*n*]arene derivatives with bovine serum albumin (BSA) were determined using electrospray ionization mass spectrometry. Silva *et al.* [80] concluded that the strength of the interactions between BSA and macrocycle is inversely proportional to the size of calix[*n*]arene ring: $(4 > 6 \gg 8)$.

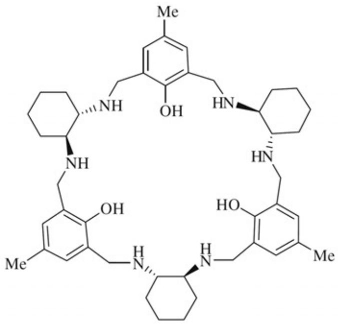
10. Determination of vitamins

Indian chemists [81] studied the electrochemical behavior of nicotinamide at modified carbon paste electrodes with macrocyclic compounds including *c*-methylcalix[4]resorcenarene and calix[8]arene. The increase in anodic peak current was used for finding a linear working range, which was $0.1\text{–}500\,\mu\mathrm{g\,mL^{-1}}$ with a detection limit of $0.03\,\mu\mathrm{g\,mL^{-1}}$ by DPV. They also studied the interference from other vitamins like thiamine HCl (vitamin B_1), riboflavin (vitamin B_2), pyridoxine HCl (vitamin B_6), cynocobamine (vitamin B_{12}), *para*-aminobenzoic acid, and ascorbic acid (vitamin C). They claimed that the modified electrode could be used for simultaneous determination of riboflavin, nicotinamide, and pyridoxine HCl.

Vaze and Srivastava [82] determined pyridoxine hydrochloride in pharmaceutical preparations based upon the use of calix[8]arene as a neutral carrier in a potentiometric sensor between a pH of 3.0 and 7.2. It showed a short response time of 20 s in the concentration range 1×10^{-1} to $6.2 \times 10^{-6}\,\mathrm{mol\,L^{-1}}$ and a detection limit of $1.6 \times 10^{-6}\,\mathrm{mol\,L^{-1}}$. They found that the mediator *o*-nitrophenyl octyl ether significantly increased the lifetime of the sensor. Vaze and Srivastava [83] studied the adsorptive stripping voltammetric behavior of folic acid at plain carbon paste electrode and *p-tert*-butyl-calix[6]arene modified electrode with a detection limit of $1.24 \times 10^{-12}\,\mathrm{mol\,L^{-1}}$.

11. Determination of alcohols

Tanaka and Fukuda [84] reported calixarene-like chiral macrocycle amine functions (**27**) as a highly sensitive chiral shift reagent for several kinds of secondary alcohols, cyanohydrins, and propargyl alcohols.



(*S,S,S,S,S,S*)-(+)

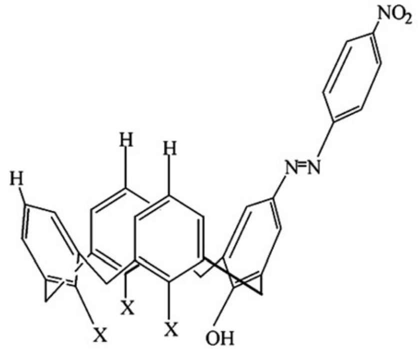
27

Koshets *et al.* [85] used calixarenes as sensitive coatings for quartz crystal microbalance (QCM)-based gas sensors. By changing the number of aryl fragments and the functional groups on calixarenes, sensitivity and selectivity of QCM have been studied for a wide range of volatile organic compounds (aromatics, chlororganics, ketones, and alcohols). They found that sensors coated with phosphorous-containing calixarenes showed maximal sensitivity. Shirshov *et al.* [86] described the recognition of several volatile alcohols (ethanol, isopropanol, and penthanol) by the digital registration of RGB components variation in interferential colored sensitive tetra-amyl-calix[4]resorchinolarene films.

Filenko *et al.* [29] designed a conductivity gas sensor functionalized with different calixarenes to measure volatile compounds such as methanol, ethanol, and propanol. Zhou *et al.* [87] made a new type of diglycidyloxy-calix[4]arene coated fiber by sol–gel method. Using the combination of headspace solid-phase microextraction and capillary zone electrophoresis, the simultaneous determination of propranolol enantiomers in human urine was achieved. In Russia, Kharlamov *et al.* [88] investigated the association properties of water-soluble calix[4]resorcinarene with 2-naphthol and 1,5-naphthalenediamine by NMR methods, concluding that the pH dependency of those complexes makes them prime candidates for pH-responsive molecular machine applications.

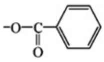
12. Determination of amines

When Liu *et al.* [89] investigated spun films of nitrophenylazocalix[4]arenes (**28**–**31**) as gas-phase optical sensors under amine vapors, they observed a red shift of the visible absorption bands. The highest sensitivity was observed for *n*-hexylamine.



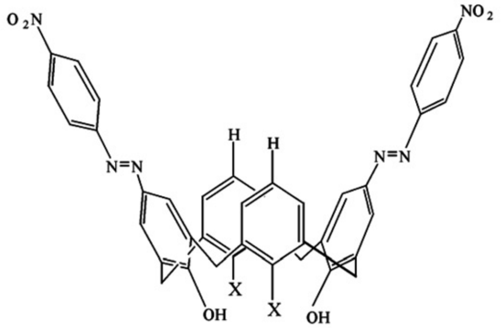
X = OH 5-(4’-Nitrophenyl)azo-25,26,27,28-tetrahydroxy-calix[4]arene (TQ-OH)

X =

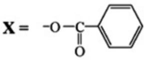


5-(4’-Nitrophenyl)azo-25,26,27-tribenzoyloxy-28-hydroxycalix[4]arene (TQ-B)

28 and **29**



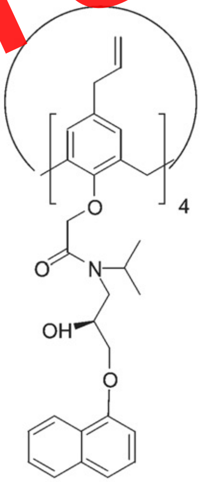
X = OH 5,17-Bis((4'-nitrophenyl)azo)-25,26,27,28-tetrahydroxycalix[4]arene (DQ-OH)

X =


5,17-Bis((4'-nitrophenyl)azo)-25,27-dibenzoyloxy 26,28-dihydroxycalix[4]arene (DQ-B)

30 and **31**

Lynam and Diamond [90] developed a fluorescent molecular sensor, which could distinguish enantiomers of chiral amines. Fluorescence quenching studies were carried out using a calix[4]arene derivative (**32**) and excellent selectivity was observed for a long-chain amino alcohol, phenylalaninol. They studied the solvent effect on the fluorescent properties of calix[4]arene and phenylalaninol in methanol, acetonitrile, and chloroform, demonstrating that varying solvent polarity allows the wavelength of enantiomer selectivity to be tuned from 227 to 440 nm.



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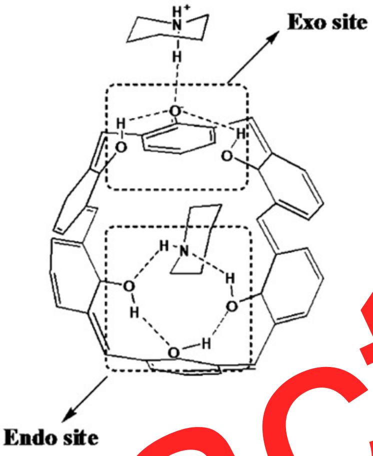
Japanese chemists investigated extraction behaviors of catecholamines using calix[6,8]arene carboxylic acid derivatives. The calix[6]arene derivative selectively extracted dopamine with 1 : 1 complexation over other catecholamines, while calix[8]arene derivative extracted both dopamine and adrenaline due to the large cavity for induced-fit recognition. They stripped the dopamine extracted with the calixarene by contacting the organic solution with a fresh acidic solution [91]. Korean researchers [92] investigated the hydrogen bonding networks by studying the binding of 1,2,3-alternate calix[6]arene with piperidine (**33**) and triethylamines. They reported that calix[6]arene derivative strongly binds with triethylamines and piperidines at endo and exo binding sites. They discussed the proton transfer within the hydrogen bonding and the hydrogen bonding types, low-barrier hydrogen bonding, normal hydrogen bonding, and short–strong hydrogen bonding.



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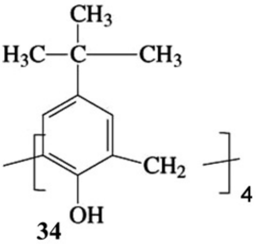
13. Determination of aromatic species and PAHs

Addition of calix[4]arenes to two mobile phases improves chromatographic separation of benzene or uracil derivatives on separon supports [93]. They also discussed the structure of calixarenes and their complexes with benzene or uracil derivatives in the context of chromatographic separation. Liu *et al.* [94] and Wu *et al.* [95] used polydimethylsiloxane (PDMS) membranes filled with calixarene and calixarene derivatives (**34** and **35**) for the evaporative removal of benzene from dilute aqueous solution revealing that due to the higher hydrophobicity of calixarene derivative over calixarene, calixarene derivative-filled PDMS membranes exhibited higher separation factor than calixarene-filled PDMS membranes. Both calixarene and calixarene derivative-filled PDMS membranes showed better permselectivity than control PDMS membranes.



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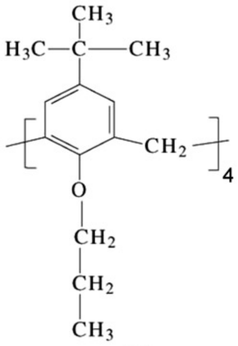

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Tieke *et al.* [96] in Germany made a layer-by-layer assembled membrane containing polyelectrolytes, *p*-sulfonato-calix[*n*]arenes, and Prussian blue-type complex salts and studied them as molecular sieves and ion sieves for size-selective separation of neutral and charged aromatic compounds. The ability of functionalized calix[*n*]arenes to form complexes to act as extractants in liquid–liquid extraction for ammonium ion, amines, amino acids, and peptides has been the topic of recent papers.

Li and Qu [97] used calix[4,7]arene-coated silica nanospheres, which were prepared *via* a sol–gel technique in aqueous media, allowing highly sensitive determinations of PAHs by changing the calixarene coating *via* response enhancement of fluorescence intensity. They optimized the sensor conditions and found that the relative fluorescence intensities of calix[4,7]arenes increased linearly with increasing anthracene and pyrene concentration in the range 1.0×10^{-7} to $5.0 \times 10^{-5}\,\mathrm{mol\,L^{-1}}$ and with detection limits of $2.45 \times 10^{-8}\,\mathrm{mol\,L^{-1}}$ and $2.94 \times 10^{-8}\,\mathrm{mol\,L^{-1}}$, respectively. Its fluorescence to other PAHs (acenaphthene, anthracene, 9,9-difluorofluorene, phenanthrene, fluoranthene, carbazole, biphenyl, fluorene, pyrene) was negligible. Chromatographic performance of six calixarene-bonded silica gel stationary phases was investigated using PAHs, aromatic positional isomers, and *E*- and *Z*-ethyl 3-(4-acetylphenyl) acrylate isomers as probes.

14. Determination of pesticides, caffeine, and other molecular compounds

Dong *et al.* [98] used a sol–gel calix[4]arene/hydroxy-terminated silicone oil-coated fiber for headspace solid-phase microextraction of 12 organochlorine pesticides and their metabolites in radish sample, followed by gas chromatographic determination. Xiong and Li [99] synthesized two silver nanoparticles modified with *p*-sulfonatocalix[4]arene and *p*-sulfonatocalix[8]arene for the detection of optunal with $10^{-7}\,\mathrm{mol\,L^{-1}}$ limit of detection as a novel colorimetric probe for colorimetric detection of pesticides.

Iranian chemists [100] presented the adsorptive square wave voltammetry of 2-furaldehyde on a polyvinyl chloride (PVC) membrane electrode doped with tetrabenzyl ether calix[4]arene to elucidate the adduct formation between 2-furaldehyde and Girard's reagent T. They studied some interferences including Na^+, K^+, NH_4^+, formaldehyde, 5-hydroxymethyl 2-furaldehyde, excess of Girard's reagent T, organic solvents, isopropyl alcohol, and *N*,*N*-dimethylformamide on the sensor's response.

