1,3-Alternate, the Smart Conformation of Calix[4]arenes

Lassaad Baklouti[1,*], Jack Harrowfield[2], Buncha Pulpoka[3,*] and Jacques Vicens[4]

[1]*Faculté des Sciences de Bizerte, Laboratoire de Chimie des Interactions Moléculaires, 7021 Zarzouna, Tunisie*

[2]*Institut de Science et d'Ingénierie Supramoléculaires, Université Louis Pasteur, Laboratoire de Chimie Supramoléculaire, 8, allée Gaspard Monge, Strasbourg 67083, France*

[3]*Supramolecular Chemistry Research Unit and Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330 Thailand*

[4]*Ecole Chimie Polymères et Matériaux, Laboratoire de Chimie des Interactions Moléculaires Spécifiques, associé au C.N.R.S., 25 rue Becquerel, F-67087 Strasbourg, France*

Abstract: The syntheses and fascinating properties of calix[4]arene derivatives in the 1,3-alternate conformation are reviewed. Particular attention is given to the supramolecular chemistry and applications in nanochemistry of such calixarenes.

Keywords*:* Calix[4]arenes, 1,3-alternate conformation, synthesis, complexation, applications.

INTRODUCTION

The macrocyclic polyphenols termed "calixarenes" have been widely employed as scaffolds for the construction of highly sophisticated molecules with numerous applications [1-3]. The number of phenolic units, n, linked together in the ring of the macrocycle is indicated by the designation calix[n]arene, the term "calix" deriving from the resemblance of the shape of the simplest calixarene, calix[4]arene, to that of the classical Greek vase, the *calix crater*. Calix[4]arene derivatives are by far best known, largely because of their ease of synthesis and functionalisation, though also because they are readily fixed in each of four conformations termed "*cone*", "*partial cone*","*1,2-alternate*" and "*1,3-alternate*" (Fig. **1**). The last of these has proved particularly useful as the basis for numerous molecules with practical applications [4] and it is this versatility that leads us to dub it the "smart" conformation of the molecule. With symmetrical substitution, it is the only apolar isomer [5-7] and it is particularly advantageous for the construction of two molecular cavities connected by a "tube" or "tunnel" [8,9] composed of the four π-base phenyl groups linked to form the basic macrocycle. Cations bound within the molecular cavities may, in some cases, pass from one cavity to the other *via* this tunnel [10,11] (Fig. **1**). A subtle variation on the structure giving a ditopic metal ion ligand is the use of unsymmetrical functionalisation to provide inequivalent metal binding sites, so that it is possible to simultaneously bind both a hard and a soft metal ion [12,13]. Further, appropriate design can be used to provide a ligand of this type where initial coordination occurs at one site which can then be modified by protonation so as to cause an internal transfer to the other [14,15]. Elaborate molecular devices based on 1,3-alternate calix[4]arenes include "*mappemondes*" (molecules resembling a globe map of the earth in its stand) [16,17], "*molecular mills*" [17,18] and "*nanotubes*" (tubular molecules of nanometre dimensions) [19,20].

Recognising that calixarenes may be readily functionalised both at oxygen and at the p-position of the phenyl rings, it is useful to classify (Fig. **2**) 1,3-alternate calix[4]arenes in terms of six types: (a) those where all the substituents are simply pendent (and the cavities they create therefore "open") and the four *O*-substituents are identical but there are two pairs of p-substituents; (b) those where the cavities are again "open" but here the *p*-substituents are all the same and the *O*-substituents occur in pairs; (c) those where the *p*-substituents are identical but the *O*-substituents differ in pairs with one pair in fact forming an intramolecular bridge; (d) those where both pairs of oxygen atoms are bridged, not necessarily identically, and the p-substituents are identical; (e) those with identical bridges of the oxygen pairs but different pairs of *p*-substituents; (f) multiple 1,3-alternate calix[4]arenes formed by intermolecular bridging involving the substituents. In nearly all these cases, the cavities defined by the substituent arrays must be inequivalent.

TYPE (A) - OPEN CAVITIES RENDERED INEQUIVALENT BY DIFFERENT *P*-SUBSTITUENTS

This type is rare but the strategy used for its synthesis is instructive. It is based on the ease of obtaining 1,3-di-*O*-alkylated calix[4]arenes with an *O*-alkyl substituent sufficiently large to prevent inversion of the phenoxo group to which it is attached by passage through the macrocyclic ring [21]. Such alkylations typically are conducted by reaction of a calix[4]arene with an alkyl halide or tosylate, using Cs_2CO_3 as a base catalyst in solvents such as DMF [22], acetonitrile [23] or acetone [24]. Because reactivity at the p-positions differs greatly depending upon whether the O-site is *O*-alkyl or OH, it is then possible to selectively react at the p-sites of the phenolic rings, using reactions such as bromination [26,27] or nitration [28,29]. Since the intermediate dialkylated and di-*p*-substituted species need

*Address correspondence to these authors at the Faculté des Sciences de Bizerte, Laboratoire de Chimie des Interactions Moléculaires, 7021 Zarzouna, Tunisie; E-mail: bakloutilassaad@yahoo.fr; Supramolecular Chemistry Research Unit and Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330 Thailand; E-mail: Buncha.P@chula.ac.th

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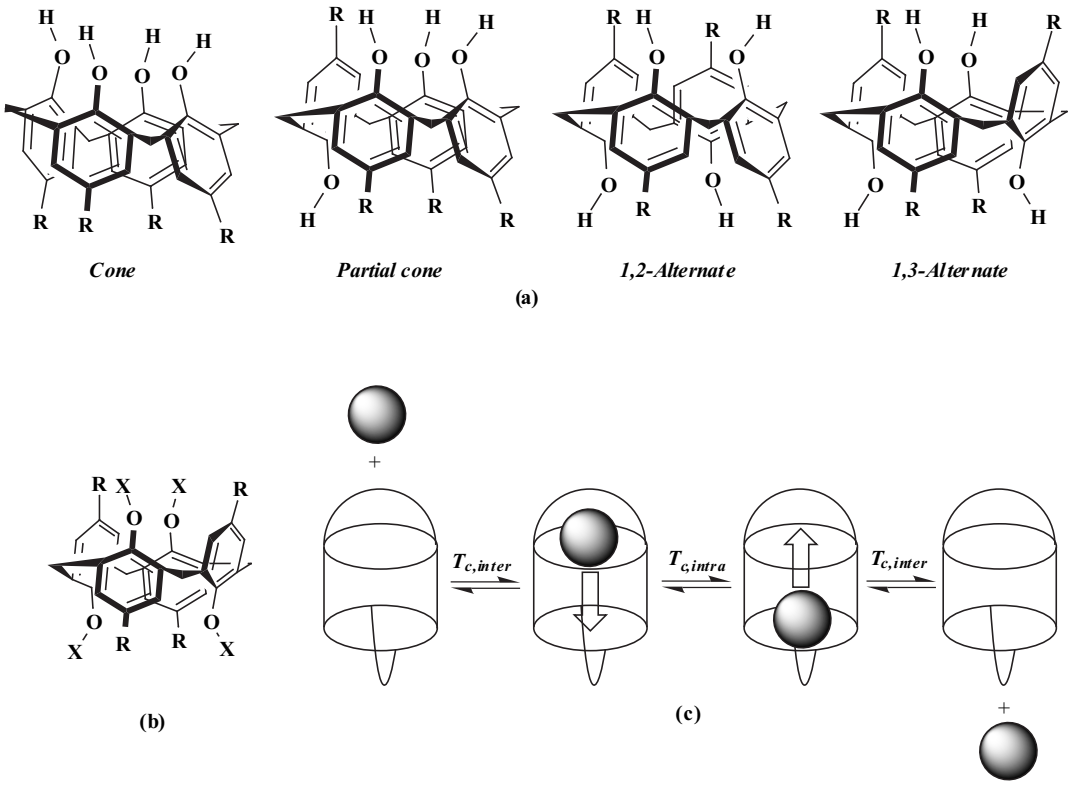


Fig. (1). (a) The four conformers of calix[4]arene; (b) a symmetrically functionalised calix[4]arene in the 1,3-alternate conformation; (c) a representation of such a calixarene where the groups X define a macrocyclic ligand unit and a bound metal ion may pass from one unit to the other *via* the central "tunnel".

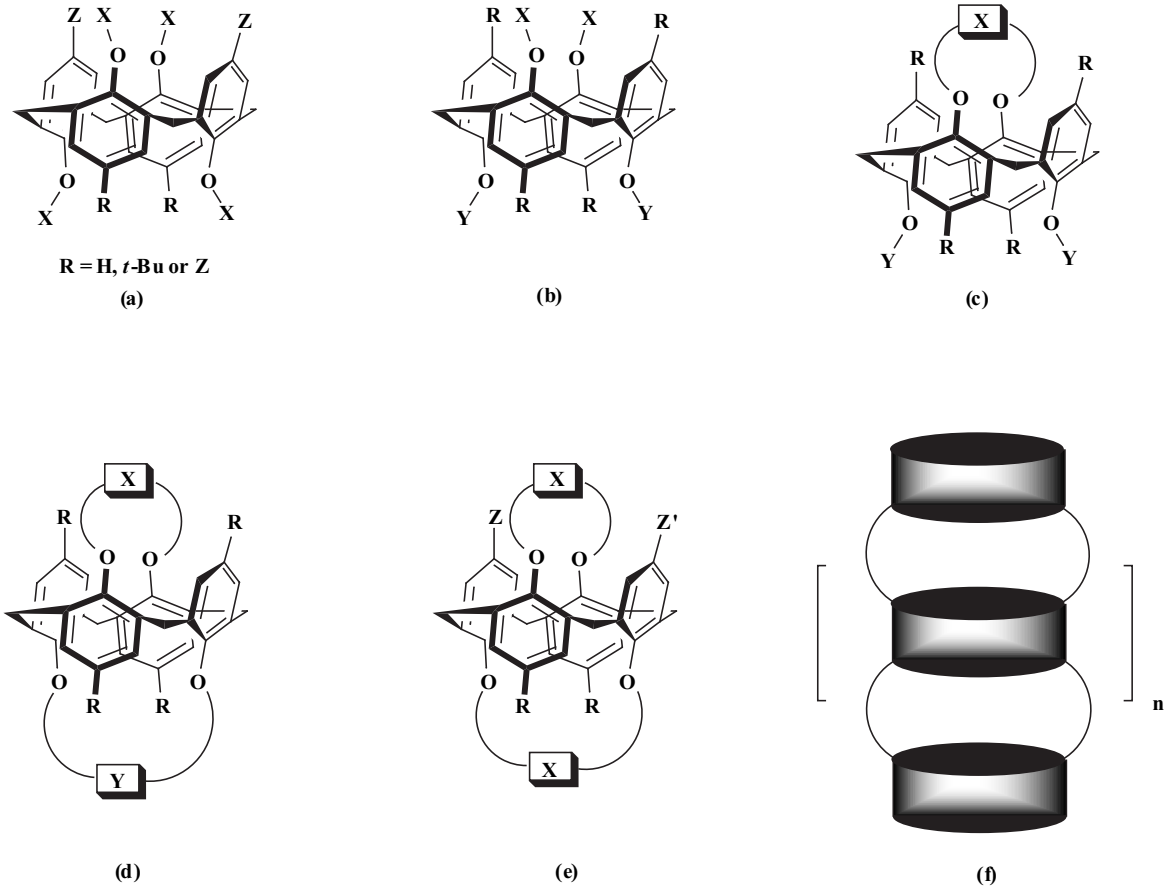
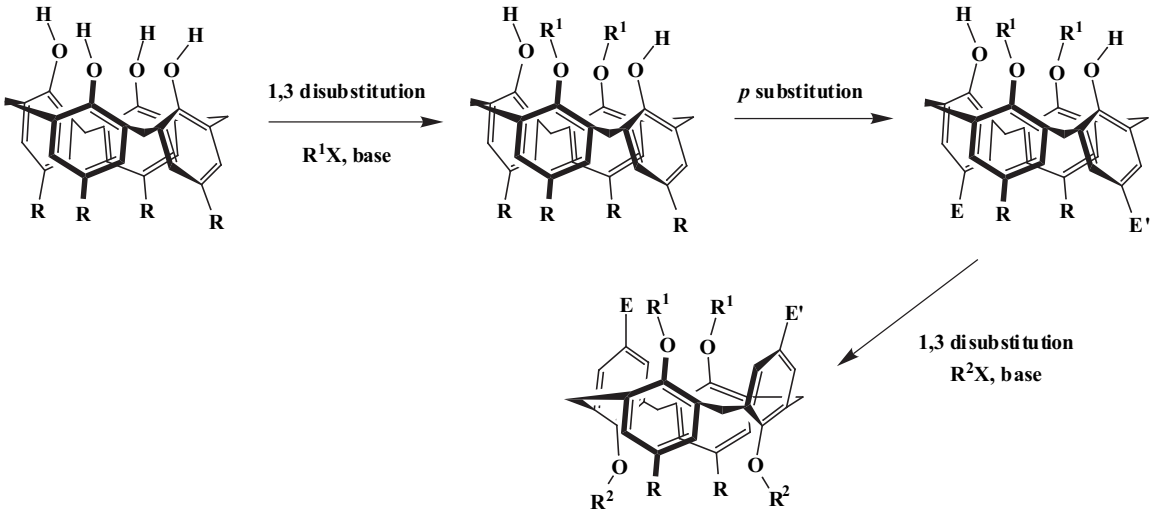


Fig. (2). Six types of 1,3-alternate calix[4]arenes (a)-(f) as described in the text.