Kimiko *et al.* [101] compared naphthyl-calix[4]arene and *t*-butyl-calix[4]arene-bonded silica on the retention of caffeine and showed that naphthyl-calix[4]arene-bonded silica retained caffeine strongly, similar to calix[4]arene bonded silica. Simultaneous determination of paracetamol, caffeine, and acetylsalicylic acid in a tablet formulation was done by Hashem [102] using calixarene stationary phases with detection limits of 0.488, 0.977, and 7.813 $ng\,\mu L^{-1}$, respectively.

Hungarian researchers [103] summarized different applications of optical spectroscopic methods in calixarene chemistry including vibrational spectroscopy, UV-Vis spectrometry, luminescence spectroscopy, ellipsometry, and various optical microscopic methods in a review. Chemists at Athens [104] prepared an electrochemical flow injection analysis with resorcin[4]arene for measuring carbofuran in foods using a drop (50 μL) of sample. The response time and limit of detection were 80 s and 1.0 $nmol\,L^{-1}$, respectively.

15. Lithium determination

Lithium affects the body by changing how nerve cells communicate, significantly affecting a person's mood. It is commonly used to treat bipolar disorder, and has been used since the 1950s to treat all mood disorders. Its dramatic effects on the body also produce several side effects, ranging from mild to severe. Lithium alters the flow of sodium between the nerve cells, changing how these cells communicate with each other. This prevents the nerve cells from adversely affecting how a person acts emotionally.

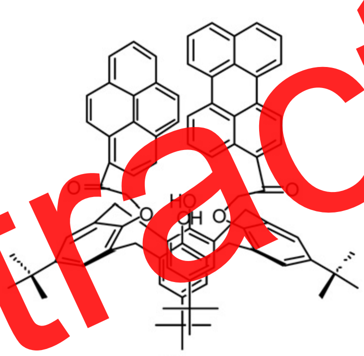
Calix[4]arene derivatives bearing one or two hydroxystyryl cyanine dyes at the wide rim were synthesized and the influence of Li^+ on UV-Vis spectra was investigated [105]. In Japan, Perez-Casas *et al.* [106] examined the binding behavior of 1,3-alternate thiacalix[4]arene with Li^+ by ^{1}H-NMR titration. The exclusive formation of mononuclear complexes was observed even though the formation of heterobinuclear complexes was expected. Polish and French chemists [107] prepared the *cone* and *partial cone* conformers of *p*-*tert*-butylcalix[4]crown-6 derivatives to examine their complexation ability toward Li^+ as ionophores in ion-selective PVC membrane electrodes.

16. Sodium determination

About 85% of the sodium in the body is found in blood and lymph fluid. Sodium levels in the body are partly controlled by a hormone called aldosterone, which is made by the adrenal glands. The levels of aldosterone cause the kidneys to retain sodium in the body instead of passing it in the urine. Small amounts of sodium are also lost through the skin when the person sweats.

Nabeshima *et al.* [108] synthesized a calix[4]arene framework bearing two ester units, two polyether units, two urea units, and two bipyridine units and used it to recognize Na^+. Casas and Yamato [109] assessed the complexation behaviors of both *cone* and 1,3-alternate tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy] thiacalix[4]arene by ^{1}H-NMR titration experiments. They obtained the evidence for 1 : 2 (homo- and hetero-binuclear) complex formation of 1,3-alternate derivative with K^+ and Na^+ cations.

Nishimura *et al.* [110] in Tokyo synthesized a calix[4]arene (**36**) having pyrene and perylene moieties as a Na^+ detectable fluorescent ionophore. By exciting the pyrene at 342 nm, an energy transfer occurred from pyrene to perylene and caused a strong fluorescence emission of the perylene moiety at 535 nm. Na^+ at a concentration range of 2.5×10^{-6} to 1.0×10^{-5} mol L^{-1} remarkably quenched the fluorescence. By exciting the pyrene moiety at 342 nm, an excimer emission also occurred from a calix[4]arene derivative. In contrast, Na^+ at a concentration range of 5.0×10^{-5} to 2.0×10^{-4} mol L^{-1} decreased excimer emission.



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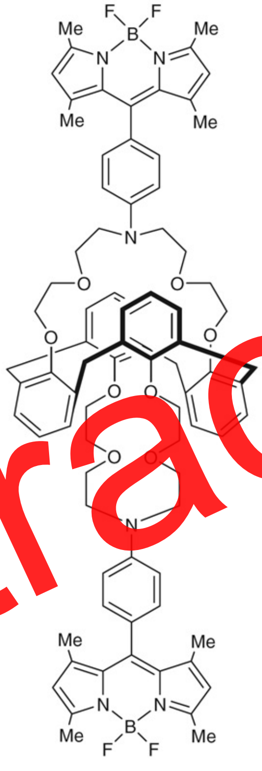
Miyaji *et al.* [111] synthesized a calix[4]pyrrole derivative and controlled its fluorescence emission properties by the addition of Na^+ and anions. Fluorescence quenching by anions was observed only in the presence of Na^+. Ohto *et al.* [112] investigated the solvent extraction of alkali metal ions with *p*-*t*-octylcalix[4]arene tetracarboxylic acid and *p*-*t*-octylcalix[6]arene hexacarboxylic acid. The first one selectively extracted sodium ion among alkali ions at extremely low pH, while the other one exhibited only poor extraction ability for all alkali metals examined. They observed that two sodium ions were simultaneously extracted by a single molecule of calix[4]arene derivative and found that the second sodium extraction was facilitated by the uptake of the first sodium. The authors proposed a self-coextraction mechanism of sodium ions.

17. Potassium determination

Potassium keeps the body's electrical charges balanced, involved in transmitting nerve signals, and is needed to keep the heart beating and muscles contracting.

It is essential for maintaining the pH level of the body (neither too acidic nor too alkaline). High blood potassium is a symptom of a rather serious underlying problem.

The stability constants of complexes of boron–dipyrromethene dye 1,3-alt calix[4]bisazacrown-5 (**37**) with Na^+, K^+, Cs^+, Ca^{2+}, and Ba^{2+} ions were determined by Sliwa and Girek [113]. Two azacrown-5 ether binding sites fitted K^+ well and showed a very high K^+/Na^+ selectivity in acetonitrile, ethanol, and ethanol/water mixtures.



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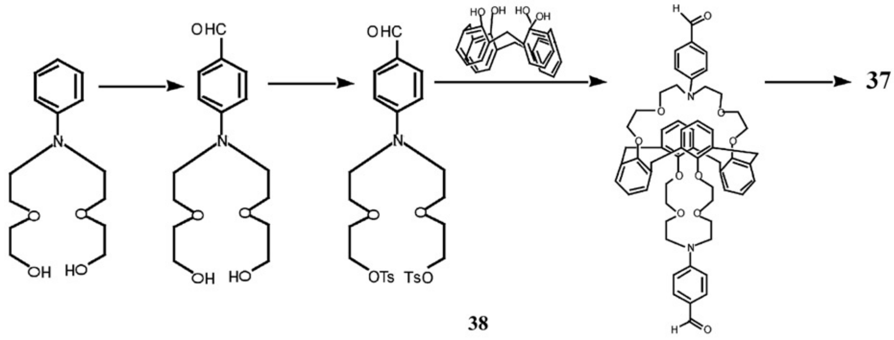
Chemists in Canada and Jordan [114] synthesized two new large-ring *n*-homocalixnaphthalenes that demonstrated high extraction capability for K^+. Zine *et al.* [115] described potassium-ion-selective microelectrodes with calix[4]crown-5 ionophore with a linear response range of 6×10^{-6} to $1 \times 10^{-1}\,mol\,L^{-1}$ and a detection limit of $1.8 \times 10^{-6}\,mol\,L^{-1}$.

Chang *et al.* [116] synthesized their on–off chemosensor from a triazole-calix[4]crown derivative, with its emission achievable by the addition of K^+ and its quenching by Hg^{2+}, Cu^{2+}, Pb^{2+}, and Cr^{3+}. Malval *et al.* [117] synthesized a fluorophore containing a boron–dipyrromethene and a 1,3-alternate calix[4]bisazacrown-5 derivative (**38**). An efficient charge transfer reaction occurred in the excited state and led to dual emission and strong quenching. The sensor showed high sensitivity and selectivity for potassium over sodium, cesium, calcium, and barium cations in acetonitrile, ethanol, and ethanol–water mixtures.



A calix[4]crown fluoroionophore bearing two-photon absorbing chromophores has been synthesized by Kim *et al.* [118] and it absorbed light at 461 nm and weakly emits fluorescence at 600 nm. Fluorescence intensity of Pb^{2+} with calix[4]crown $\cdot K^+$ was increased rather than the fluorescence intensity of calix[4]crown $\cdot Pb^{2+}$ complex because of the allosteric effect induced by the complexation of K^+ with a crown loop.

18. Cesium determination

Complementary alternative medicine therapies based on the use of cesium chloride preparations for the treatment of cancer and radiation poisoning have generated therapeutic interest, but oral or intravenous administration of cesium chloride to cancer patients as an alternative mode of cancer therapy have not been approved by the US Food and Drug Administration.

Leray and Valeur [119] presented various calixarene-based sensors designed for the recognition of Cs^+ in a review. Lee *et al.* [120] synthesized a calix[4]arene bearing one 2,3-naphthocrown-6 and two coumarin amide units at the lower rim as a fluorometric sensor for Cs^+. Intramolecular electron transfer from the naphthalene emission to the coumarin absorption afforded high fluorescence selectivity toward Cs^+.

Li *et al.* [121] synthesized triazole-modified calix[4]diethylester and dimethylester and examined their selectivity toward alkali metal cations *via* two-phase extraction experiments. The cavity formed by two ester groups is preferable for complexing alkaline metal ions such as Cs^+. Meanwhile, both modified calix[4]arenes displayed different selectivity toward alkali metal ions.

Arora *et al.* [122] reported that calix[4]arene bearing azopyridyl moieties at the upper rim can be used as a selective filter for radioactive wastes containing Cs^+. Polish chemists [113] presented the complexation of 1,3-alt-calixbiscrowns with hard cations like Cs^+ *via* π interaction. They reported that 1,3-alternate derivatives have oxygens able to bind hard cations and they have *p*-basic aromatic cavity which may bind soft electron acceptors.

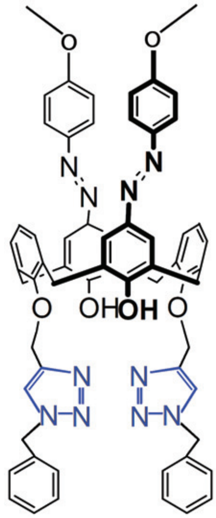
Indian chemists [123] extracted Cs^+ using nitrobenzene solutions of calixcrowns from nitric acid solution of nuclear waste. They used calix[4]arene-*bis*(crown-6), calix[4]arene-*bis*(benzocrown-6), and calix[4]arene-*bis*(napthocrown-6) for that propose. Recently, Chinese chemists [124] synthesized 1,3-[(2,4-diethylheptylethoxy)oxy]-2,4-crown-6-calix[4]arene and immobilized it into the pores of SiO_2–P particles. It showed strong adsorption ability and excellent selectivity for Cs^+ over all the tested metals including Mo^{6+}, Pd^{2+}, La^{3+}, Y^{3+}, Ru^{3+}, Rh^{3+}, Cs^{+}, and Zr^{4+}. Vicens [125] described the development of calixbiscrowns for Cs^{+} removal in nuclear waste and related extraction methods.

19. Calcium determination

Calcium plays a pivotal role in the physiology and biochemistry of cells and organisms and an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. Many enzymes require calcium ions as a cofactor, those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across the membrane of excitable cells, as well as proper bone formation.

A *cone*-shaped calixarene that influenced the Mg^{2+}, adenosine triphosphate (ATP)-dependent Ca^{2+} accumulation in mitochondria and sarcoplasmatic reticulum of the smooth muscle cells was synthesized and investigated in Ukraine by Klyachina *et al.* [126]. A 5,11,17,23-tetra-*tert*-butyl-25,27-*bis*(diethylcarbamoylmethoxy)-26,28-*bis*(diphenylphosphinoylmethoxy)calix[4]arene has been used in Iran [127] as an ionophore in a PVC-coated graphite membrane Ca^{2+}-selective electrode. The membrane comprised 6% calix[4]arene, 61% *ortho*-nitrophenyloctyl ether as solvent mediator, 30% PVC, and 3% sodium tetraphenylborate as anion excluder. The electrode exhibited a near-Nernstian response over a Ca^{2+} concentration range of 1×10^{-5} to 1×10^{-3} mol L^{-1} and the detection limit was 3.6×10^{-6} mol L^{-1}. The working pH range of the electrode was 4–7.

Lee *et al.* [128] synthesized *bis*(indolyl)calix[4]crown-6 and investigated the selective colorimetric changes of this calix-chromophore for alkaline earth cations. They observed that the binding ability of calix[4]crown for Ca^{2+} enhances in the presence of F^{-}. Chang *et al.* [129] designed and synthesized triazole- and azo-coupled calix[4]arene (**39**) to recognize Ca^{2+} cations in a chromogenic sensor.



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Chen and Chung [130] used two calix[4]arene derivatives as chromogenic sensors to sense Ca^{2+}. American and Turkish researchers [131] linked the lower rims of di-ionized calix[4]arene to two dansyl (1-dimethylaminonaphthalene-5-sulfonyl) groups and investigated the influence of Ca^{2+} cations on the spectroscopic properties of complexes using spectrofluorimetric titration experiments in acetonitrile. On complexation by Ca^{2+}, both absorption and emission spectra shifted to red and dansyl fluorescence was quenched. These effects were weaker with alkali metal cations. In Seoul, Kim and Kim [132] synthesized a calix[4]arene diethyl ester derivative containing two proximal hydroxyl groups and two facing ethyl esters, which showed Ca^{2+} ion selectivity. A calix[4]arene-based fluorescence chemosensor with a strong excimer emission was prepared by Kim *et al.* [133] and exhibited a marked quenched excimer emission after Pb^{2+} complexation. Ca^{2+} broke the calix[4]arene. Pb^{2+} complex and the excimer emission band was revived, by which their on/off switch was proposed.

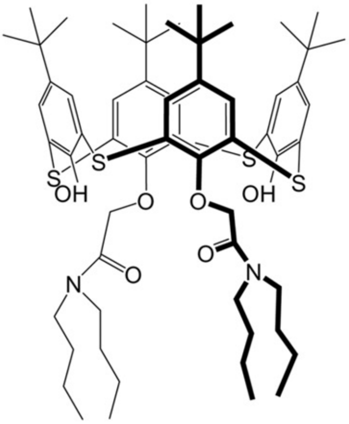
20. Strontium determination

The bone absorbs strontium such as calcium because of its compositional similarity. Stable strontium substances do not pose a threat. In fact, currently a drug is produced that combines ranelic acid with strontium which aides in bone growth and denser bones, and lessens vertebral, peripheral, and hip fractures.

Stable strontium can cause cancer when present in strontium chromate, but the carcinogenic effect is assigned more to chromium. High does of radioactive ^{90}Sr isotope can cause cancer. Researches have registered this element ^{90}Sr as part of the cause for several types of cancers, including leukemia, and cancer of the bone, nose, lung, and skin. Chinese researchers [134] synthesized cone conformers of 1,2-calix[4]crown-7, 1,3-calix[4]crown-7, 1,2-calix[4]crown-9, and 1,3-calix[4]crown-9. Synthetic calixarenes showed mediocre affinity for alkali and alkaline earth metal picrates in two-phase extraction experiments. They reported the selective extraction of Sr^{2+} by 1,2-calix[4]crown-9 among other alkaline earth metal cations.

Zhang *et al.* [135, 136] synthesized two kinds of macroporous silica-based polymeric materials, calix[4]arene-R14/SiO_2-P and TODGA/SiO_2-P, and used them to partition Sr^{2+} effectively from a highly active liquid waste by extraction chromatography. In packed column of calix[4]arene-R14, all of the simulated elements were separated effectively into two groups: Sr group (Na, K, Sr, Fe, Ba, Ru, Pd, Zr, and Mo) and Cs group (Cs, Rb). The harmful element Cs^{+} flowed into the second group along with Rb^{+} because of their close sorption and elution properties toward calix[4]arene-R14/SiO_2-P, while Sr^{2+} showed no sorption and flowed into the Sr-containing group. In packed column of TODGA, the Sr group was separated into four groups: non-sorption group (Ba, Ru, Na, K, Fe, and Mo); Sr; Pd; and Zr. Packed column of TODGA showed excellent separation efficiency from others.

Gupta *et al.* [137] evaluated an ionophore for the analysis of Sr^{2+} by a carboxy methoxy calix[6]arene derivative. The sensor was used as an indicator electrode in the potentiometric titration of sodium carbonate with Sr^{2+}. Korean researchers [138] prepared a thiacalix[4]arene diamide derivative (**40**) and investigated its electrochemical property and complexation behavior toward various metal ions by voltammetry. The electrode exhibited selectivity toward Sr^{2+} over alkali, alkaline earth, and transition metal ions, while conventional calix[4]arene diamides showed selective binding with Ca^{2+}. They reported that this is due to the bigger size of thiacalix[4]arene than calix[4]arene.



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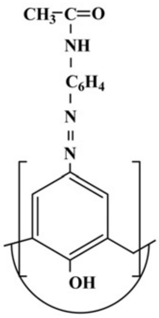
21. Chromium determination

Chromium helps the body regulate insulin, metabolism, and blood sugar levels. Moreover, it helps the body lose weight by stimulating enzymes that metabolize glucose for energy. Chromium plays an important role in the synthesis of fatty acids in liver (burns fat). It helps the body's metabolism after the food is in the blood stream and helps the pancreas and other organs keep all of these in balance. This is why chromium is so very important. When the body is deficient in chromium, it takes twice as long for insulin to remove glucose from the blood. This slows down the whole sugar glucose process causing the whole body to become more reactive to every other thing that is happening within it. Chromium enhances glucose utilization and insulin performance and helps to carry proteins in the body.

Agrawal and Sharma [139] used 37,38,39,40,41,42-hexahydroxy7,25,31-calix[6]crown hydroxamic acid to investigate extraction mechanism, kinetic of transport, speciation, liquid–liquid extraction, sequential separation, and trace the determination of Cr^{3+}. The maximum transport was observed at 35 min. Tabakci [140] in Turkey used *p*-*tert*-butylcalix[6]arene hexacarboxylate containing both amide and acid moieties and immobilized it on the aminopropyl silica gel surface. The prepared sorbent was highly effective for Cr^{6+} at a pH of 1.5. They also studied the effect of pH, contact time, sorbent dosage, initial Cr^{6+} concentration, and temperature on Cr^{6+} sorption and the sorption isotherms.

Kumar and Shim *et al.* [141] prepared a Cr^{3+}-selective electrode using *p*-(4-acetanilidazo)calix[4]arene (**41**) ionophore. Linear concentration range of 9.8×10^{-7} to 1.0×10^{-1} mol L^{-1} and response time of 14 s were reported. The electrode selectivity over most of the common cations including Li^{+}, K^{+}, Na^{+}, Ni^{2+}, Co^{2+}, Cu^{2+}, Sr^{2+},

Ba^{2+}, Cs^{+}, Pb^{2+}, Zn^{2+}, Mg^{2+}, Cd^{2+}, Al^{3+}, Fe^{3+}, and La^{3+} was examined successfully.



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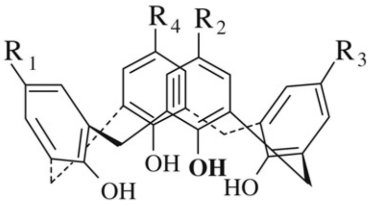
A sensitive ion induced fluorescent sensor for Cr^{3+} was prepared by Zheng *et al.* [142] using 1,3-alternate thiacalix[4]arene bearing two rhodamine β-lactams. Lu *et al.* [143] synthesized a water-soluble chromium-selective chromogenic azocalix[4]arene. It possessed an absorbance maximum at 365 nm in buffered aqueous environment, but the addition of Cr^{3+} induced a weak blue shift to 350 nm and a new absorption at 520 nm, which increased along with the augment of the concentration of Cr^{3+}. They used the new method for the determination of Cr^{3+} in the range of 9.35×10^{-4} to 4.45×10^{-3} mol L^{-1}.

22. Iron determination

The main role of iron in the body is in the red blood cells where it combines with a protein to form hemoglobin. Lack of iron in the body is known as iron deficiency, causing a general lack of energy and tiredness.

Chinese and Japanese chemists synthesized 1,3-alternate thiacalix[4]arene bearing two rhodamine β-lactams to capture Fe^{3+} in a fluorescent sensor. The association constants and stoichiometric ratios of the complexes were determined, and they showed that the presence of Fe^{3+} induced the sensor to form a stable 1 : 1 complex [48]. Japanese chemists discussed the extractability of Fe^{3+} from water into dichloromethane by hexahomotrioxacalix[3]arene triamide [144]. Deligöz [145] reported the use of azocalixarenes in liquid–liquid extraction of various transition metal cations from the aqueous phase to the organic phase. He presented the structures of mono-, di-, tri-, and tetra-azocalix[4]arenes (**42**–**46**), some substituted azocalix[4]arenes (**47**–**57**), three novel bisazocalix[4]arenes (**58**–**60**), *o*-, *m*-, *p*-substituted azocalix[4]arenes (**61**–**72**), and hetarylazocalix[4]arenes (**73**–**78**).



R_1 = N=N—Ar $R_{2,3,4}$ = H

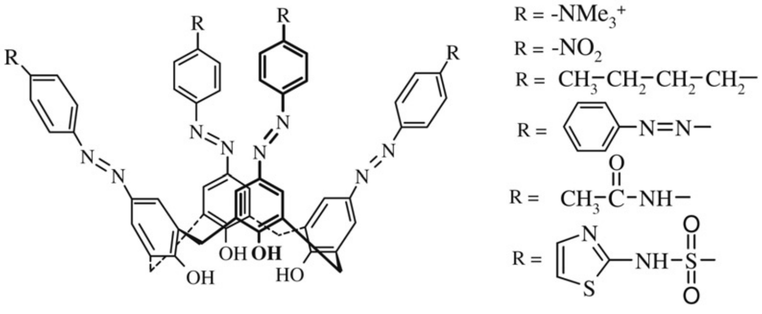
$R_{1,2}$ = N=N—Ar $R_{3,4}$ = H

$R_{1,3}$ = N=N—Ar $R_{2,4}$ = H

$R_{1,2,3}$ = N=N—Ar R_4 = H

$R_{1\text{-}4}$ = N=N—Ar

42–46



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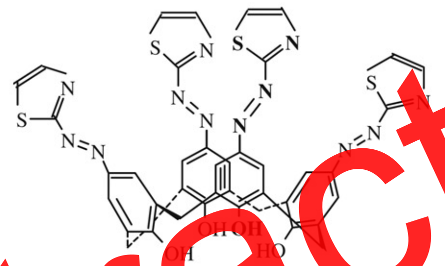

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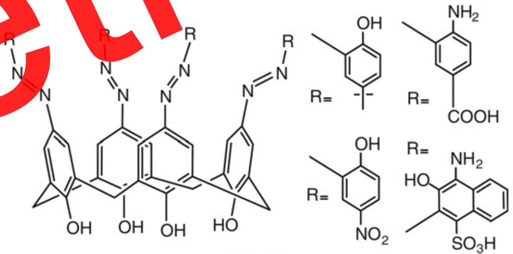

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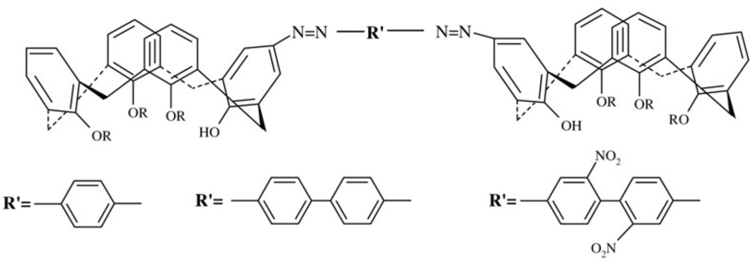