Scheme 1. Synthesis of a type (a) 1,3-alternate calix[4]arene.

not adopt a 1,3-alternate conformation (and in fact rarely seem to do so), it is fortuitous that a final dialkylation of the residual *O*-sites, again with a large alkyl group, appears to be associated with a preference for this conformation (Scheme **1**).

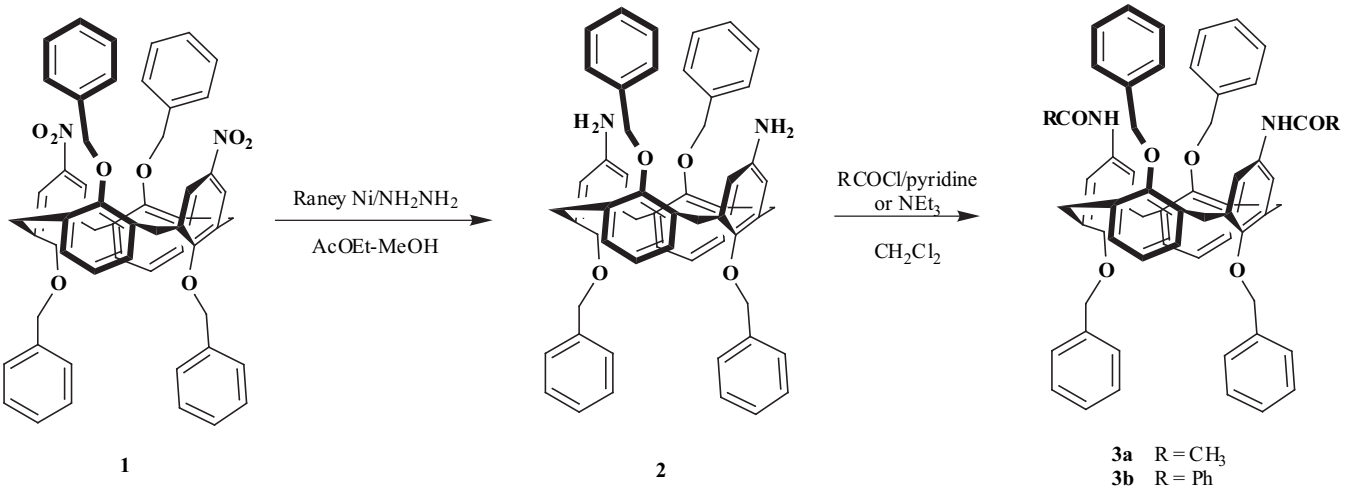
This synthetic strategy (Scheme **2**) was employed to synthesize 1,3-alternate dinitro-tetrakis(benzyloxy) calix[4] arene **1** [28] which can be further reduced to the 1,3-alternate diaminocalix[4]arene **2** and condensed to afford the calix[4]arenediamides **3a** and **3b** [29].

Similarly, 1,3-alternate bis[3-(4-oxo-1-hydropyrimidin-2-yl)ureido] calix[4]arenes **4a** and **4b** were prepared by passing through 1,3-alternate-5,17-dibromo-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene [27]. Preferential formation of dimers involving a *syn* rather than an *anti* arrangement of the H-bonded units was demonstrated by the use of ^{1}H NMR spectroscopy.

A related synthesis is that of the "fullerenocalix[4]arene" **5**, in which the [60]fullerene unit serves as a "lid" for the ionophoric cavity by bridging two p-substituents. In fact, the lid appears to obstruct metal binding in the cavity closer to the C_{60} unit, so that a so-called "exohedral metallofullerene" is formed more readily from the cone isomer **6** than from **5** [30].

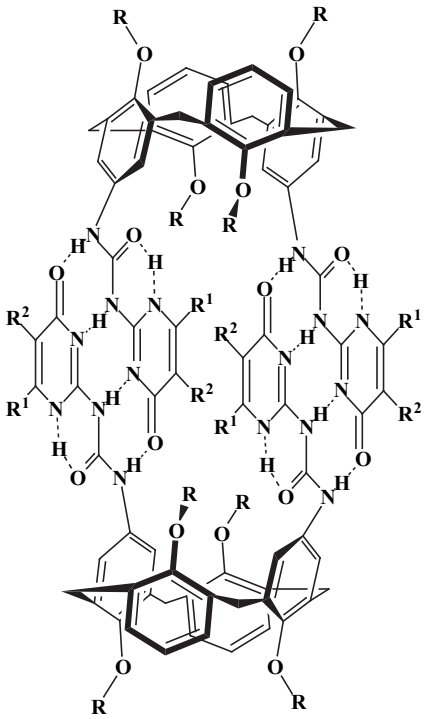
Of course, the chemistry used to vary the *p*-substituents, most commonly starting from the *p*-*t*-butyl species, can be applied to all four, both before [25] and after [24] phenolic-O alkylation. Strictly speaking, this does not produce a 1,3-alternate calix[4]arene of type (a), since the cavities are now equivalent, but many of the applications are similar. The 1,3-alternate tetrakis(3-phenylureido)calix[4]arene **7**, for example, was prepared by nitration of 1,3-alternate tetrapropoxycalix[4]arene followed by reduction and reaction with phenyl isocyanate. Intended for use as a ditopic anion host, **7** in fact appears to bind but one, indicating that the initial interaction changes the properties of the second cavity in such a way as to render it then inequivalent to the first. The binding properties of **7** are actually very similar to those of the 1,3-*bis*-*p*-(3-phenylureido)calix[4]arene in cone conformation, although, as a halide ion binder, it shows a better selectivity for chloride [24].

Though a receptor cannot bind an anion unassociated with a cation (or a cation unassociated with an anion), it can

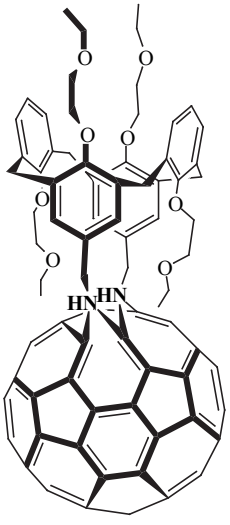


1 **2**

Scheme 2. Synthesis of **1-3**.



4a: R = $EtO(CH_2)_2$, R^1 = n-C_9H_{19}, R^2 = H
4b: R = $EtO(CH_2)_2$, R^1 - R^2 = $(CH_2)_4$



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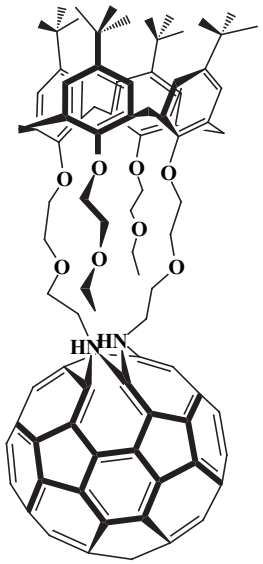

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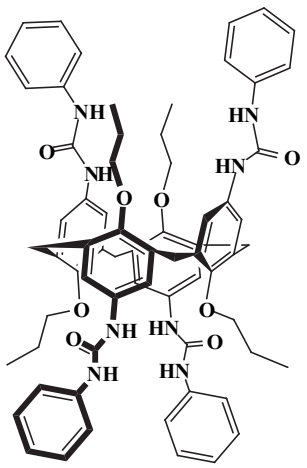
be designed to incorporate separate sites to bind particular cations and anions, *i.e.* to act as a selective ion-pair receptor. An example is provided in the 1,3-alternate calix[4]arene nucleic base derivatives **8a** and **8b** [25]. The water-stabilised dimer of the guanosine conjugate **8b** acts as an ion-pair receptor capable of extracting alkali halides into apolar solvents, showing modest selectivities for K^+ over Na^+ and Br^- over Cl^- [25].

TYPE (B) - OPEN CAVITIES RENDERED INEQUIVALENT BY DIFFERENT *O*-SUBSTITUENTS

Such calixarenes are obtained by two steps of 1,3-dialkylation. The dialkylated intermediate is conformationally labile and there is evidence that metal ion template effects are important in determining whether or not the final product has the 1,3-alternate conformation [31-37]. While almost any base can be used in the first step, the second



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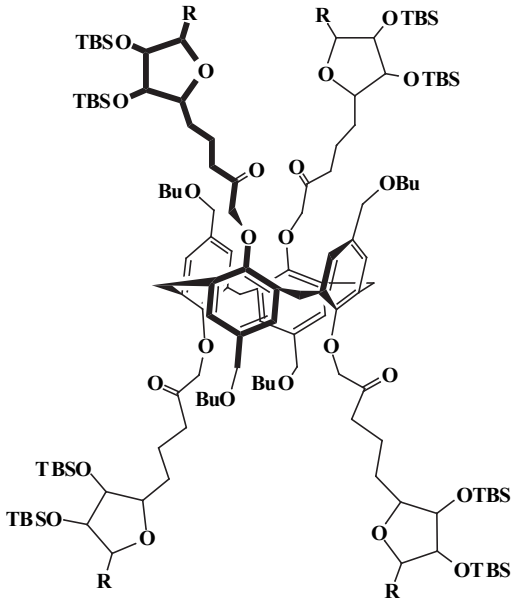
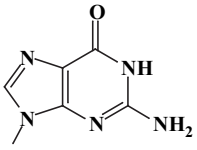
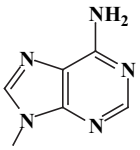


Bu = *n*-butyl
TBS = *tert*-butyldimethylsilyl

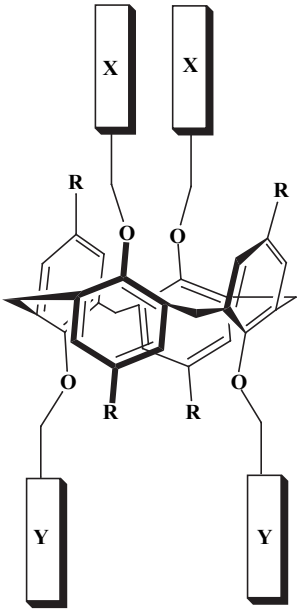
8a: R =



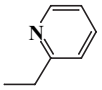
8b: R =



works best when potassium or caesium carbonates are used to promote reactions with alkyl halides or tosylates, and a highly selective synthesis of **9e**, for example, can be achieved using KH in THF [35].



9a R = Bu^t, X = CO_2Et, Y =



9b R = H, Bu^t, X = CO_2Me, Y = $(CH_2)_nCO_2Et$

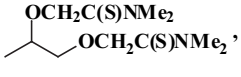
9c R = H, X = $C(O)NMe_2$, Y = Pr

9d R = H, X = $C(S)NMe_2$, Y = Pr

9e R = Bu^t, X = CO_2Me, Y = *n*-Bu

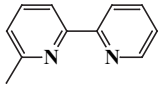
9f R = Bu^t, X = CO_2H, Y = *n*-Bu

9g R = H, X =



, Y = Pr

9h R = H, X =



, Y = Pr

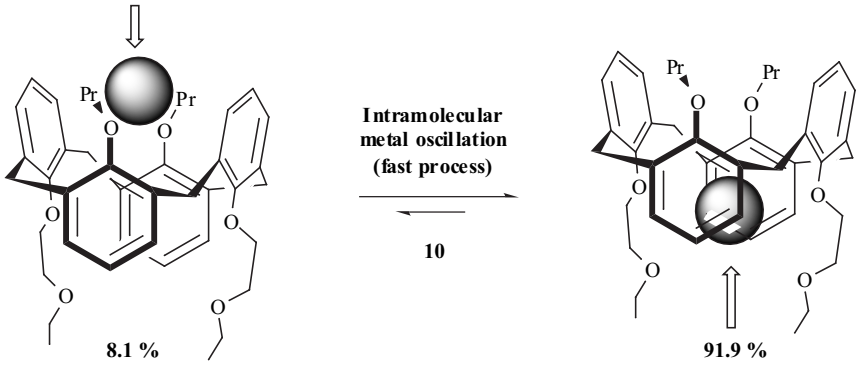


Fig. (3). Different proportions of Ag^{+} in the two different cavities of **10**.