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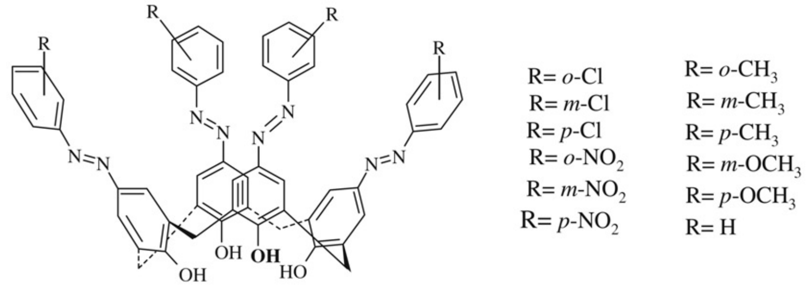

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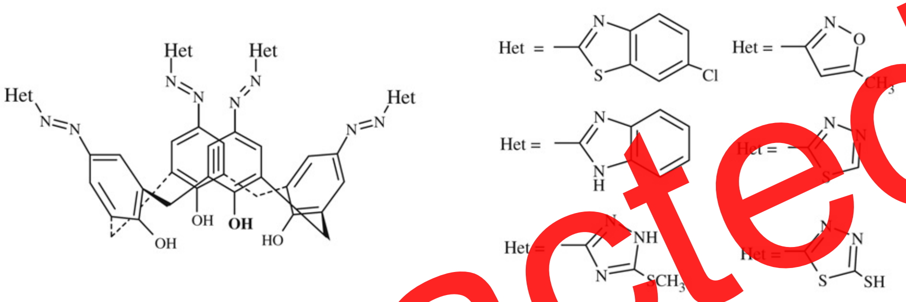


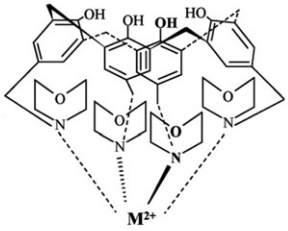
73–78

Chinese and Japanese chemists [146] synthesized a fluorescent sensor based on the rhodamine amide-armed homotrioxacalix[3]arene and investigated its sensing behavior toward metal ions by fluorescence spectroscopy. Upon the addition of Fe^{3+}, they observed a significant fluorescent enhancement from 500 to 600 nm. Indian chemists [147] used *p*-[4-(3,5-dimethylisoxazolyl)azophenylazo]calix[4]arene to extract iron cations and determined them by spectrophotometric methods. The interference of various ions was studied and optimum conditions were developed for the extraction of Fe^{3+}.

23. Cobalt determination

Cobalt is an essential part of vitamin B_{12} complex, essential for red blood cell formation. The body cannot make vitamin B_{12} and depends on diet for its supply, liver being the richest source. Cobalt is also a necessary activator of some important enzymes.

Russian and Ukrainian chemists [148] synthesized monomeric and polymeric 1 : 2 complexes of a tetraphosphineoxide calix[4]arene with Co^{2+} nitrate. In the monomeric complexes, each metal cation was coordinated by two bidentate NO_3 ligands and two proximal P=O groups at the calixarene skeleton. In Lyon, a new chromogenic calix[4]arene molecule was introduced to elaborate an optical fiber sensor able to detect Co^{2+} [149]. Qureshi *et al.* [150] studied the complexation behavior of *p*-morpholinomethylcalix[4]arene **(79)** toward Co^{2+} by UV-Vis and fluorescence techniques.



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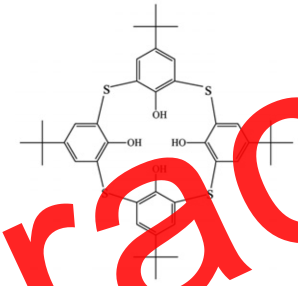
Gupta *et al.* [151] used a bridge-modified 4-*tert*-butylthiacalix[4]arene (**80**) to prepare a cobalt-selective sensor with detection limits of 0.3 ppm, linear working range of 5.3×10^{-6} to $1.0 \times 10^{-1}\,\mathrm{mol\,L^{-1}}$, and response time of 10 s. The sensor possesses excellent selectivity for Co^{2+} over a large number of cations such as Na^+, K^+, Ag^+, Ca^{2+}, Mg^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+}, Li^+, Ba^{2+}, Zn^{2+}, Sr^{2+}, Cr^{3+}, and Ni^{2+}.



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Arena *et al.* [152] introduced sulfonato groups into the backbone of a bipyridyl-based calixarene to obtain a novel water-soluble compound able to complex Co^{2+} and showed different stoichiometries and stabilities of new complexes from the analogous water-insoluble calixarene by spectrophotometric titration.

Russian and Ukrainian researchers [153] used calix[4,6]arenes bearing four or six phosphine oxide donor groups at the upper or lower rim to study the extraction of non-ferrous two-valent metal nitrates. The extraction constants for both types of upper and lower rims were determined to be $Zn^{2+} > Cu^{2+} > Co^{2+} > Ni^{2+}$. For the upper (wide) rim, phosphorylated calix[4]arenes, M_2L, and ML_2 complexes were more stable, while for the lower (narrow) rim, phosphorylated calix[4]arenes provided better stability of ML complexes. Hungarian and Indian researchers [154] extracted cobalt cations from nitric acid by 25,26,27,28-tetrahydroxy-5,11,17,23-tetra-[4-(*N*-hydroxyl-3-phenylprop-2-enimidamido)phenylazo] calix[4]arene and determined the trace amounts of cations spectrophotometrically.

24. Nickel determination

Nickel is a trace element linked to skin allergies or dermatitis in regard to eyeglass frames, dental materials, and costume jewelry. However, of the approximately 10 mg in the body, significant amounts of nickel are found in RNA and DNA where it interacts with these nucleic acids. Most of the plasma nickel is a constituent of the circulating proteins nickeloplasmin and albumin, and it is thought to be a factor in lipid, hormone, and cell membrane metabolism. Insulin response is increased after ingesting nickel, which may be related to its activation of enzymes associated with the breakdown or utilization of glucose.

Turkish scientists [155] synthesized four azocalix[4]arenes and investigated their complexes with Ni^{2+} by UV-Vis, IR, and ^{1}H-NMR spectroscopic techniques. They reported that the complexes have a metal : ligand ratio of 2 : 1 and the azocalix[4]arenes complexes with Ni^{2+} are square-planar, while the Co^{2+} complexes are octahedral with water molecules as axial ligands. Iki [156] reviewed thiacalixarenes as a pre-column derivatization reagent for highly selective and sensitive determination of Ni^{2+} at sub-ppb levels with reversed-phase HPLC. Belhamel *et al.* [157] made a PVC membrane with 5,11,17,23,29,35-hexakis-*t*-octyl-37,38,39,40,41,42-hexakis(*n*-phenylthiocarbamoylmethoxy)calix[6]arene ionophore to make a nickel-ion-selective PVC membrane electrode with a linear response range of 5×10^{-6} to 1×10^{-2} mol L^{-1}. Qureshi *et al.* [150] applied the Pederson method for the extraction of Ni^{2+} by morpholinomethylcalix[4]arene using their picrates in two-phase extraction experiments.

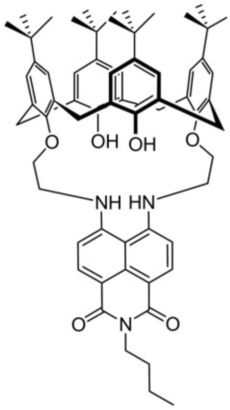
25. Copper determination

Copper is an essential trace metal that is absorbed from the diet. The concentration of copper in the body must be maintained within certain boundaries; too little or too much copper in the body will cause problems and can cause death. Fortunately, the body is able to regulate the concentration of copper through the homeostasis process. When the body's burden of copper gets too high, copper is excreted; if it falls too low, then more is absorbed from dietary sources. Copper plays both a structural and a catalytic role in certain metallo-enzymes, implicated in both oxidative and reductive enzymes and acts as an electron transfer intermediate in these systems. More than 65% of the body's copper burden is associated with ceruloplasmin, an oxidase. Copper species are responsible for functions such as cellular respiration and iron metabolism, protection from free radical damage, melanin pigment synthesis, and connective tissue biosynthesis. There is also compelling evidence to suggest that copper has a role to play in gene expression.

Seigle-Ferrand *et al.* [158] synthesized a calixarenic ditopic podand incorporating at the lower and upper rims, two bipyridine and two dipyrrolyl groups, respectively. This calixarene fixed in cone conformation formed complexes with Cu^{+} but with different stoichiometries. Veauthier *et al.* [159] used a calix[4]pyrrole Schiff base as binucleating ligand for Cu^{+} and Cu^{2+}. In Cu^{+} complexes, the metal centers had a distorted tetrahedral geometry, while with Cu^{2+} the metal centers were distorted square-planar.

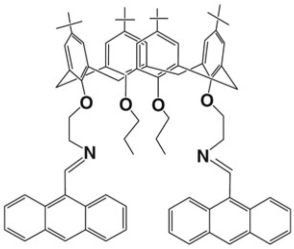
Indian chemists [160] synthesized *meso*-tetra(methyl) *meso*-tetra(4-hydroxy phenyl) calix[4]pyrrole, *meso*-tetra(methyl) *meso*-tetra(3,5-dihydroxy phenyl) calix[4]pyrrole, and their azo dyes and studied their efficiency toward Cu^{2+} using UV-Vis spectrophotometry. The experimental results showed a distinct color change from yellow to red upon complexation. In Turkey, Canpolat *et al.* [161] measured trace amounts of copper with a calix[4]arene modified carbon paste electrode by differential pulse anodic stripping voltammetry with a detection limit of 1.1 $\mu g\,L^{-1}$ in a preconcentration time of

10 min. Xu *et al.* [162] synthesized a naphthalimide–calix[4]arene derivative (**81**) which was a highly selective fluorescent chemosensor for Cu^{2+}. It showed a selective fluorescence quenching effect only with Cu^{2+} among the perchlorate salts of various metal ions (Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cs^+, Cu^{2+}, Hg^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Rb^+, and Zn^{2+}).



81

Indian chemists [163] synthesized calix[4]arene-based podands of *cone* (**82**) and of 1,3-alternate (**83**) conformations possessing imine units and bearing anthracene moieties and examined them for their cation recognition abilities by UV-Vis and fluorescence spectroscopy. The 1,3-alternate calix[4]arene derivative showed a selective fluorescence enhancement in the presence of Cu^{2+} among the various cations tested (Li^+, Na^+, K^+, Ni^{2+}, Cd^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Ag^+, and Hg^{2+} ions). The color of the tested solution changed from colorless to yellow in the presence of Cu^{2+}.



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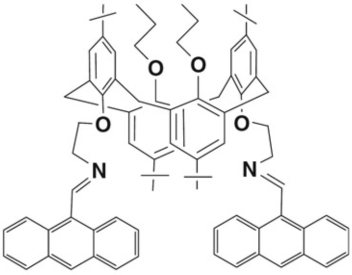

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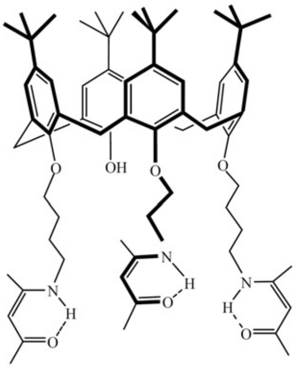
Kumar *et al.* [164] synthesized thiacalix[4]arenes carrying azophenol appendage and studied their binding abilities toward Li^+, Na^+, K^+, Cd^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ag^+, Pb^{2+}, and Hg^{2+} ions. Their results revealed that the calixarene derivative showed selective chromogenic sensing for Cu^{2+}. Sliwa and Deska [165] reviewed the calixarene complexes with soft metal ions including copper, silver, gold, zinc, cadmium, and mercury cations. Calixarenes bearing β-ketoimine groups (**84**) enable complex with Cu^{2+} in a cone conformation.



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As described earlier, Chang *et al.* [116] synthesized an on–off quenching chemosensor from a triazole-calix[4]crown derivative. The fluorescence of macrocycle was strongly quenched by Cu^{2+}; however, the revival of emission was achievable by the addition of K^+, Ba^{2+}, or Zn^{2+}.

26. Silver determination

Animal studies have shown that silver builds up in tissues of the body. The chronic intake of silver products and the silver build-up from colloidal silver can result in an accumulation of silver or silver sulfide particles in the skin, hair, kidneys, liver, heart, and muscles due to high methionine-containing proteins (keratin, myosin, tropomyosin, troponin, and the key dipeptide glutathione).

As in photography, these particles in the skin darken with exposure to sunlight, resulting in a blue or gray discoloration of the skin. This condition is known as argyria, which is a dermatological condition, characterized by grayish-blue pigmentation of the skin, nails, gums, and deep tissues; and, in similar manner, it can lead to silver in the eye (argyrosis) and in other organs. Localized argyria can occur because of the topical use of substances containing silver, while generalized argyria results from the chronic ingestion of silver.

Korean chemists [166] synthesized two calix[4]arene derivatives containing four alkyl thiol linkages that allow the calixarenes to attach to the gold surface. The silver ion had affinity only to one of the monolayers, which had hydrophobic polarity. O'Dwyer and Cunnane [167] investigated the stoichiometry of *O*,*O''*-*bis*[2-(methylthio)-ethyl]-*tert*-butylcalix[4]arene-silver complex in water/1,2-dichloroethane interface, and they found that the stoichiometry shifted from 1 : 1 to 1 : 2 (metal : ligand) with increasing ionophore concentration. The complexation and binding behaviors of 1,3-alternate thiacalix[4]arene with Ag^+ were examined by ^{1}H-NMR titration experiments in Japan [106]. Tanaka *et al.* [168] studied the complexation of thiacalix[4]arene with Ag^+. Japanese chemists [169] investigated the complexation of π-coordinate calix[4]arene derivatives toward Ag^+. Competitive complexation of three calix[4]arene derivatives demonstrated a significant effect of olefinic substituents and their location on Ag^+ complexation. Stability constants for Ag^+ : calix[4]arene derivative complexes in methanol using a reference ligand (18-crown-6) were determined.

Yamato *et al.* [170] synthesized *distal-bis*[(2-pyridylmethyl)oxy]thiacalix[4]arenes and described conformational studies. The calix[4]arenes showed strong Ag^+ affinity in two-phase solvent extraction, which led to 97% extraction, while no significant extraction was observed for K^+. Japanese chemists [171] synthesized three different resins by methylene cross-linking of 2-pyridylcalix[4]arene and investigated their adsorption behavior toward metal ions existing in photographic waste. The resins showed absolute efficiency for the adsorption of Ag^+ with no affinity for other coexisting ions. The range of maximum loading capacity of Ag^+ on the resins was 0.69–1.29 mol kg^{-1}. Column chromatographic separation of Ag^+ in the presence of excess Na^+ was carried out and selective adsorption of Ag^+ was achieved.

Csokai *et al.* [172] in Hungary synthesized thiacalix[4]arene ionophores comprised of cyclic or linear *O*,*S*,*N* ligating and π-coordinate groups on the lower rim and used H-NMR to study their ability for Ag^+ binding. They found that calix[4](*O*,*S*,*N*)crowns were stronger binders than π-coordinators and thiacalixarene ionophores were superior to calixarenes. Evtugyn *et al.* [173] in the Russian Federation developed a Ag^+ ISE with thiacalix[4]arene ionophore. Linear response range from 1.0×10^{-2} to 5.0×10^{-7} mol L^{-1} and response time of 12 s was reported. They fully eliminated the interfering effect of Hg^{2+} and Fe^{3+} ions by controlling the pH and using NaF as a masking agent, respectively. Mousavi *et al.* [174] also prepared potentiometric Ag^+ sensors with three ionophores including *p*-sulfonic calix[4]arene, *p*-sulfonic calix[6]arene, and *p*-sulfonic calix[8]arene.

Demirel *et al.* [175] used 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-calix[4]arene-thiacrown-4 to prepare a silver-selective PVC membrane potentiometric sensor with Nernstian response in the concentration range of 1.0×10^{-2} to 1.0×10^{-6} mol L^{-1}. The electrode showed high selectivity toward Ag^+ over Pb^{2+}, Cd^{2+}, Co^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Sr^{2+}, Mg^{2+}, Ca^{2+}, Li^+, K^+, Na^+, and NH_4^+ ions, but not over Hg^{2+}. Parsa *et al.* [176] constructed a coated-wire-type silver ISE using a *p-tert*-butylcalix[4]arene modified by amide-phosphoryl groups (**85**) with linear Nernstian response over the range 1×10^{-6} to 1×10^{-2} mol L^{-1} and detection limit of 6.3×10^{-7} mol L^{-1}. The selectivity of the sensor was examined relative to NH_4^+, Li^+, Na^+, K^+, Ca^{2+}, Sr^{2+}, Ba^{2+}, Mn^{2+}, Pb^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{3+}, La^{3+}, Sm^{3+}, and Th^{4+}.

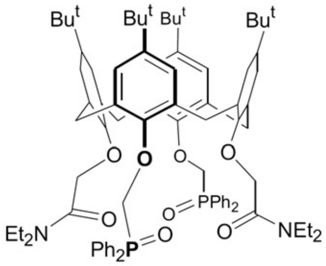

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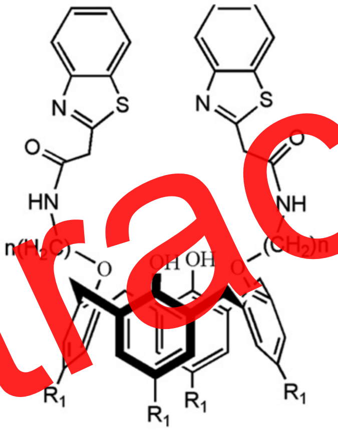
Table 1. The linear response ranges and limits of detection for Ag^+ ISE based on four benzothiazolyl-acetamidoalkoxy-calix[4]arenes [177].

Parameters	Calixarene 1	Calixarene 2	Calixarene 3	Calixarene 4
Linear range ($mol\,L^{-1}$)	5.0×10^{-6} to 1.0×10^{-2}	3.2×10^{-7} to 1.0×10^{-2}	8.0×10^{-6} to 1.0×10^{-2}	1.3×10^{-7} to 6.3×10^{-3}
Detection limit ($mol\,L^{-1}$)	5.01×10^{-6}	3.16×10^{-7}	7.94×10^{-6}	1.26×10^{-7}

Morakot *et al.* [177] in Thailand synthesized and used four calix[4]arene derivatives (**86**) with benzothiazolylacetamidoalkoxy pendant groups to prepare silver ISEs. For calixarene 1, $n = 4$ and $R_1 = t$–Bu; calixarene 2, $n = 4$ and $R_1 = H$; calixarene 3, $n = 2$ and $R_1 = t$–Bu; and calixarene 4, $n = 2$ and $R_1 = H$. All the ionophores showed response times less than 12 s. Table 1 presents their linear response range and limits of detection.



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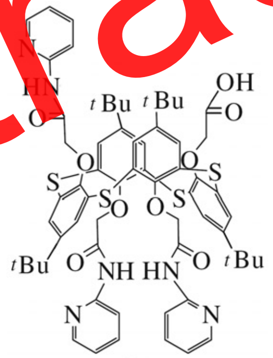
Ngeontae *et al.* [178] also synthesized calix[4]arenes derivatives with benzothiazolyl pendant groups to prepare macro and micro Ag^+-selective membrane electrodes with detection limits of $5.0 \times 10^{-7}\,mol\,L^{-1}$ and linear working range of 1.0×10^{-6} to $1.0 \times 10^{-2}\,mol\,L^{-1}$. Iranian chemists [179] used differential pulse anodic stripping voltammetry to determine Ag^+ at *p*-isopropylcalix[6]arene modified carbon paste electrode with dynamic range of 5.0×10^{-8} to $2 \times 10^{-6}\,mol\,L^{-1}$ and detection limit (3δ) of $4.8 \times 10^{-8}\,mol\,L^{-1}$. A modified glassy carbon electrode with Langmuir–Blodgett film of a calix[4]arene derivative was prepared for silver recognizing by a stripping voltammetric method with a detection limit of $8 \times 10^{-9}\,mol\,L^{-1}$ at an accumulation time of 180 s [180].

27. Zinc determination

Zinc is the most ubiquitous of all trace elements involved in the human metabolism. More than 100 specific enzymes require zinc for their catalytic function. If zinc is removed from the catalytic site, activity is lost; replacement of zinc restores activity. Zinc participates in all major biochemical pathways and plays multiple roles in the perpetuation of genetic material, including transcription of DNA, translation of RNA, and ultimately cell division. When the supply of dietary zinc is insufficient to support these functions, biochemical abnormalities and clinical signs may develop. Studies in individuals with acrodermatitis enteropathica, a genetic disorder with zinc malabsorption resulting in severe deficiency, have provided much insight into the functional outcomes of zinc deficiency.

Gaetano *et al.* [181] synthesized a calix[4]arene derivative incorporating two bipyridyl groups and one primary amino attachment function at the lower rim. They coupled it to Wang benzaldehyde resin and displayed its complexation abilities toward Zn^{2+} cations. Ulewicz *et al.* [182] investigated transport of Zn^{2+} through a polymer inclusion membrane using calix[4]crown-6 derivatives and studied the influence of the group attached type to the calix[4]crown-6 on the selectivity and efficiency of cation transport across polymer.

Russian and Ukrainian researchers [183] synthesized the calix[4,6]arenes grafted with different phosphine oxide groups and used them to extract Ru/Zn complexes. They investigated the Ru/Zn synergism and the calixarene macrocyclic effect in the extraction process and concluded that calixarene conformation, its size, and electronic nature of substituents at phosphorus atom influence the extraction. Chinese researchers [184] synthesized a 1,3-alternate thiacalix[4]arene possessing three aminopyridyl and one carboxylic group (**87**) and they studied it in the solvent extraction of Zn^{2+} from aqueous solutions into chloroform.



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Dessingou *et al.* [185] described a *p*-*tert*-butyl-calix[4]arene derivative to be selective for Zn^{2+} ion over Ti^{4+}, VO^{2+}, Cr^{3+}, Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Mg^{2+}, Cd^{2+}, and Hg^{2+}. The reaction of calix[4]arene derivative and Zn^{2+} was 1 : 1 stoichiometric; while H^+ quenched the fluorescence of the complex and OH^- restored it.

28. Cadmium determination

Cadmium is widely distributed in the body, with the major portion located in the liver and kidney. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure. The cadmium concentration in the liver of occupationally exposed workers generally increases in proportion to intensity and duration of exposures to values up to 100 $\mu g\,g^{-1}$. The concentration of cadmium in the kidney rises more slowly than in the liver after exposure and begins to decline after onset of renal damage at a critical concentration of 160–285 $\mu g\,g^{-1}$.

Most non-occupationally exposed people are exposed to cadmium primarily through the diet. Cadmium can be detected virtually in all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney. Average cadmium concentrations in the kidney are near zero at birth, and rise roughly linearly with age to a peak (typically around 40–50 $\mu g\,g^{-1}$ wet weight) between ages 50 and 60, after which kidney concentrations plateau or decline. Liver cadmium concentrations also begin near zero at birth, increase to typical values of 1–2 $\mu g\,g^{-1}$ wet weight by age 20–25, and then increase only slightly thereafter.

The most dangerous characteristic of cadmium is that it accumulates throughout lifetime. Cadmium accumulates in the liver and kidneys and has a long biological half-life, from 17 to 30 years in man. After an uptake from the lung or the gastrointestinal tract, cadmium is transported in blood plasma initially bound to albumin, as shown in experimental animals. The liver preferentially takes up cadmium bound to albumin. In the liver, cadmium induces the synthesis of metallothionein and a few days after exposure, metallothionein-bound cadmium appears in the blood plasma. Because of its low molecular weight, cadmium-metallothionein is efficiently filtered through the glomeruli and thereafter taken up by the tubules. Cadmium accumulates in the human kidney over the entire lifetime.