When used as the sensor in a chemically-modified field-effect transistor (CHEMFET), the calix[4]arene *bis*-(thioamide) **9d** in the 1,3-alternate conformation engenders a higher selectivity for Pb(II) than does its cone isomer. The introduction of two thioamide units into each substituent, as in **9g**, produces a high selectivity for Cd(II) [36]. The molecule **9h**, with bipyridine units, forms complexes of high stability with both Co(II) and Cu(II). It has been suggested that the Co complex might have application as an oxygen carrier and that the Cu complex could function as an enzyme mimic in non-aqueous media. A interesting system where it has been possible to evaluate the preference of a metal ion for one of two inequivalent cavities is that of the Ag(I) complex of **10**. Low temperature dynamic NMR studies indicated that, at -82 °C, 91.9 % of the Ag(I) is located in the cavity defined by two $EtOCH_2CH_2O$ arms and two phenyl rings, with evidence being provided also that passage of the metal to the minor site occurs through the macrocyclic ring [38] (Fig. **3**).

Inclusion of small polyatomic molecules by calixarenes is well known and that of NO and NO^{+} has received

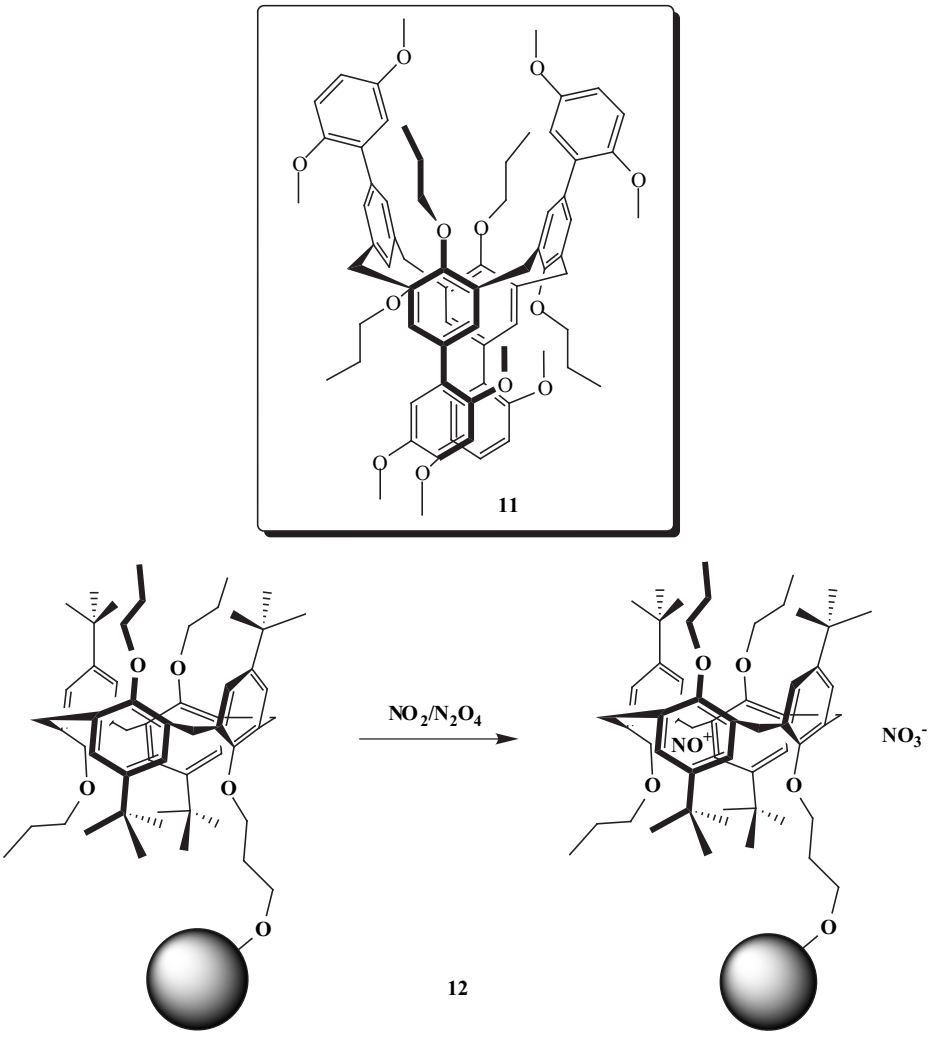
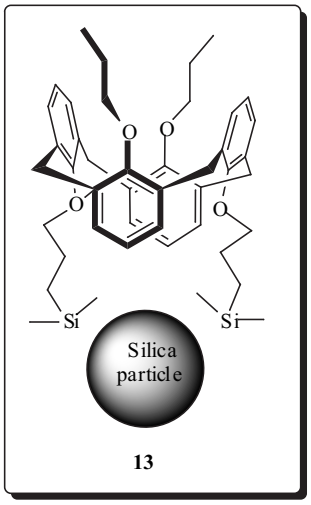


Fig. (4). Complexation of nitrosonium ion by the polymer-supported calix[4]arene **12**.

particular interest, in part because of its possible relevance to biological transport of these species [39]. The 1,3-alternate calix[4]arene **11** bearing 2,5-dimethoxybenzene units as *p*-substituents can be used to generate a stable cation radical **11+** useful as a colorimetric sensor for NO. The bright green colour of the radical changes to dark blue in the presence of NO (formally as a result of a redox reaction generating NO^+) and the crystal structure of the adduct shows a single guest molecule trapped inside the calixarene [39] between two distal phenyl rings, as previously observed for NO complexes of all conformers of a simpler calix[4]arene.



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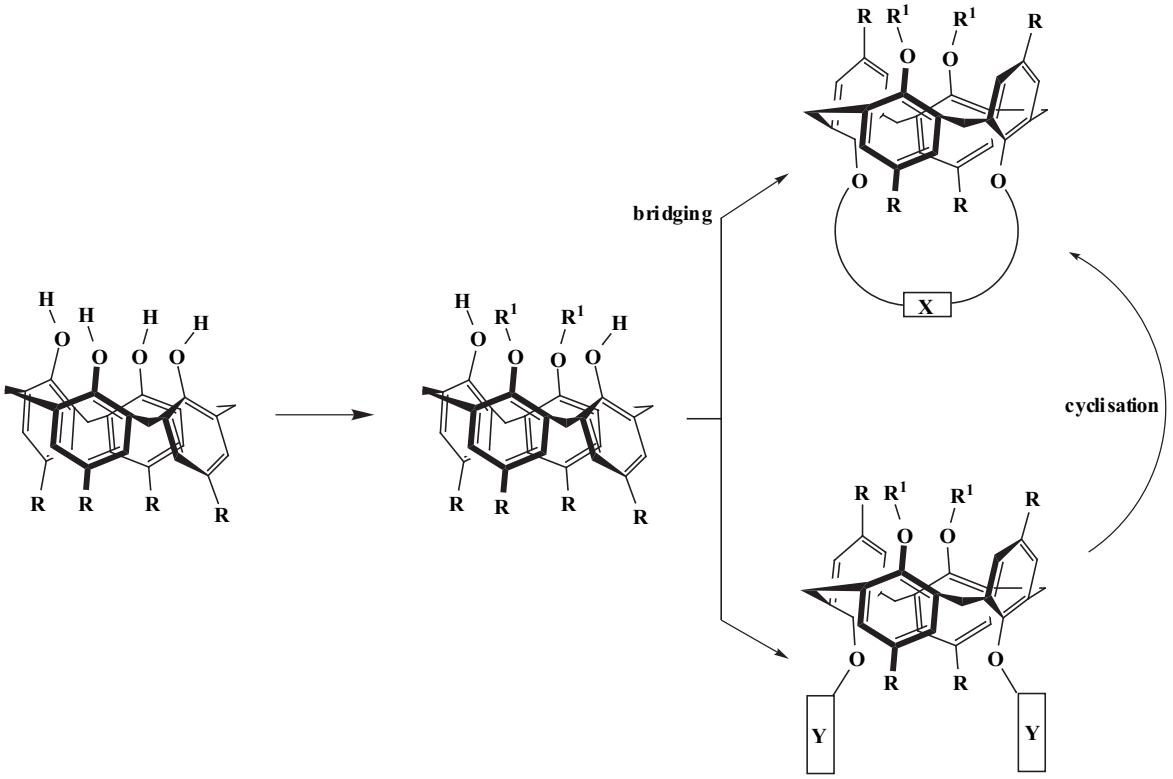
The polymer-immobilised 1,3-alternate calix[4]arene **12** (Fig. **4**) also shows a dramatic colour change on exposure to NO_2/N_2O_4 mixtures (which effectively act as NO^+ NO_3^-). The remarkably high stability shown by these NO adducts has led to the suggestion that they might be used as convenient sources of NO^+ for organic syntheses [40].

Another example of the versatility of 1,3-alternate calix[4]arenes is the use of 1,3-alternate 25,27-dipropoxy-26,28-*bis*[3-propyloxy]-calix[4]arene **13** bound to silica as a stationary phase for HPLC separation of di- and trisubstituted aromatics such as aminobenzhydrazides, hydroxypyridines and nitroanilines. It provides a reverse-phase system where binding and inclusion through hydrophobic interactions, hydrogen-bodning and π-π-interactions may all play a role [41].

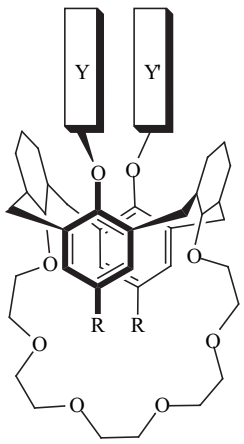
TYPE (C) - INEQUIVALENT CAVITIES DUE TO THE BRIDGING OF ONE PAIR OF OXYGEN ATOMS

Formation of a bridge betwee one pair of oxygen atoms is the simplest synthetic pathway to unsymmetrical 1,3-alternate calix[4]arenes. These derivatives are useful because the open cavity allows kinetically labile inclusion while the "closed" cavity can engender binding selectivity. Their synthesis usually involves creation first of the open cavity, then of the closed, either by direct bridging using a difunctional reagent or by cyclisation of reactive substituents introduced in a preliminary alkylation (Scheme **3**).

Where the bridge formed involves a polyether chain, the "calixcrowns" produced have been widely studied as ion-selective receptors. The conformationally labile 1,3-dimethoxy-*p*-*t*-butylcalix[4]arene-crown-6 shows a high selectivity for Cs(I) and a determination of the crystal



Scheme 3. Synthetic pathways to open- and closed- cavity 1,3-alternate calix[4]arenes.



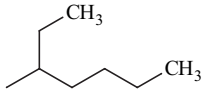
14a R = H; Y , Y ' = Pr

14b R = H;Y , Y ' = *i*Pr

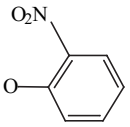
14c R = H;Y , Y ' = *n*Oct

14d R = H; Y , Y ' = $nC_{11}H_{23}$

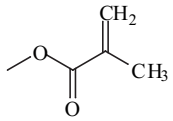
14e R = H; Y , Y ' =



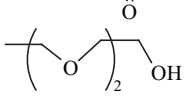
14f R = H;Y , Y ' = $(CH_2)_8O$



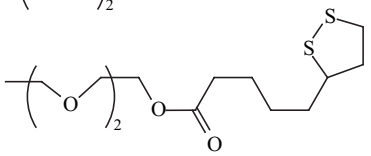
14g R = H; Y = Pr, Y ' =



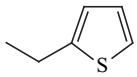
14h R = Bu^t; Y , Y ' =



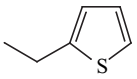
14i R = Bu^t; Y , Y ' =



14j R = H; Y = Me, Y ' =



14k R = H; Y = Bn, Y ' =



structure of the caesium picrate complex shows the ligand to be in the 1,3-alternate conformation [42,43]. To test the importance of this conformation, many conformationally fixed 1,3-alternate calix[4]crowns, *e.g.* **14a-j**, have been synthesised, mainly by direct bridging [42,44-50].