Thiacalixarenes are a class of calixarenes in which the bridging methylene groups are replaced with sulfur. Figure 2 illustrates that they are able to capture guest metal ions by coordinating with the bridging sulfur and adjacent phenol oxygen as well as *p*-substituent, aromatic ring, and hydrophobic cavity. Iki [156] reviewed a 200-fold

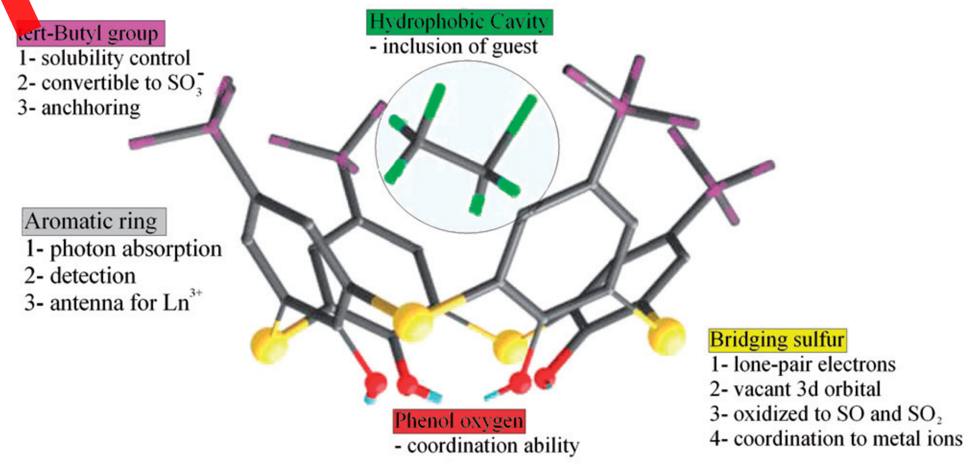


Figure 2. Illustration of interaction sites in thiacalixarenes.

preconcentration of Cd^{2+}. Zheng *et al.* [186] also used a similar way to recognize cadmium ions. Linear response range and detection limits were 20.7–5200 $\mu g\,L^{-1}$ and 2.2 $\mu g\,L^{-1}$, respectively. Dong *et al.* [187] described a glassy carbon electrode coated with Langmuir–Blodgett film of *p*-allylcalix[4]arene for the trace determination of cadmium by anodic stripping voltammetry. Linear voltammetric response of Cd^{2+} was in the range of 10–300 $\mu g\,L^{-1}$ and 0.07–40 $\mu g\,L^{-1}$, respectively. Their detection limits were also estimated to be 2.2 $\mu g\,L^{-1}$ and 0.04 $\mu g\,L^{-1}$, respectively. Leray and Valeur [119], in their microreview, present various calixarene-based sensors designed for the detection of cadmium. Park *et al.* [188] described the synthesis and evaluation of a calix[4]arene derivative for the detection of Cd^{2+} by the addition of various metal ions *via* fluorescent spectra changes.

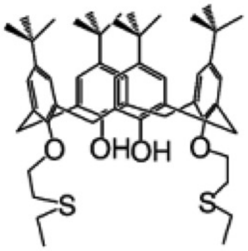
29. Mercury determination

The human body continuously eliminates mercury and other toxins in feces, urine, hair, sweat, nails, and skin. If excessive exposure is avoided, the body will efficiently eliminate most toxins. Mercury, for example, has a half-life in the body of only 2–3 months with no treatment at all.

Alpoguz *et al.* [189] made a flat-sheet-supported liquid membrane by calix[4]arene derivatives as carriers and Celgrad as solid support and investigated the transport behavior of Hg^{2+} into membrane from aqueous solution. Tu *et al.* [190] synthesized di-ionizable calix[4]arene-1,2-crown-4 ethers, which exhibited high extraction ability for Hg^{2+} in single species extraction. The extraction of Hg^{2+} in single species solvent extractions by a *p*-*tert*-butylcalix[4]thiacrown-5 derivative was presented by Tu *et al.* [191]. Dong *et al.* [192] described a glassy carbon electrode coated with Langmuir–Blodgett film of *p*-allylcalix[4]arene for trace determination of mercury by anodic stripping voltammetry. Linear voltammetric response and the limit of detection were in the range of 0.07–40 $\mu g\,L^{-1}$ and 0.04 $\mu g\,L^{-1}$, respectively.

Chinese researchers [193] determined the trace amounts of Hg^{2+} by a glassy carbon electrode coated with the film of 4-*tert*-butyl-1-(ethoxycarbonylmethoxy)thiacalix[4]-arene *via* anodic stripping voltammetry. The linear voltammetric response was in the range of 8.0×10^{-9} to $3.0 \times 10^{-6}\,mol\,L^{-1}$ with a detection limit of $5.0 \times 10^{-9}\,mol\,L^{-1}$. Mahajan *et al.* [194] prepared Hg^{2+} sensors by incorporating three different calix[4]arene derivative ionophores that showed linear concentration ranges and detection limits of $\sim 10^{-6}\,mol\,L^{-1}$ with response time of 20 s. Tyagi *et al.* [195] used a PVC-based membrane containing *p*-*tert*-butyl-calix[4]arenethioether to measure Hg^{2+}. The sensors work in partially non-aqueous media up to 40% (v/v) acetone, methanol, or ethanol with a linear concentration range of 7.2×10^{-8} to $1.0 \times 10^{-1}\,mol\,L^{-1}$ and response time of 14 s.

Li *et al.* [196] prepared luminescent and stable quantum dots capped with sulfur calixarene (**88**) for the selective determination of mercury ions in acetonitrile *via* its quenching effect. Even at a relatively higher concentration, the interference influences of other metal ions (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}) were very weak. Only Pb^{2+} at a higher concentration produced a measurable quenching of luminescence.



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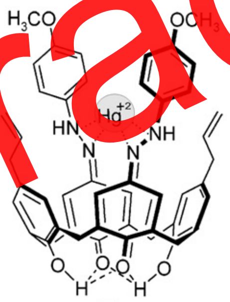
Othman *et al.* [197] synthesized a calix[4]arene-based chemosensor in CH_3CN solution for which Hg^{2+} significantly induced fluorescence resonance energy transfer at 575 nm from pyrenyl excimer to rhodamine ring. Ho *et al.* [198] prepared the upper-rim allyl- and *p*-methoxyphenylazocalix[4]arenes (**89**) and examined their efficiencies in chromogenic sensing of Hg^{2+}. Bingol *et al.* [199] determined a rapid test kit for early detection of Hg^{2+} in an aqueous environment in the concentration range of 1×10^{-4} to 1×10^{-2} mol L^{-1} using calix[4]arene derivative bearing benzothiazole azo groups at the upper rim as chromogenic chemosensor and investigated its sensing properties with Pb^{2+}, Hg^{2+}, Ni^{2+}, Cd^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Cr^{3+}, and Ag^{+}. The chromogenic chemosensor showed high selectivity toward Hg^{2+} over the other heavy metal ions.



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Ak and Deligöz [155] in Turkey synthesized azocalix[4]arenes and studied the solvent extraction of Hg^{+} and Hg^{2+} from the aqueous phase to the organic phase. American and Turkish chemists [131] studied the influence of some transition metal cations including Ag^{+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Hg^{2+}, Mn^{2+}, Zn^{2+}, and Fe^{3+} on the spectroscopic properties of calix[4]arene complexes bearing dansyl groups. They reported that transition metal cations interact strongly with the calix[4]arene. In particular, Hg^{2+} caused greater than 97% quenching of the dansyl fluorescence.

30. Aluminum determination

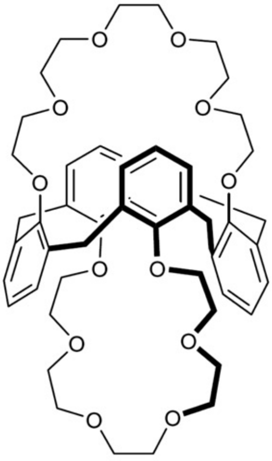
It has been established that the average human body contains from 35 to 50 mg of aluminum, of which approximately 50% is in the lungs, 25% in the soft tissues, and 25% in the bones. There is no known biological role for aluminum. It does not appear to be an essential trace element and the human body has effective barriers against aluminum uptake. Only a minimal fraction of aluminum in the diet is absorbed from the digestive tract and, in healthy individuals, the kidneys very quickly excrete most of this. When aluminum blood levels are very high, bones appear to act as sink, taking up aluminum and subsequently releasing it slowly over a long period. The brain is vulnerable to many chemical and biological agents but is protected by a blood brain barrier, a collection of cells forming the inner lining of capillary blood vessels which prevent many substances from entering the brain.

Othman *et al.* [197] synthesized an Al^{3+}-calix[4]arene-based chemosensor for which Al^{3+} significantly induced pyrenyl excimer emission at 475 nm. Deligoz and Erdem [200] used nine ligands including two diazo-coupling calix[*n*]arenes, four phenol derivatives, and three ester derivatives to investigate ionophore solvent extraction of Al^{3+} and revealed that the best extraction efficiency was obtained with *p*-(4-phenylazophenylazo)calix[4]arene and 2-(5-bromo-2-pyridylazo)-5-diethylamino phenol.

31. Thallium determination

Thallium can enter the body when persons eat food or drink water contaminated with thallium, breathe thallium in the air, and when their skin comes in contact with it. When thallium is swallowed, most of it is absorbed and rapidly goes to various parts of the body, especially the kidney and liver. Thallium can affect the nervous system, lung, heart, liver, and kidney if large amounts are eaten or drunk for short periods of time. Temporary hair loss, vomiting, and diarrhea can also occur and death may result after exposure to large amounts of thallium for short periods. Thallium can be fatal from a dose as low as 1 g. No information was found on health effects in humans after exposure to smaller amounts of thallium for longer periods. Birth defects observed in children of mothers exposed to small amounts of thallium did not occur more often than would be expected in the general population. The length of time and the amount of thallium eaten by the mothers are not known exactly.

Sliwa and Girek [113] reported that 1,3-alt-calixbiscrowns coordinate metal ions *via* π interaction. They contain π-basic aromatic cavity that may bind soft electron acceptors and they have oxygen atoms that are able to bind hard cations. Therefore, **(90)** may serve as a receptor for Tl^{+}.



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Konishi *et al.* [169] used electrospray ionization mass spectrometry to study complexation of π-coordinate calix[4]arene derivatives toward Tl^+. Competitive complexation of three calix[4]arene derivatives demonstrated no effect of olefinic substituents and their location on the Tl^+ complexation. They also determined the stability constants for the complexes in methanol using 18-crown-6 as the reference ligand. Guo *et al.* [201] reported that Tl^+ is particularly favorable to be included into the cavity of *p*-sulfonatothiacalix[4]arene due to the cation polarizability.

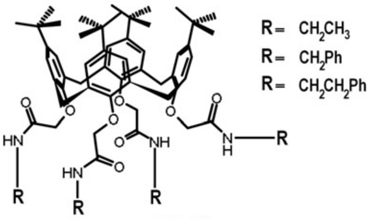
Dong *et al.* [187] determined trace amounts of thallium using a glassy carbon electrode coated with Langmuir–Blodgett film of *p*-allylcalix[4]arene by anodic stripping voltammetry with linear voltammetric response of 5–250 $\mu g\,L^{-1}$ and detection limit of 1.0 $\mu g\,L^{-1}$, respectively. Talanov *et al.* [202] synthesized a one pendent *N*-dansylcarboxamide calix[4]arene derivative and demonstrated selective optical recognition of Tl^+ by changing the fluorescence spectrum of sensor.

32. Lead determination

Lead can cause many health problems after short-term high-level exposure. Children and adults who absorb large amounts of lead may develop blood anemia, colic (severe stomachache), muscle weakness, kidney damage, brain damage, and death. Studies have shown that people had an increase in blood pressure at lower levels of lead exposure. Other studies in workers exposed to low levels of lead over time have shown a worsening of reaction time, memory, and ability to learn new information. Lead can be measured in the blood, bone, teeth, urine, and feces. The most common method is to test current lead levels through blood testing.

Ulewicz *et al.* [182] investigated Pb^{2+} transportation through a calix[4]crown-6 derivative/membrane and studied the influence of attached group of calix[4]crown-6 on the selectivity of Pb^{2+} transport. Tu *et al.* [191] examined the extraction ability of cone conformation of *p-tert*-butylcalix[4]arene-1,3-thiacrown-5 ether toward Pb^{2+} and showed its high extraction ability in single-species solvent extractions.

Bochenska *et al.* [203] applied five tetrasubstituted *p-tert*-butylcalix[4]arene-thioamides as ionophores in lead-ion-selective membrane. The tertiary calix[4]thioamides showed remarkable selectivity to lead while the secondary calix[4]thioamides formed less stable electrode membranes. Chen *et al.* [204] tested seven double-armed calix[4]arene amide derivatives to make lead ISEs. Jain *et al.* [205] used 5,11-dibromo-25,27-dipropoxycalix[4]arene ionophore in PVC-based membrane sensors selective to Pb^{2+}. Sensor exhibited a Nernstian response in the concentration range of 2.5×10^{-6} to $5.0 \times 10^{-2}\,mol\,L^{-1}$. In Poland, Bochenska and Lesinska [206] evaluated three lipophilic *t*-butylcalix[4]arene amides (**91–93**) as lead ionophore. One of them had the best selectivity coefficients toward Pb^{2+} in the presence of copper and cadmium ($\log K_{Pb,M} < -3$) and cobalt, nickel, and alkaline earth metal ions ($\log K_{\mathrm{Pb,M}} < -4$).



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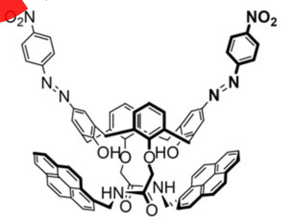
Yaftian *et al.* [207] made a coated-wire-type Pb^{2+} ISE based on a 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis-(diphenylphosphinoylmethoxy)calix[4]arene over a concentration range of 1×10^{-5} to $1 \times 10^{-2}\,\mathrm{mol\,L^{-1}}$, detection limit of $1.4 \times 10^{-6}\,\mathrm{mol\,L^{-1}}$, and response time of 17 s. They also investigated the selectivity of the electrode performance toward lead ions over Th^{4+}, La^{3+}, Sm^{3+}, Dy^{3+}, Y^{3+}, Ca^{2+}, Sr^{2+}, Cd^{2+}, Mn^{2+}, Zn^{2+}, Ni^{2+}, Co^{2+}, NH_4^+, Ag^+, Li^+, Na^+, and K^+ ions. Torma *et al.* [208] made a calixarene-based chemically modified bismuth-film electrode on glassy carbon substrate for the determination of lead ions *via* square wave anodic adsorptive stripping voltammetry with a detection limit of $0.02\,\mu\mathrm{g\,L^{-1}}$ and a dynamic range of 0.05–$0.6\,\mu\mathrm{mol\,L^{-1}}$.

Zheng *et al.* [186] provided a glassy carbon electrode coated with Langmuir–Blodgett film of allylcalix[4]arene for the trace determination of lead. Limits of detection and linear response range were $1.7\,\mu\mathrm{g\,L^{-1}}$ and 22–$5600\,\mu\mathrm{g\,L^{-1}}$, respectively. Chang *et al.* [129] described a switchable fluorescent chemosensor which was composed of a triazole-modified calix[4]crown derivative (**94**). The fluorescence of macrocycle was strongly quenched by Pb^{2+} and the revival of emission from the strongly quenched complex was achieved by the addition of K^+, Ba^{2+} or Zn^{2+}.



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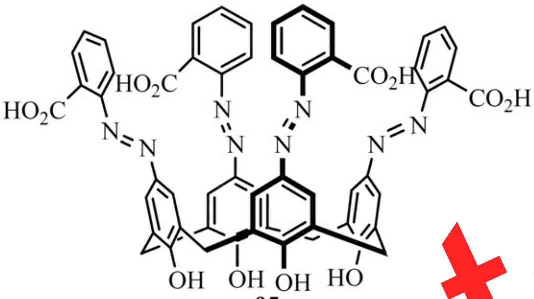
Kim *et al.* [133] prepared a strong excimer emission based on a calix[4]arene fluorescence chemosensor to recognize Pb^{2+}. When Pb^{2+} was bound to the two amide oxygens linked to the fluorophores, the ligand exhibited a marked quenched excimer emission which was revived by the addition of Ca^{2+} into the complex excimer emission band, by which an interesting on–off switch fluorescence chemosensor was proposed. Liu *et al.* [209] synthesized a *p*-*tert*-butyl-calix[4]arene derivative in CH_3CN–H_2O that exhibited highly selective fluorescent response to Pb^{2+} over alkali, alkali earth metal ions, and some transition metal ions. Some calixarene sensors, designed for lead recognition, were reviewed by Leray and Valeur [119].

Kim *et al.* [210] synthesized a calix[4]azacrown bearing two pyrene amide pendent groups as a selective sensor for Pb^{2+} owing to the ratiometric changes of monomer and excimer emissions. Ocak *et al.* [131] investigated the influence of Pb^{2+} on spectroscopic properties of calix[4]arenes bearing dansyl using spectrofluorimetric titration experiments in acetonitrile. Pb^{2+} caused greater than 97% quenching of the dansyl fluorescence in the calix[4]arene derivative. Chinese chemists [130] reported Pb^{2+} determination by calixarene chromogenic sensors. Vietnamese chemists [211] determined trace amounts of lead ions in aqueous environmental samples using benzoic acid azophenylcalix[4]arene (**95**) *via* a colorimetric method at 440 nm. The calixarene derivative showed strong binding ability to Pb^{2+} with the formation of a 1 : 1 complex. The dynamic range was determined to be 2.0×10^{-6} to 2.4×10^{-5} mol L^{-1} and the detection limit was 1.4×10^{-6} mol L^{-1}.



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33. Fluoride determination

Fluoride is considered a trace element because only small amounts are present in the body (about 2.6 g in adults) and because the daily requirement for maintaining dental health is only a few milligrams per day. About 95% of the total body fluoride is found in bones and teeth. Although its role in the prevention of dental caries is well established, fluoride is not generally considered an essential mineral element because humans do not require it for growth or to sustain life. However, if one considers the prevention of chronic disease, an important criterion in determining essentiality, then fluoride might well be considered an essential trace element. Fluoride is absorbed in the stomach and small intestine. Once in the blood stream, it rapidly enters mineralized tissue (bones and developing teeth). At usual intake levels, fluoride does not accumulate in soft tissue. The predominant mineral elements in bone are crystals of calcium and phosphate, known as hydroxyapatite crystals.

Lee *et al.* [128, 212] studied selective colorimetric changes of *bis*(indolyl)calix[4]-crown-6 and amido-coumarin-calix[4]arene sensors for recognition of fluoride. Lee *et al.* [213] used preorganized tetra-amidourea-derived calix[4]arene sensor for fluoride detection. The complex excited at 343 nm and revealed excimer emissions at 448 nm. A colorimetric on–off sensor achieved recognition of F^-. It was prepared using a calix[4]arene-crown-6 derivative that was synthesized by Lee *et al.* [120].

As discussed, phenolic units bridged by methylene spacers in *meta*-position are called calixarenes, although in recent years, macrocycles with related subunits such as resorcin or pyrrole and other spacers such as sulfur are also considered to belong to the same class. Calixpyridines and calixpyrroles belong to calixarenes and there are some analytical applications of them. In Korea [214], a calix[4]imidazolium[2]pyridine cation was synthesized and formed a complex with F^- anion in 1 : 1 stoichiometry, which can be used as a macrocyclic ionophore for F^-. Szymanska *et al.* [215] used a neutral redox-active receptor, based on ferrocene functionalized calix[4]pyrrole, as an active component in carbon paste ISEs using Osteryoung square-wave voltammetry to detect F^-.

A two-faced naphthalimide–calix[4]arene was synthesized by Xu *et al.* [162] as a selective fluorescent-quenching chemosensor for F^- over $H_2PO_4^-$, HSO_4^-, $CH_3CO_2^-$, I^-, Br^-, and Cl^- anions. They investigated the binding mode with F^- using H-NMR and fluorescence changes. Chen *et al.* [216] analyzed dihydrogen phosphate anion in the presence of F^- using a sensitive fluorescence probe prepared by calix[4]arene bearing naphthol-hydrazone groups. An amidourea-based calix[4]arene derivative was synthesized by Quinlan *et al.* [217] to prepare a bifunctional fluorescent calix[4]arene chemosensor. At high concentration of F^-, significant colorimetric changes were observed.

Liu *et al.* [218] prepared two-armed calix[4]arenes bearing thiourea and amide as neutral anion receptors with excellent selectivity for fluoride. Those derivatives showed no binding ability with dihydrogen phosphate, acetate, chloride, bromide, and iodide. Kim *et al.* [219] introduced a fluoride chemosensor based on the formation of a static excimer. Complexation of fluoride by calixarene-based fluorescent chemosensor caused a red shift in the absorption band (346–400 nm) and a blue shift of the excimer emission (482–470 nm).

34. Chloride determination

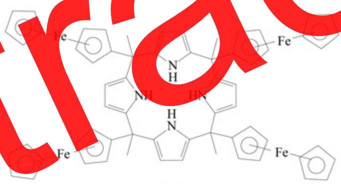
Chloride is one of the most important minerals in the blood, along with sodium, potassium, and calcium. It helps keep the amount of fluid inside and outside of cells in balance. It also helps maintain proper blood pressure, blood volume, and pH of body fluids. Most of the chloride in the body comes from table salt in the diet. The intestine absorbs chloride during food digestion and any excess chloride is passed out of the body through the urine. Chloride is the major extracellular anion and contributes to many body functions, including maintenance of osmotic pressure, muscular activity, acid–base balance, and the movement of water between fluid compartments. Chloride is an electrolyte, along with sodium and potassium, and it affects nerves, blood, and epithelium, aids digestion and elimination, and normalizes osmotic pressure in blood and tissues. It helps maintain normal heart function, acid–base balance, and water balance. Chloride increases the capacity of blood to carry carbon dioxide to lungs for excretion and helps to cleanse both the intestines and body of toxins. Chloride produces the normal acid environment in stomach (this aids in absorption of iron and vitamin B_{12}).

Lang *et al.* [220] in the Czech Republic investigated the stoichiometry of complexation of calix[4]arenes bearing two *p*-nitrophenyl-ureido functions at the upper rim.

Substitution pattern and chloride concentration were studied on distal and proximal isomers and showed that while the distally substituted receptor forms 1 : 1 complex with chloride, the corresponding proximal derivative prefers the 2 : 1 stoichiometry under identical conditions.

Babu *et al.* [221] synthesized a ureido calix[4]arene derivative and examined its anion recognition abilities toward fluoride, chloride, bromide, iodide, nitrate, and acetate by UV-Vis spectroscopy and H-NMR. The ionophore showed a strong binding affinity for chloride and a chloride ISE was formed with the detection limit of $2.51 \times 10^{-5}\,\mathrm{mol\,L^{-1}}$.

Sessler *et al.* [222] studied the interaction of calixpyrrole with several chloride salts. Schazmann *et al.* [223] bridged urea functional groups with single methylene spacers to pyrene moieties, synthesizing a 1,3-alternate tetrasubstituted calix[4]arene derivative. The excimer emission of pyrene was quenched, with a simultaneous rise in monomer emission solely by chloride, among other anions tested. The method had an LOD of $8 \times 10^{-6}\,\mathrm{mol\,L^{-1}}$ with chloride in acetonitrile–chloroform solution. Miyaji *et al.* [111] synthesized a fluorophore based on calix[4]pyrrole and determined its association constants with chloride using fluorescence titration. The fluorescence was quenched by chloride in the presence of Na^+. Nishiyabu and Anzenbacher [224] prepared calix[4]pyrrole anion sensors with high selectivity for chloride. Romanian chemists [225] investigated the electrochemical behavior of *meso*-tetraferrocenyl–tetramethylcalix[4]pyrrole (**96**) modified graphite electrodes *via* cyclic voltammetry. They used this technique to recognize chloride.