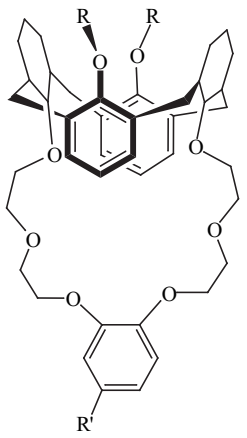
The high extraction efficiency and selectivity for caesium over sodium shown by the calixcrowns **14a-c** have been attributed to the low polarity of the 1,3-alternate array, the size of the crown bridge and the optimisation of cation-π interactions for Cs(I) [9,42]. Cation-π interactions involving Na(I), K(I), Rb(I) and Cs(I) appear to be important influences upon the photophysical properties of calixcrowns [51]. The high Cs selectivities of 1,3-alternate calix[4]crown-6 ligands and the high lipophilicity of the complexes, coupled nonetheless to an ease of stripping of bound Cs(I), has generated great interest in the use of such ligands in treatment of radioactive waste using the supported liquid membrane technique [42,49,52]. Cs sensors have also been based on the exploitation of such properties. Attachment of the 1,3-alternate calix[4]crown-6 **14g** to a polysiloxane, for example, provides durable CHEMFET membranes without loss of either sensitivity or selectivity for Cs(I) [45]. Self-assembled monolayers (SAMs) formed by 1,3-alternate *bis*(thioctic ester)-*p*-*tert*-butylcalix[4]crown-6 **14i** on a gold electrode surface have been shown by electrochemical methods to recognise Cs(I), while this property is indetectable for SAMs composed of the cone isomer. Conducting polythiophenes generated form thiophenyl derivatives **14j** and **14k** of 1,3-alternate calix[4]crowns have been shown to be selective electrochemical sensors for various alkali metal ions depending on the crown size [46].

The replacement of ethylene by phenylene links in the crown ring of a 1,3-alternate calixcrown-6 results in a significant improvement in the Cs/Na selectivity of extraction from radioactive waste [53,54]. The selectivity coefficients of both the mono-benzocrowns **15a-f** [55-58] and the dibenzocrowns **16a,b** [59,60] are higher than those of analogous simple calix[4]arene-crown-6 ligands, though a crystal structure determination indicates that this is not to be associated with any cation-π interactions involving the benzo units [59].

In order to enhance the release of cesium ion after complexation, primary amino groups were introduced onto the benzocrown ether loop (**15b**) or onto the open cavity (**15c**). Although the amino groups of both **15b** and **15c** did not enhance the extraction of cesium in alkaline solution, their protonated forms permitted a remarkable pH-switched back-extraction [58]. Other pH-dependent systems result when an *N*-anthracenyl-azacrown ether substituent is introduced as in **15e**. Emission from the anthracenyl group is influenced by interactions of the N atom with protons or metal ions, so that **15e** acts as a fluorescent sensor for Cs(I) in acid solutions and for K(I) in alkaline solutions [55]. With a cyano group in place of the aza-crown, as in **15f**, luminescence is retained along with improvements in both Cs/K and Cs/Na selectivities, and such molecules represent a new class of Cs-selective optical sensors [56,57]. Although *ab initio* calculations had justified the prediction of improved properties on replacing the central ethylene link of **16b** by a propylene unit [61], in practice this led to weaker complexation and poorer Cs(I) selectivity.

Recent molecular mechanics calculations led to the conclusion that the dehydroxylated 1,3-alternate calix[4]crown analogues **17a-f** should exhibit enhanced affinity for K(I) and Cs(I). In fact, the Cs/K selectivity is improved by this structural change, possibly because of unusually short Cs(I) interactions with the benzo-link oxygen atoms [62]. Variations on the crown loop , as in the chiral, binaphthyl substituted calixcrown **18**, produce other useful Cs extractants, though the molecule was designed for extractive resolution of chiral ammonium ions [63]. Selectivity for K(I) is readily engendered by decreasing the size of the crown loop, as in the calix[4]crown-5 ligands **19a-c** [45,64.65].

Grafting of the 1,3-alternate calix[4]arene-crown-5 **19b** directly to the membrane of a CHEMFET produced sensors of greater durability and greater resistance to leaching by aqueous solutions than those derived from **19a** [45]. The

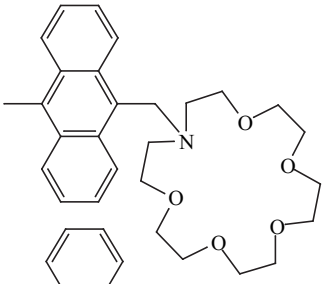


15a R = *n*-C_8H_{17}, R' = H

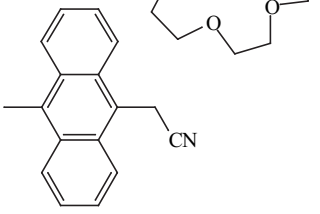
15b R = *n*-C_8H_{17}, R' = CH_2NH_2

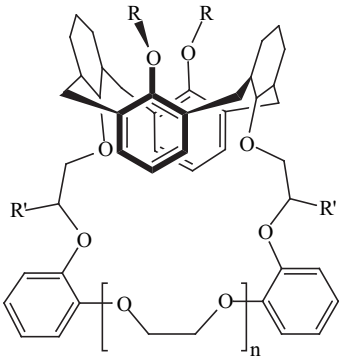
15c R = $(CH_2)_3NH_2$, R' = $CH(CH_2CH_3)(CH_2)_3CH_3$

15e R = *i*-C_3H_7, R' =



15f R =  , R' =





16a n = 0, R = *n*-C_3H_7, R' = H

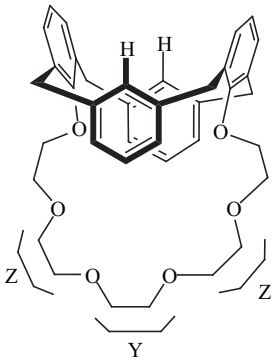
16b n = 1, R = *n*-C_3H_7, R' = H

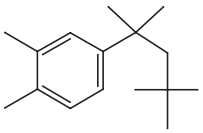
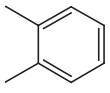
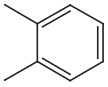
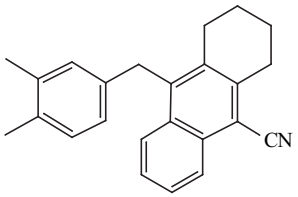
16c n = 1, R = *n*-C_3H_7, R' = C_4H_9

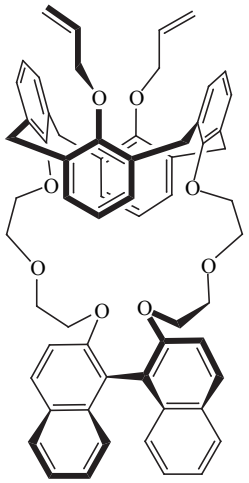
16d n = 1, R = *n*-C_8H_{17}, R' = H

16e n = 1, R = *n*-C_8H_{17}, R' = C_4H_9

16f n = 2, R = *n*-C_3H_7, R' = H



	Y	Z
17a	CH_2CH_2	CH_2CH_2
17b		CH_2CH_2
17c		CH_2CH_2
17e	CH_2CH_2	
17f		CH_2CH_2



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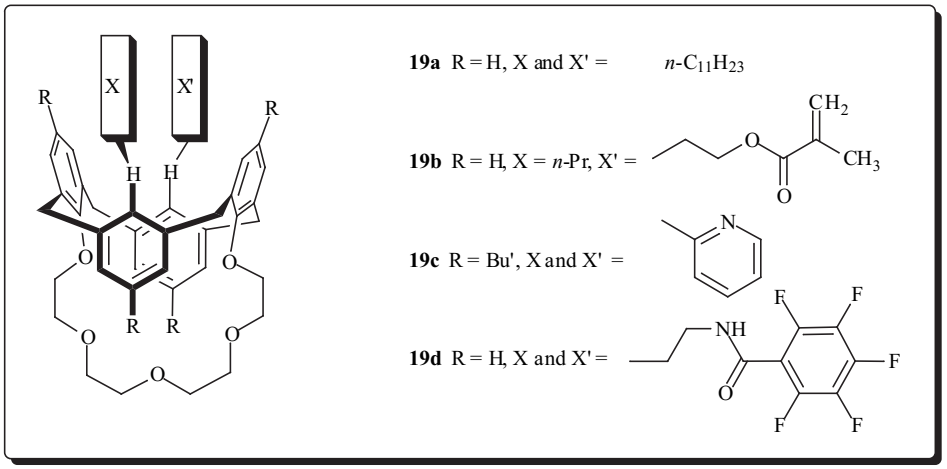
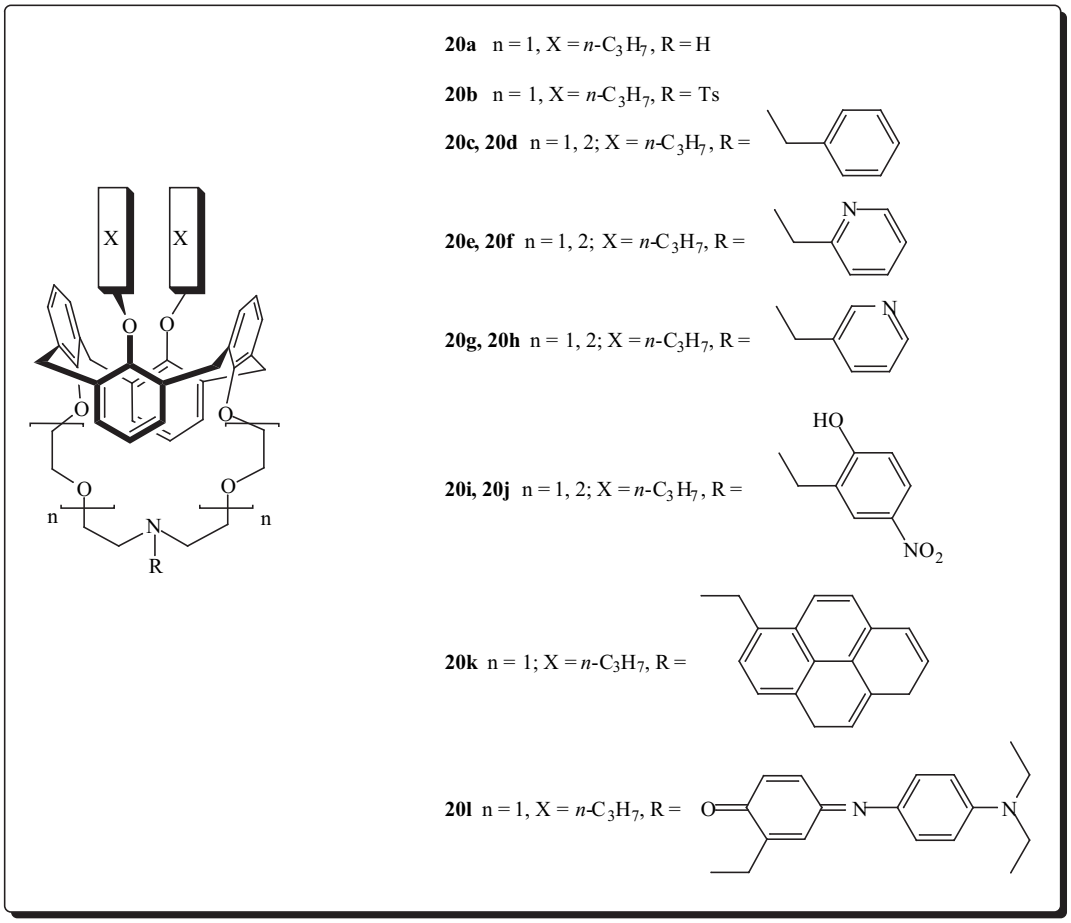


introduction of picolyl substituents in **19c** produced K(I) sensors of sensitivity comparable to or even better than that of valinomycin [64]. By adding pentafluorobenzamide groups as anion binders to the 1,3-alternate calix[4]arene crown-5, the resulting heteroditopic receptor **19d** accommodated both a cation and an anion simultaneously. Its assembly into a 2:2:2 (calixarene:potassium:acetate) complex was shown by an X-ray crystal structure determination [66].

Using symmetrical azapolyetherdiol tosylates as the alkylating agent after preliminary 1,3-dialkylation of a calix[4]arene, 1,3-alternate calix[4]azacrown species **20a-j** [67-72] and **21** [20] can be obtained. These have served variously as selective extractants for K(I) [60], ionophores for transition-metal-selective polymer-membrane electrodes [70], a fluoroionophore (**20k**) showing marked chelation-enhanced fluorescence effects for Cu(II), K(I), Rb(I) and Pb(II) [71], and a chromoionophore (**20l**) for M(II) species, in particular, Zn(II) [72].

This 1,3-alternate calix[4]arene aza crown ether topology has been used to design a "molecular syringe" **21** [20]. Addition of acid to the 1:1 Ag(I)/**21** complex, where the metal is bound within the azacrown loop, results in *N*-protonation and rejection of the metal, apparently by passage



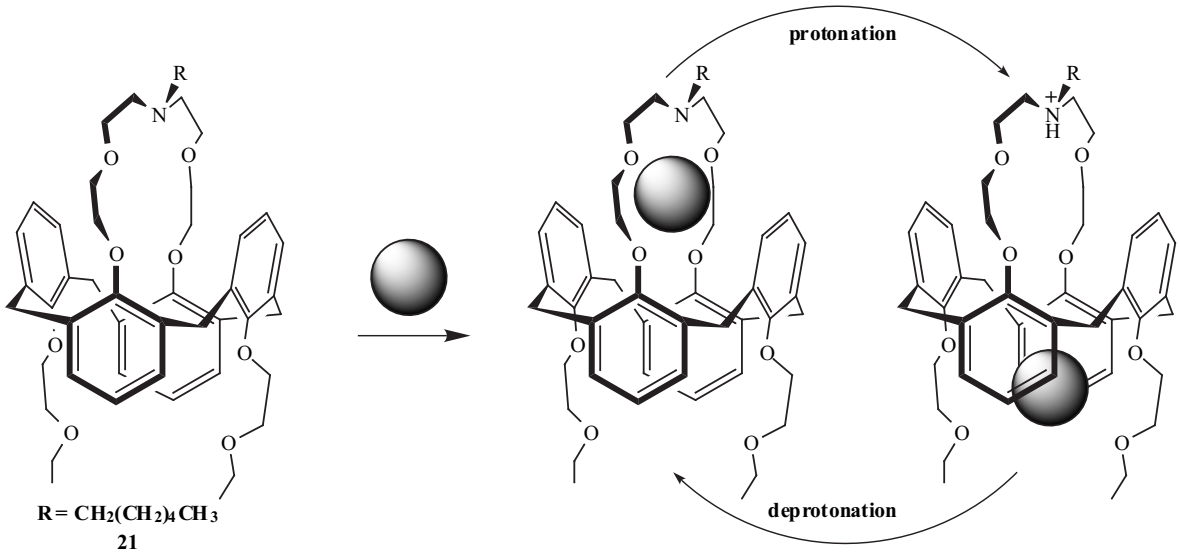
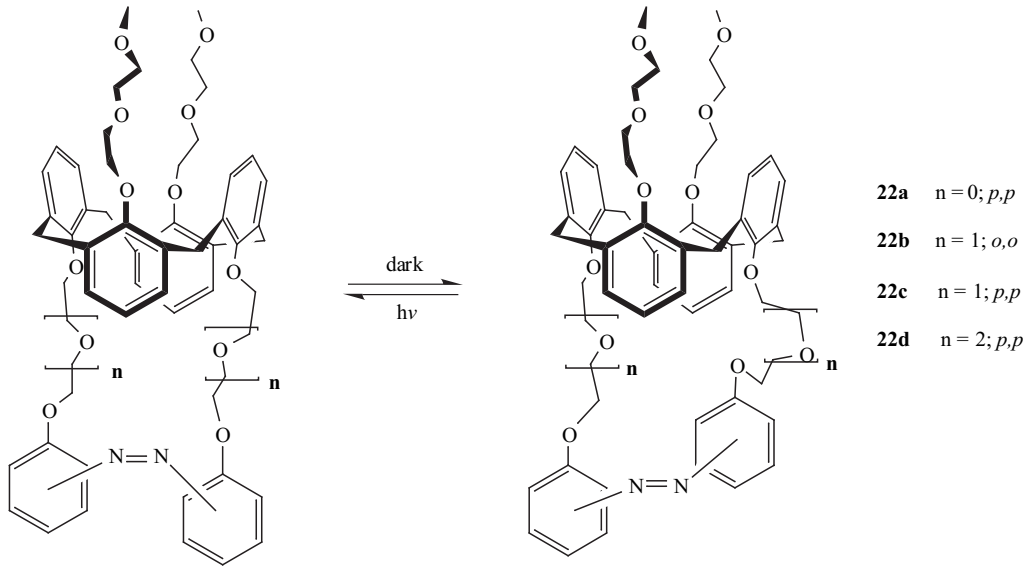
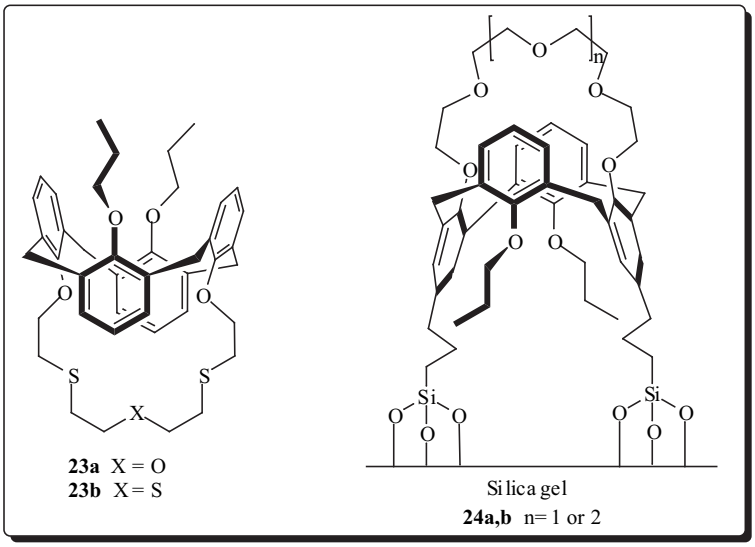


Fig. (5). Action of the "molecular syringe" **21** derived from a 1,3-alternate calix[4]arene azacrown.

through the "π-base tube" of the calixarene ring, into the *bis*(ethoxyethoxy) cavity. These reversible motions mimic, at the molecular level, the functions of a syringe [20] (Fig. **5**).



Scheme 4. Photoisomerisation of receptors **22**.

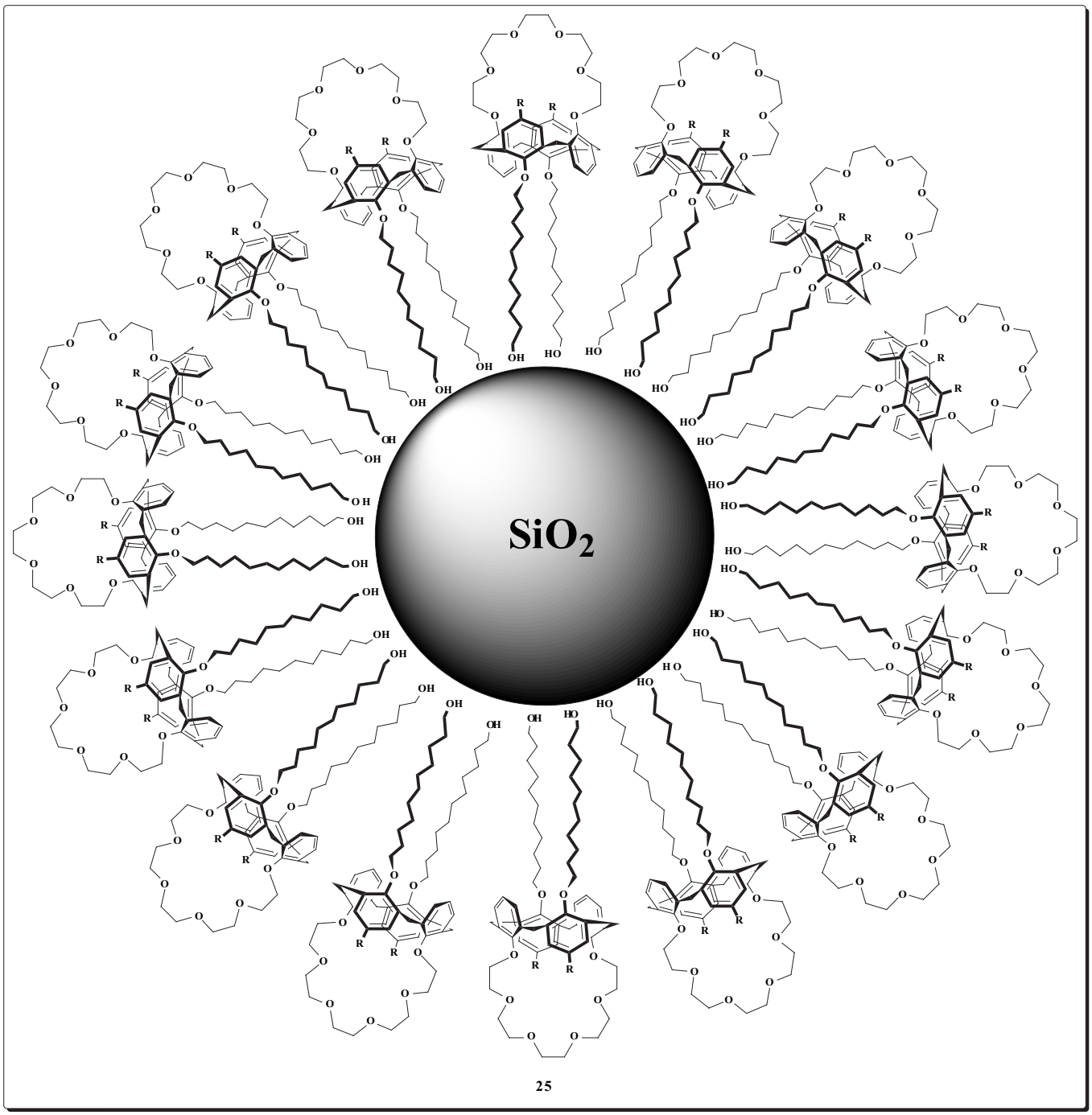


Another series of 1,3-alternate azocalix[4]crowns **22a-c** was synthesized in order to study the influence of binding of alkali metal ions on photoisomerisation about the azo unit [73,74]. In the case of **22b**, for example, alkali metal ion (Na, K, Rb and Cs) binding completely inhibits thermally induced isomerisation, while photoisomerisation results in different equilibrium E:Z ratios in each case. For transport of Rb and Cs through supported liquid membranes, the Z-isomer proved inferior to the E (Scheme **4**) [73,74].

Replacement of some ether oxygen atoms by sulfur, as in **23a,b**, produces 1,3-alternate calix[4]thiacrowns showing a high selectivity for Ag(I). This has been attributed to strong Ag-S coordination being assisted by Ag(I)-π interactions [75].

Surface-immobilised 1,3-alternate calix[4]crowns **24**, grafted *via* hydrosilylation reactions onto silica, are useful for the chromatographic separation of K(I) and Cs(I) form other alkali metal ions [76]. Attachment of 1,3-*bis*[1-(11-hydroxyundecyl)oxy]calix[4]crown-6 to colloidal silica particles produces the colloidal receptor **25**, shown by both NMR spectroscopy and electrophoresis to bind Cs(I) [77].

More recently, self-assembled monolayers of 1,3-alternate *bis*(7-thiatridecyloxy)calix[4]crown-5 on gold were prepared for use in an ion selective electrode [78]. Cyclic voltammetry provided evidence of complexation of K(I) and Ba(II) but not of Li(I), Na(I), Cs(I), Mg(II) or Ca(II).