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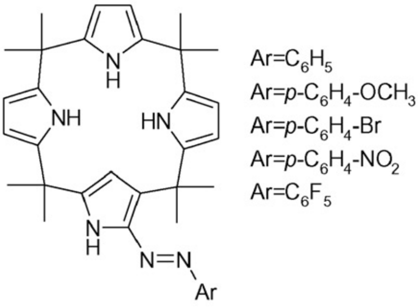
35. Iodide determination

Thyroid function is affected by various physiological conditions such as food deprivation, pregnancy, and iodine deficiency. Iodide is an essential element for the production of thyroid hormones. Its uptake by the thyroid gland is an active process that is regulated by thyroid-stimulating hormone or thyrotropin and the thyroidal blood flow. Alterations in the thyroidal uptake of iodide can cause changes in the production of thyroid hormones. Calix[4]pyrroles are used as a complexation agent for anion recognition. Guest anions are bound to the macrocycles by hydrogen bonds to nitrogen but complex stability is not high enough for analytical use; to improve the binding ability, the basic calix[4]pyrrole skeleton was functionalized with various substitutions, in the *meso*-position of macrocycle or the *beta*-positions of the pyrrole units. Gu *et al.* [226] studied the complexation of six *α*-arylazo-*N*-confused calix[4]pyrrole derivatives (**97–101**) with tetrabutylammonium salt of I^- using UV-Vis spectroscopy in dichloromethane and acetonitrile solvents.



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36. Acetate determination

Changes in blood concentrations of glucose, acetate, and other blood intermediary metabolites have been examined as well as the disposal of an intravenous glucose load during successive glucose-free acetate and control bicarbonate hemodialysis in random order, in non-diabetic and diabetic subjects. Plasma acetate levels increase about 10-fold in both the diabetic and non-diabetic subjects during the first hour of acetate dialysis. This is accompanied by about five-fold increase in the levels of the ketone bodies – acetoacetate and 3-hydroxybutyrate. Ketone body levels do not change during bicarbonate dialysis. Additionally, the changes in blood levels of glucose, non-esterified fatty acids, pyruvate, lactate, glycerol, and insulin are similar with either bicarbonate or acetate treatment in each subject group. The blood acetate levels ranged from 0.1–0.2 to 0.8–1.0 mmol L^{-1}.

A bridged fluorescent calix[4]arene with glycine and 1,8-diaminoanthracene at the upper rim was prepared by Miao *et al.* [227]. This fluorescent ionophore recognized AcO^- over F^-, Cl^-, Br^-, $H_2PO_4^-$, NO_3^-, I^-, and HSO_4^- anions. Irish researchers [228] used amidourea-based 1,3-disubstituted calix[4]arene with acetate, fluoride, hydrogen phosphate, and hydrogen pyrophosphate anions in DMSO. Yoo *et al.* [229] synthesized calix[4]pyrroles bearing dipyrrolylquinoxaline as strapping elements and examined their selective colorimetric response when exposed to acetate. Farinha *et al.* [230] in Portugal used (*E*)-3-(*meso*-octamethylcalix[4]pyrrol-2-yl)propenal to recognize acetate. They [231] also synthesized a calix[4]pyrrole derivative which displayed sharp changes in color in the presence of acetate anions.

37. Hydrogen phosphate determination

Phosphates are widely distributed in the body, the largest amounts being in the bones and teeth. They are continually excreted in the urine and feces, and must be replaced in the diet. Inorganic phosphates function as buffer salts to maintain the acid–base balance in blood, urine, saliva, and other body fluids. The principal phosphates in this buffer system are monosodium and disodium phosphate. Organic phosphates, in particular ATP, are used to store the chemical energy released during oxidation of compounds, such as glycogen or fatty acids, which may later be expended in muscle contraction.

Kivlehan *et al.* [232] evaluated one urea-functionalized calix[4]arene and one thiourea-functionalized calix[4]arene for monohydrogen orthophosphate (HPO_4^{2-}) sensing with a linear concentration range of 5.0×10^{-5} to $1.0 \times 10^{-1}\,\mathrm{mol\,L^{-1}}$. Gupta *et al.* [233] also used another ionophore to recognize monohydrogen orthophosphate anions with 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-exakis(carbamoylmethoxy)calix[6]arene. The linear response range was reported as 1.77×10^{-5} to $1.0 \times 10^{-1}\,\mathrm{mol\,L^{-1}}$. Irish researchers [234] characterized the interaction of a urea-functionalized calix[4]arene ionophore and phosphate using voltammetric ion transfer at the interface between two immiscible electrolyte solutions (ITIES). Voltammetry at the ITIES confirmed that the ionophore-facilitated transfer of monohydrogen phosphate occurred in preference to dihydrogen phosphate transfer. Linn *et al.* [235] investigated dihydrogen phosphate during interaction of Brooker's Merocyanine (BM) and calix[4]pyrrole. The interaction of BM with calix[4]pyrrole changes the color of the solution due to the formation of calix[4]pyrrole–BM. Dihydrogen phosphate displaced BM through the formation of a complex with calix[4]pyrrole, coloring the solution.

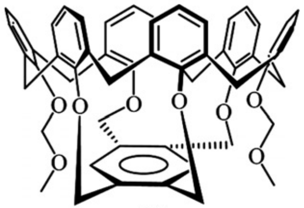
38. Organic ion determination

Organic cation transporters mediate the uptake of many organic cations from the blood into the liver where the compounds may be metabolized or secreted into the bile. Because organic cation transporters interact with a variety of structurally diverse organic cations, including clinically used drugs as well as toxic substances, it is an important determinant of organic cations in the body.

Nishiyabu and Anzenbacher [236] synthesized chromogenic calix[4]pyrroles and made octamethylcalix[4]pyrrole/polyurethane sensor films showing a strong response for aqueous carboxylates (antipyretics naproxen, ibuprofen, and salicylate) without interference from bicarbonate and carboxy termini of blood plasma proteins. Qing *et al.* [237] examined chiral anion-binding ability of a calixarene derivative and used it as a good chiral chromogenic chemosensor for the enantiomers of the α-phenylglycine anion.

Chinese chemists [238] prepared *p*-sulfonatocalix[6]arene-modified gold nanoparticles as colorimetric probes to detect diaminobenzene isomers. Due to the intense surface plasmon absorption band centered at 520 nm, the color of calixarene–nanoparticle solution was red, while the color of complex solution was changed to a deep purple. Based upon their claim, diaminobenzene isomers bridged the nanoparticles *via* electrostatic and host–guest interactions, which induced the aggregation of the nanoparticles. Upon aggregation, the surface plasmon absorption band was broadened and shifted to the red region so that the nanoparticle solution appeared a deep purple. They examined the sensitivity of host macrocycle toward *o*-diaminobenzene, *o*-nitroaniline, *m*-nitroaniline, *p*-nitroaniline, *o*-chloroaniline, *p*-chloroaniline, *o*-toluidine, *m*-toluidine, *p*-toluidine, and aniline, and concluded that the sensitivities were negligible.

Selective extraction of organic ammonium attracts research interest due to the application of biological systems. Calixarenes present attractive possibilities in host–guest chemistry, and their architecture is such that they also possess hydrophobic cavities generated by aromatic walls of phenol residues, which are potentially useful for the inclusion of alkyl ammonium ions. Korean chemists [239] synthesized a quadruply bridged calix[6]arene derivative (**102**) and extracted alkylammonium cations with picrate into chloroform by two-phase solvent extraction. They deduced the percentage extraction from the absorbance at 355 nm in the aqueous layer. The extraction efficiencies for ammonium picrate, ethylammonium picrate, *n*-propyl ammonium picrate, and *n*-butylammonium picrate were 2.4%, 3.7%, 2.7%, and 2.8%, respectively.



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Thiacalix[4]arene-*p*-tetrasulfonate (CAS) and thiacalix[4]arene-*p*-tetrasulfonate (TCAS) form luminescent complexes of $Tb^{III} \cdot (CAS)_2$ and $Tb^{III} \cdot TCAS$, respectively. They were utilized as a host for 1-ethylpyridinium, 1-ethylquinolinium, and nicotineamide adenine dinucleotide (NAD^+) guests, which quenched luminescence of $Tb^{III} \cdot (CAS)_2$ with a low detection limit of $5.94 \times 10^{-8}\,\mathrm{mol\,L^{-1}}$, $6.71 \times 10^{-10}\,\mathrm{mol\,L^{-1}}$, and $2.78 \times 10^{-7}\,\mathrm{mol\,L^{-1}}$, respectively ($S/N = 3$) [240]. Chawla *et al.* [241] synthesized a series of calix[4]arene diquinones and investigated their interactions with ammonium. The interactions induced an unprecedented downfield shift in the NH proton resonance, which was attributed to polarization of the amidocrown ring of the calix[4]arene diquinone receptor, confirmed by a significant anodic shift of the corresponding amidocrown–diquinone redox couple in cyclic and square-wave voltammetric experiments.

American researchers [242] in a review paper reported that *N*-confused calix[4]pyrroles are a relatively recent arrival to the pyrrole macrocycles family, being identified for the first time in 1999. Yet, in a relatively short time, these calix[4]pyrrole isomers attracted attention of research groups interested in colorimetric anion sensing. They reviewed the *N*-confused calix[4]pyrroles, presented the results of colorimetric assays for anions, and discussed their potential applications. Belgium and American chemists [243] investigated the properties of chromogenic octamethylcalix[4]pyrroles and their *N*-confused octamethylcalix[4]pyrrole isomers. The chromogenic octamethylcalix[4]pyrroles showed significantly stronger anion-induced color changes compared to the corresponding chromogenic octamethylcalix[4]pyrrole isomers.

Polish and Belgian researchers [244] discussed the mechanism of potentiometric signal generation by liquid membrane electrodes incorporating undecylcalix[4]resorcinarene derivatives upon stimulation by uncharged aniline derivatives. They proved that in the conditions where all aniline derivatives exist as uncharged molecules, cationic potentiometric signals were observed for all undecylcalix[4]resorcinarene liquid membrane electrodes. They claimed that the main parameters crucial for this phenomenon were the acidity–basicity of the hosts and guests and the lipophilicity of the guests played a secondary role. Japanese chemists [245] prepared a highly selective methylammonium-selective membrane electrode by *p*-1,1,3,3-tetramethylbutylcalix[6]-arene-hexaacetic acid hexaethyl ester and showed the highest response to methylammonium among various organic ammonium ions and inorganic cations. Korean and French researchers [246] reviewed the complexing properties of calixcrowns, calixbiscrowns, and resorcinarenecrowns and reported their ionophoric properties toward amines and (alkyl) ammoniums.

39. Conclusion

The results of about 250 references, published from 2005 to date, have been reviewed. The described examples illustrated the potential of calixarene derivatives in the rapidly growing field of molecular/ionic recognition. By searching literature, optimization of chelator design together with understanding of how to control the localization of calixarene-based complexes will be clarified. The functional groups, introduced on calixarene derivatives, influence the binding abilities of calixarenes toward biological compounds, drugs and ionic species, while the size and nature are responsible for effective complexation.

The binding abilities and molecular/ionic selectivities of calixarene-molecular complexes upon complexation with biological guest molecules are outlined in this article, including drug carriers, drugs, heparin and dopamine, amino acids, antigens and antibodies, hormones, enzymes, proteins and steroids, vitamins, alcohols, amines, aromatic species, PAHs, pesticides, caffeine and other molecular compounds, lithium, sodium, potassium, cesium, calcium, strontium, chromium, iron, cobalt, nickel, copper, silver, zinc, cadmium, mercury, aluminum, thallium, lead, fluoride, chloride, iodide, acetate, hydrogen phosphate, and organic ions.

The functional groups introduced in the structure of calixarene derivatives influence the binding abilities of calixarenes toward biological compounds and drugs; the size and the nature of these molecular compounds are responsible for effective complexation. In addition, no meaningful correlation has been found between complexation of biomolecules with calixarenic receptors and related analytical procedures. However, we believe that the medical and analytical potentials of calixarenes are attracting more and more interest.

The reader is introduced to the advances in the biological applications of calixarenes in terms of complexation, solvent extraction, liquid chromatography, membrane transport, potentiometry, voltammetry, conductometry, electrochemical and spectroscopic sensors, luminescence, and colorimetric techniques. Bioanalytical potential of calixarenes will attract the attention of the scientists in future.

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