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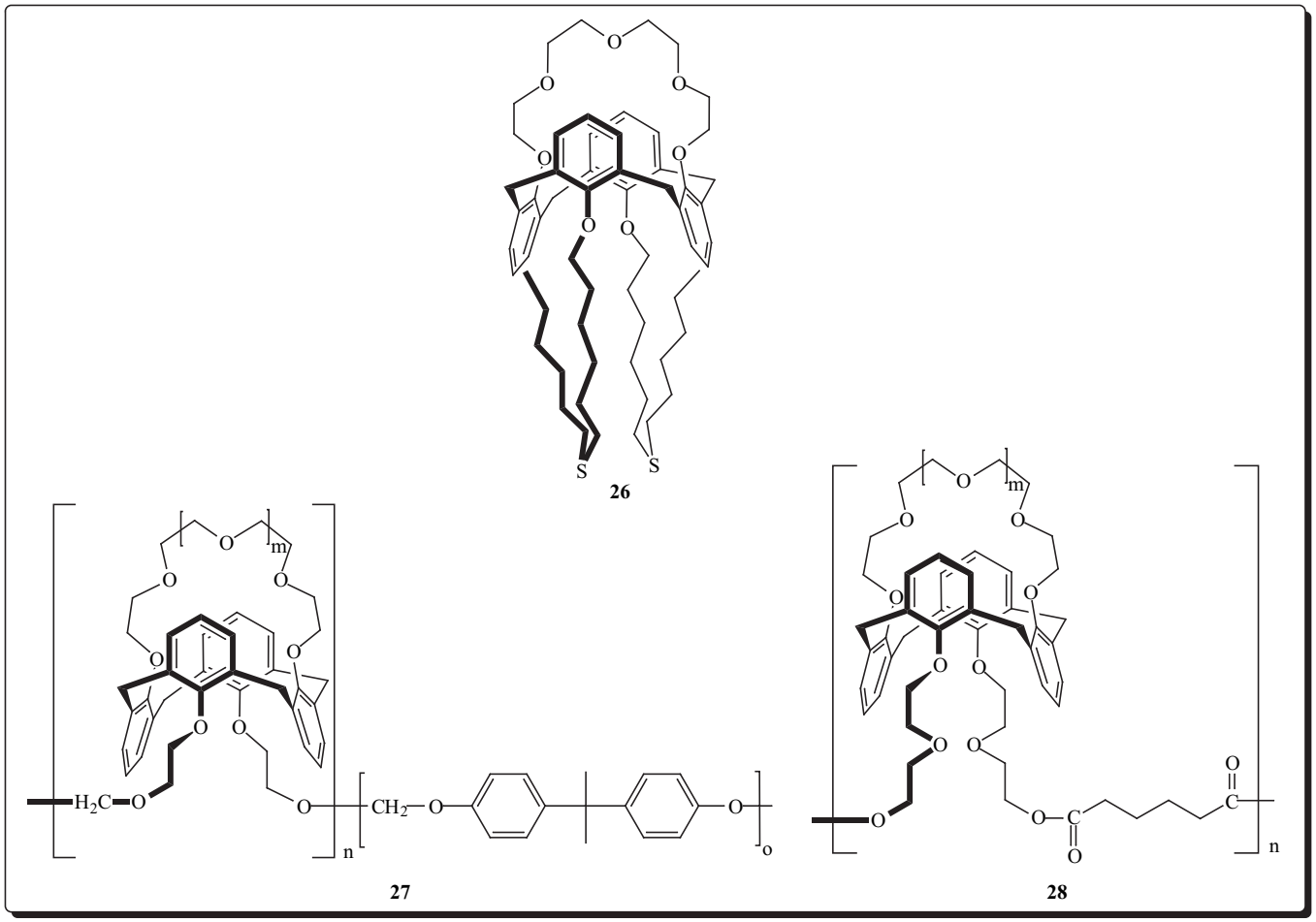
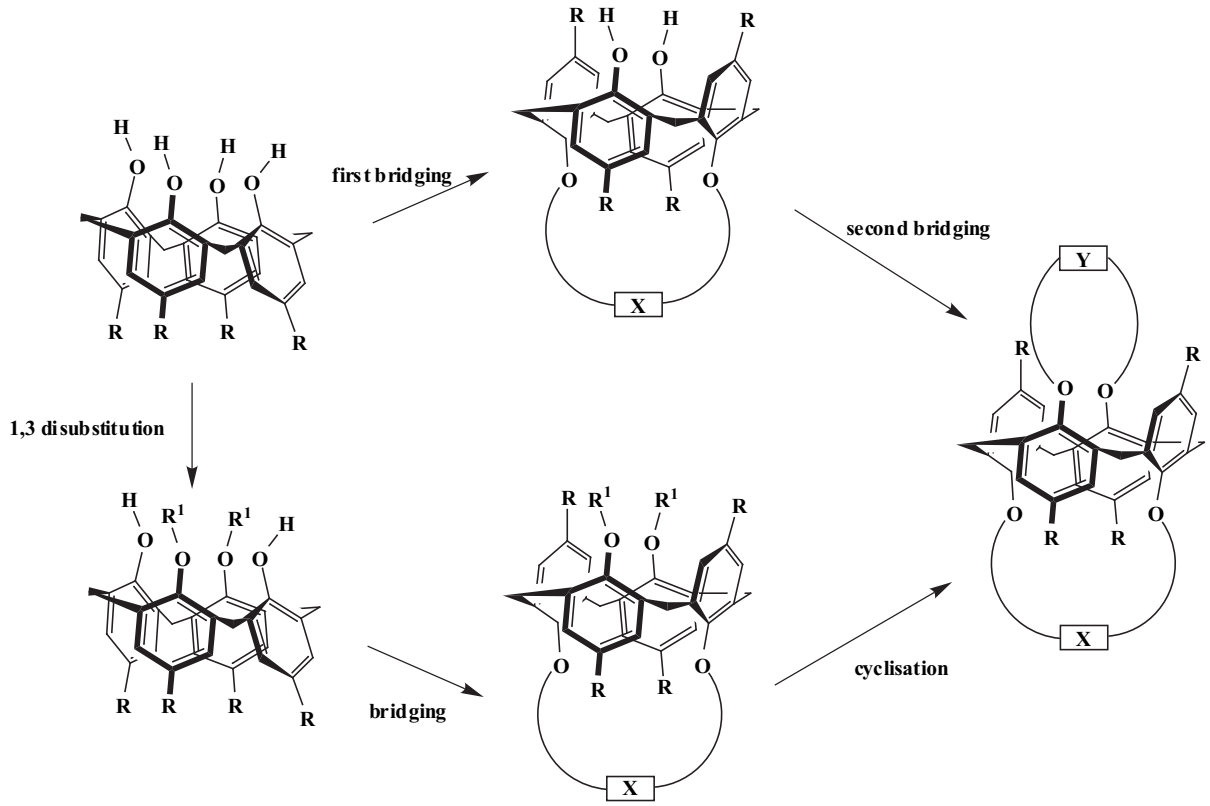


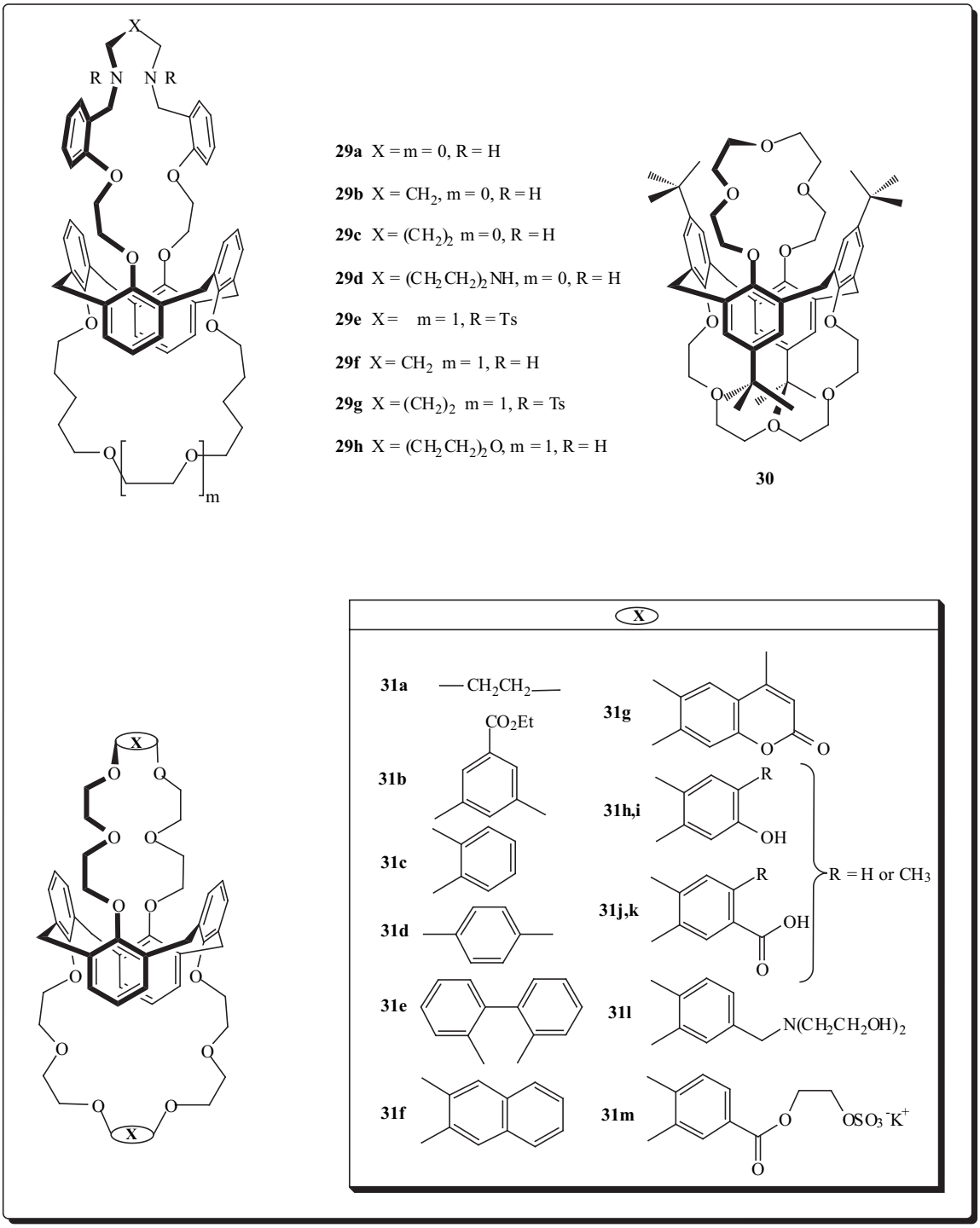


Scheme 5. Synthetic pathways to asymmetric closed cavity 1,3-alternate calix[4]arenes.

Calix[4]arene-based polymers have been prepared in order to exploit the advantages of solid-liquid over liquid-liquid extraction processes. Copolymerisation of 1,3-alternate *bis*(hydroxypropyl)calix[4]crowns with *bis*phenol-A with various bridging agents, for example, provides the polyethers **27** and **28** [79]. These materials proved to be too low in solubility for studies of their ionophoric capacities to be made. In contrast, 1,3-alternate calix[4]-crown polyesters **29** and **30** were soluble in both hexane and ethyl acetate, enabling both liquid-liquid and solid-liquid extractions of alkali and alkaline earth picrate salts to be performed. The 1,3-alternate calix[4]-crown-5 polyester **29** showed high selectivity to potassium ion with ~79 % extraction for liquid-liquid extraction and ~28 % for solid-liquid while the calix[4]-crown-5 polyester preferred cesium ion with ~52 % extraction for liquid-liquid extraction and ~36 % for solid-liquid one [80].

TYPE (D) - DOUBLY-BRIDGED 1,3-ALTERNATE CALIX[4]ARENES

This 1,3-alternate calix[4]arene architecture consists of two identical or different closed cavities on each side of the calix[4]arene framework. With unsymmetrical bridging, the



two cavities can differ in size, shape and/or type of donor atoms, providing opportunities for sophisticated variations in selectivity and stability.

Symmetric doubly-bridged 1,3-alternate calix[4]arenes can easily be prepared by a two-step, one-pot reaction [81]. In contrast, unsymmetrical bridging can be achieved in two ways, as shown in Scheme **5**. The first pathway consists of two bridging steps while the other involves three steps: 1,3-disubstitution, bridging and cyclization.

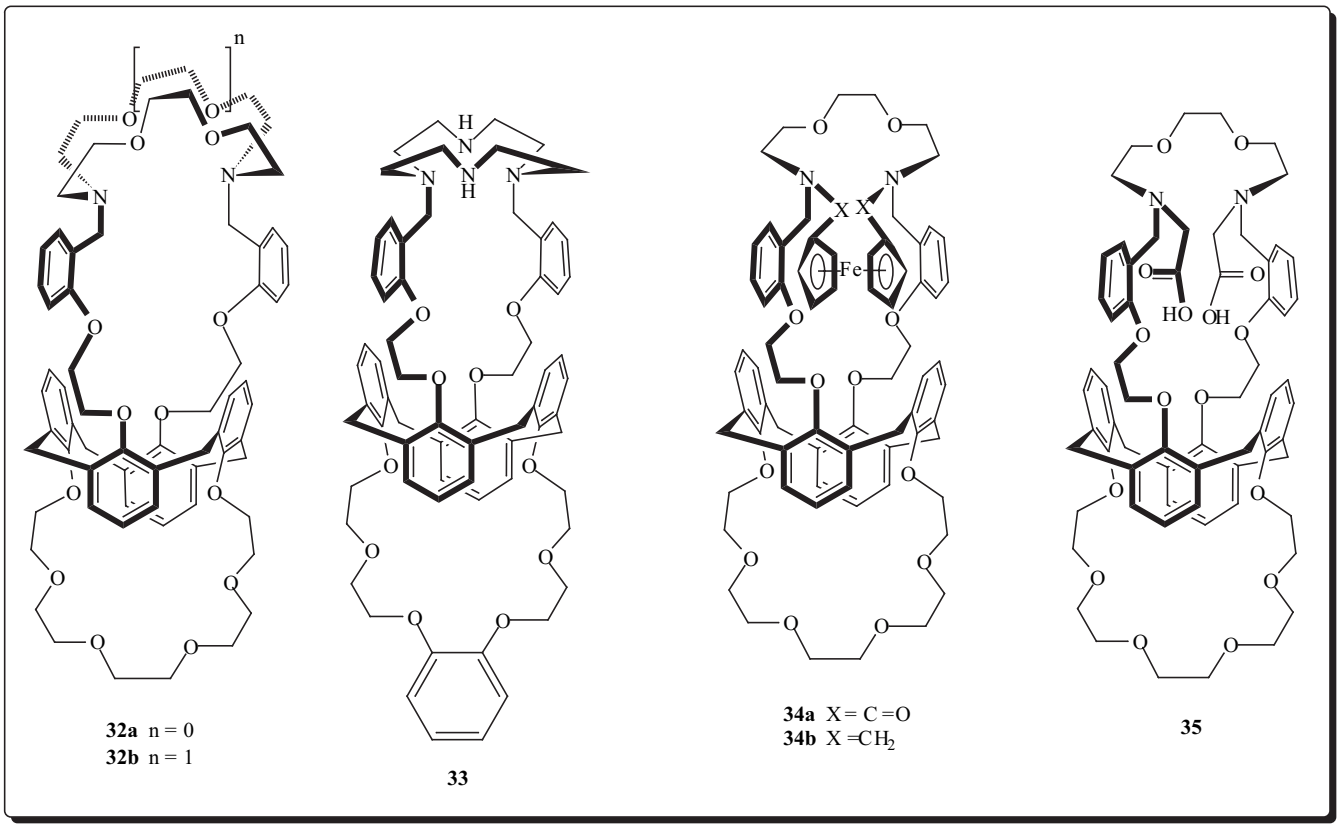
The sequence of construction of the bridges can be important for the synthesis of this class of 1,3-alternate calix[4]arenes. It was demonstrated that, in the synthesis of **29f**, the first bridging by a less flexible chain gave a better yield than bridging with a more flexible chain [82,83].

The first symmetrical double bridged 1,3-alternate calix[4]arene reported was 1,3-*p*-*tert*-butylcalix[4]-bis-crown-5 **30** [84]. Because these 1,3-alternate crowns can serve as extractants in treatment of nuclear waste containing radioactive ^{137}Cs ion, a series of 1,3-alternate calix[4]arene crown ethers **31a-g** [85-87] was synthesized and used as selective carriers in supported liquid membranes (SLM). Compounds **31c** and **31f** showed high SML stabilities and high decontamination yields [85]. Recently, 1,3-alternate calix[4]arene crown ethers **31f** were employed in the complexation and transportation of francium ion for the synthesis of radiopharmaceuticals [88]. By incorporation of coumarin as a fluorophore into the crown of 1,3-alternate calix[4]arene-crown-6, a fluorescent molecular sensor **31g** was prepared which exhibited an excellent selectivity for cesium ion over sodium ion. This calix[4]coumarin derivative showed only a moderate selectivity for potassium ion over sodium ion but was considered still quite promising for analytical biochemistry, *i.e.* for detection of potassium ion in blood and urine which contain high concentrations of sodium ions [87]. As noted above for singly-bridged 1,3-alternate calix[4]crowns, there is evidence that metal ions bound to the crown can pass through the "π-base tunnel" formed by the calixarene ring, and in the case of doubly-bridged calixarenes, a corresponding cation oscillation from one cavity to the other may occur [89,90].

The introduction of polar groups, such as hydroxy, carboxy, diethanolamino or sulfonato units on benzo-ether units provided water-soluble 1,3-alternate calix[4]-bis(benzocrown-6) ligands **31h-31m**. The binding efficiencies of these hydrosoluble receptors determined by UV spectrophotometry revealed that every ligand showed significant affinity for the alkali-metal cations. A nanofiltration-complexation study also demonstrated that receptors **31i**, **31l** and **31m** showed high Cs^+/Na^+ selectivity and allowed an efficient separation of trace cesium from a moderately concentrated salt medium [91].

The different cavities of unsymmetrical doubly-bridged 1,3-alternate calix[4]arene can be tailored to suit different metal ions, whether they are "hard" or "soft" or simply different in size [82,83,92]. Developing on the syntheses of relatively simple examples such as **29a-h**, many sophisticated 1,3-alternate calix[4]arenes **32-35** have been synthesized [17,18,83,93-95].

The 1,3-alternate calix[4]arene-cryptand-crown-6 ligands, **32a** and **32b**, for example, were intended to provide stronger coordination sites than simple crowns, and complexation studies have demonstrated that **32b** can accommodate Na^+, K^+, NH_4^+ and Rb^+ in the cryptand cavity whereas Rb^+ and Cs^+ resided in the crown-6 cavity. Moreover, $(Na^+,Cs^+)^{\bullet}$



32a n = 0
32b n = 1

33

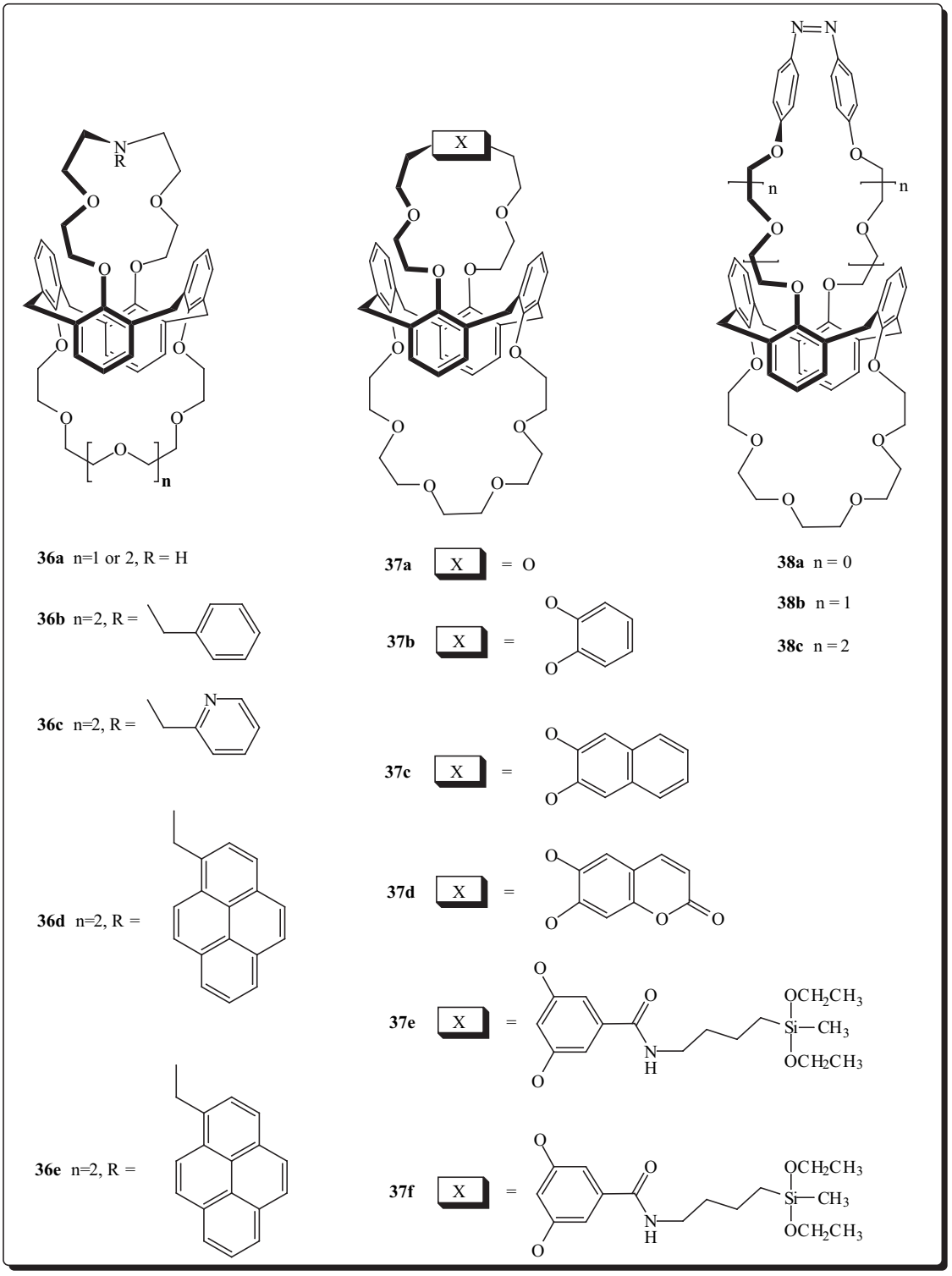
34a X = C =O
34b X =CH_2

35

32b and $(K^+,Cs^+)^{\bullet}$ **32b** heterodinuclear complexes were prepared [83]. As a "hard-soft" receptor, **32b** showed complexation abilities with Ni^{2+} and Zn^{2+} as well as with Cs^+ [96]. In the NH_4^+ complex, the NH_4^+ cation can travel from the cryptand cavity to the crown ether one by passing through a π-base 1,3-alternate calix[4]arene channel with an exchange velocity (k_c) of 169 s^{-1} and activation Gibbs energy ($\Delta G_c^{\#}$) 12 kcal mol^{-1} [83]. This is the first evidence of cation oscillation for an unsymmetrical-bridge-cavity 1,3-alternate calix[4]arene.

To enhance the affinity of a Cs(I) calixarene for transition metal ions, the 1,3-alternate calix[4]arene-cyclen-benzo-crown-6 **33** was synthesized [93]. Its cyclen unit can accommodate transition ions such as Zn^{2+} as well as some organic hydrogen bond donors, for example, phenol, aniline, catechol, resorcinol, hydroquinone and terephthalic acid, while the benzocrown moiety shows retention of its ability to complex Cs^+ [93].

With the intention to find molecular sensors and/or catalysts, a redox-active centre, ferrocene, was incorporated

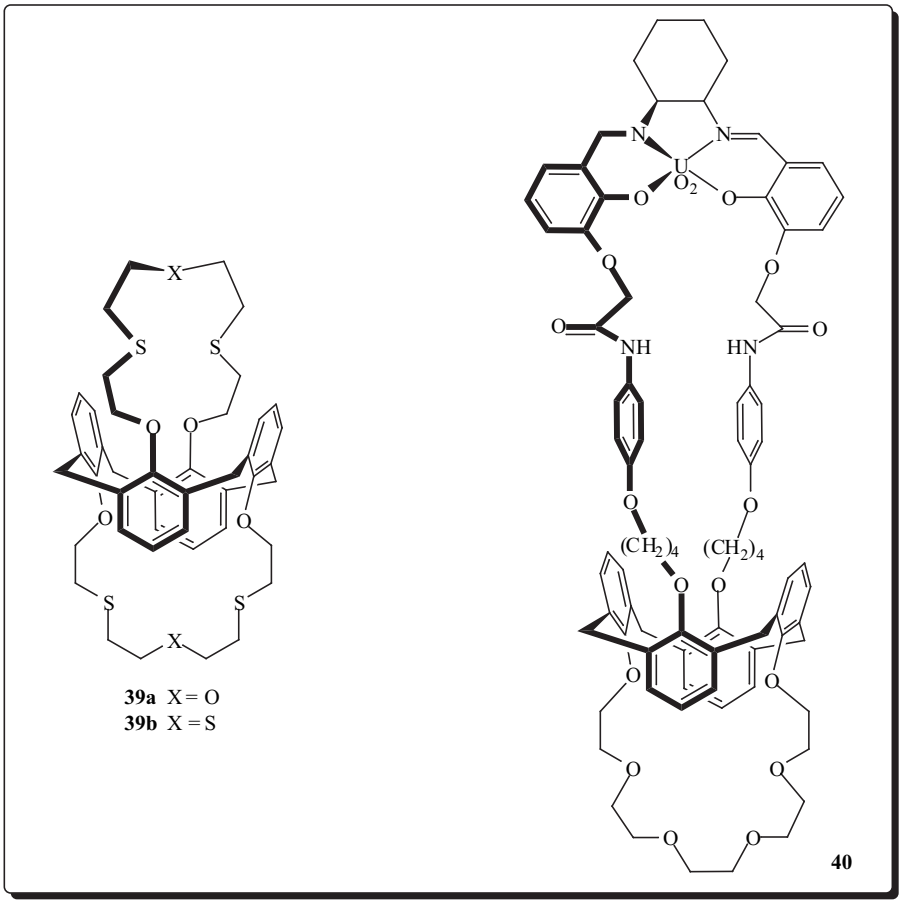


into the 1,3-alternate calix[4]arene framework [94]. Complexation properties of these two redox-active calixarenes **34a** and **34b** towards alkali and alkaline earth metal cations were studied by cyclic voltammetry. **34a** and **34b** were shown to possess *quasi*-reversible redox properties [94].

By incorporating ionizable moieties into the 1,3-alternate calix[4]arene skeleton, calix[4]arene-amino acid-crown-6 **35** was synthesized and studied for its complexation of alkali, alkaline earth, heavy and transition metal ions as well as some lanthanide ions by pH-metry and UV spectrophotometry. The results suggested that alkali metal ions were located only near the glycolic chain, and the other cations in the crown unit bearing the amino acid moieties. Essentially, the two crown units behave independently and the ligand is capable of binding two cations of different nature (e.g. alkali and transition metals ions) simultaneously [95]. The effect of nitrogen donor atoms in enhancing the binding ability was evaluated by a comparison of complexation of 1,3-alternate calix[4]azacrown-5 **36a** and 1,3-alternate calix[4]-biscrown-5. The results led to the conclusion that the replacement of the central *O* atom by an NH group in the crown ether cavity provided better binding [97]. Potassium ion-selective electrodes based on **36a** and its *N*-benzyl derivative were prepared, the electrode containing the latter calix[4]arene derivative exhibiting near Nernstian response for K(I) over a wide concentration range (1×10^{-5} to 1×10^{-1} M) with a limit of detection of 2×10^{-6} M. Although it responded to K^+ better than **30a** and the 1,3-alternate calix[4]-azacrowns-5, it, however, showed a poorer response rather than that of 1,3-alternate dipropyl calix[4]-crown-5 [98]. Studies of Ag(I) exchange with the complexes of **36a** and its corresponding symmetrical 1,3-alternate calix[4]-bisazacrown-5 provided evidence for intramolecular metal ion tunneling in the latter but not the former [99].

Substituents on nitrogen, such as the picolyl groups in **36c** and **36d**, appear to participate in Ag(I) complexation while a benzyl group (**36b**) does not [100]. When a fluorescent moiety, pyrene, was attached to the nitrogen atom, "molecular Taekwondo" processes, where one metal binds in a cavity and thus causes displacement of another metal bound in the other, were easily monitored, *via* fluorescence change, between Ag^+-K^+, Cu^{2+}-K^+ and Ag^+-Cs^+ pairs [71]. Similar phenomena involving Cu^{2+}-Cs^+ and Ag^+-Cs^+ pairs were also observed with 1,3-alternate calix[4]-cyanoanthracenylcrown-azacrown [101].

Unsymmetrical 1,3-alternate calixbiscrowns, calix[4] crown-A-crown-B, such as **37a-f**, are well known [87,102-107]. Both homobinuclear (dipotassium) and heterobinuclear (potassium:caesium) complexes of the calix[4]-crown-5-crown-6 ligand **37a** have been prepared [102]. While potassium can occupy either cavity, caesium can occupy only the crown-6 site, as confirmed by a crystal structure determination [103]. The introduction of 1,2-phenylene (**37b**) or naphthylene-2,3-diyl (**37c**) groups into the crown-6 cavities improved the Cs^+/Na^+ selectivities [104]. The ^1H NMR spectra and X-ray crystal structures of their cesium complexes showed that cesium ion preferred to be



complexed in the polyether loop containing aromatic units [104]. The coumarin unit (**37d**) also increased the Cs^+/Na^+ (4.0×10^4) and K^+/Na^+ (540) selectivities [87]. In order to reduce the loss of calix[4]arene crown-6 in the removal of cesium from high-sodium liquid wastes, 1,3-alternate calix[4]arenes **37e** and **37f** were prepared and grafted onto a polysiloxane backbone by a sol-gel process [105]. From solid-liquid extraction studies, it was found that the performance, efficiency and selectivity decreased compared with liquid-liquid extraction. This was ascribed to steric hindrance, cavity deformation and micro-environmental polarity resulting from the grafting of the carrier [105].

Allosteric systems based on 1,3-alternate calix[4]arenes were designed and synthesized by incorporating an azobenzene unit into the crown ether loop of **38a-c** [106, 107]. In the case of **38b**, preliminary complexation studies of alkali and ammonium cations showed that these cations are located in the unmodified crown-6 cavity of 1:1 complexes. The complexation can also induce changes in the *cis*/*trans* ratio of the azobenzene unit due to subtle conformational changes of the 1,3-alternate calix[4]arene platform [106]. X-ray crystallography provided evidence, for **38a** and its cesium complex, of reorganization prior to complexation [107].

With sulfur atoms integrated into the crown ether bridges, the 1,3-alternate calix[4]-bisthiacrown **3 9 a-b** exhibited very high selectivities for silver ion over alkali and other transition metal ions. However, these selectivities were much less than those of their monocrown analogues [75].

In order to complex simultaneously both a cation and an anion, 1,3-alternate uranylcalix[4]arene-salophen-crown-6 **40** was synthesized and used to study the transportation of CsCl and $CsNO_3$ from an aqueous phase to acetonitrile across supported liquid membranes (SLMs) [108].

TYPE (E) - DOUBLY-BRIDGED 1,3-ALTERNATE CALIX[4]ARENES RENDERED UNSYMMETRICAL BY DIFFERENT P-SUBSTITUENTS

This molecular structure can be prepared starting from symmetrically doubly-bridged 1,3-alternate calix[4]arenes. Many substituents, bromo [109, 110], nitro [111], carboxylic [109,110], aldehyde [110] and hydroxy groups [111], can be selectively introduced at the *para*-positions of benzene rings of the 1,3-alternate calix[4]arene framework to provide desired properties. The bromo derivatives **41a** and **41k** are very useful for the introduction of other functional groups [109,110].

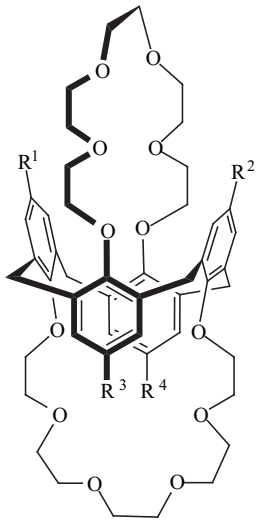
Proton-ionizable calix[4]arenes, **41c**, **41h** and **41i** have been studied to determine their affinity for alkali metal cations and their cesium-sodium selectivity. It was found that all 1,3-alternate calix[4]arene-crown-6 ligands containing ionizable groups at *para*-positions possessed higher Cs^+ extraction efficiencies than the conventional 1,3-alternate calix[4]arene-crown-6 [109,110]. The dihydroxycalix[4]arene-biscrown-6 **41i** exhibited a higher Cs^+/Na^+ selectivity than the dicarboxylate **41h** but lower than the tetrahydroxycalix [4]arene-biscrown-6 **41l** [110].

The participation in Cs^+ complexation of the nitro group in the mononitro ligand **41b** was observed but the tetranitro derivative **41m** did not extract cesium ions [111].

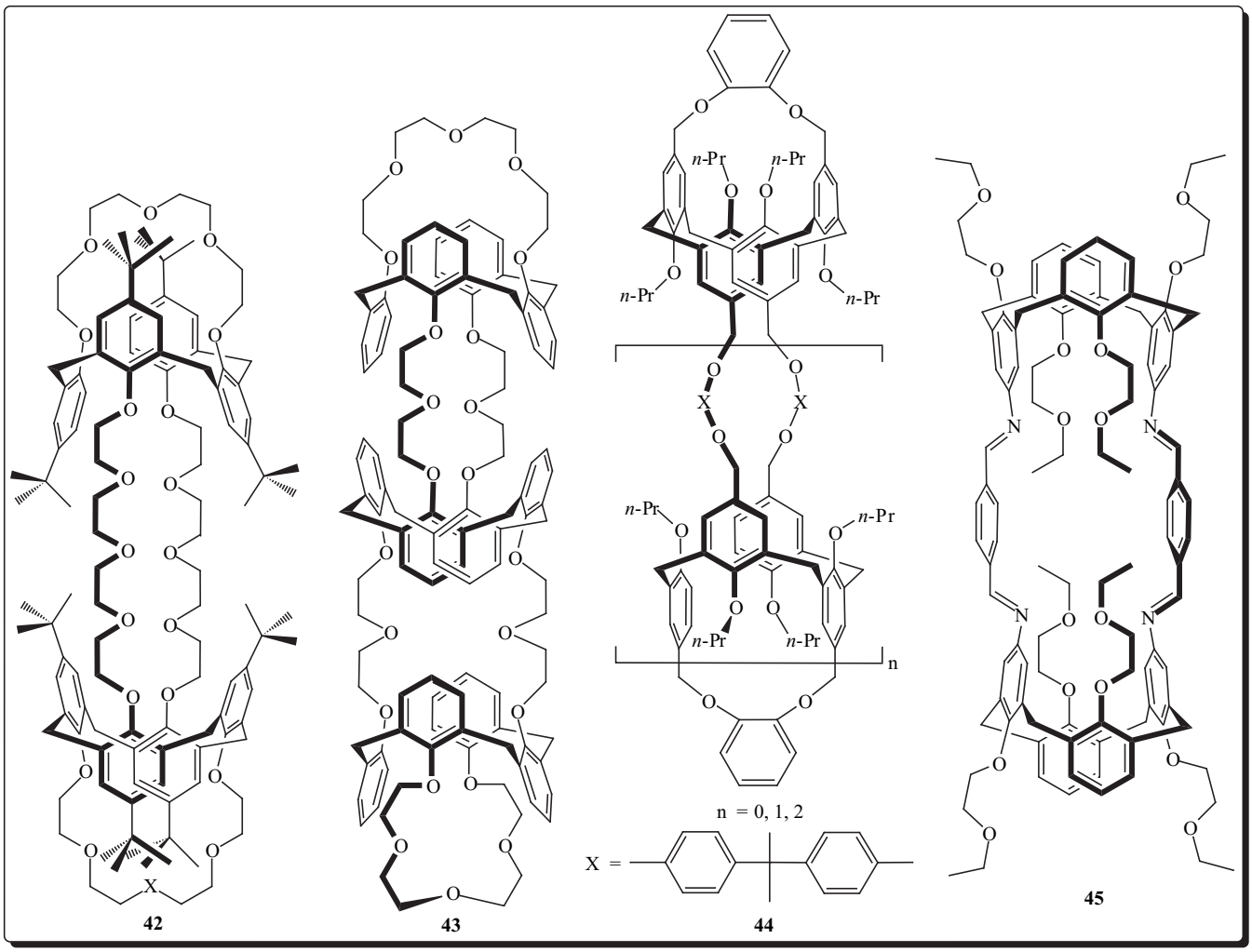
TYPE (F) - MULTI-1,3-ALTERNATE CALIX[4] ARENES: AN APPROACH TO CALIX[4]ARENE NANOTUBES

By linking 1,3-alternate calix[4]arene frameworks together at the phenoxy group or *para*-positions, calix[4]arene nanotubes have been prepared. A double 1,3-alternate calix[4]arene **42** was first prepared in 1992 [112]. From complexation studies, it was found that K^+ and Rb^+ reside only in the central crown ether cavity of **42** but not in crown-5 loops at the extremities due to the steric hindrance of the *tert*-butyl groups [112]. Analogous debutylated dimers were synthesized and their complexation studies proved, by X-ray investigation of crystal structures, that the alkali ions are preferably located in two extreme cavities [113]. Furthermore, the corresponding trimer **43a** and pentamer **43b** were also prepared and were found to form homodinuclear complexes as with the dimers [113].

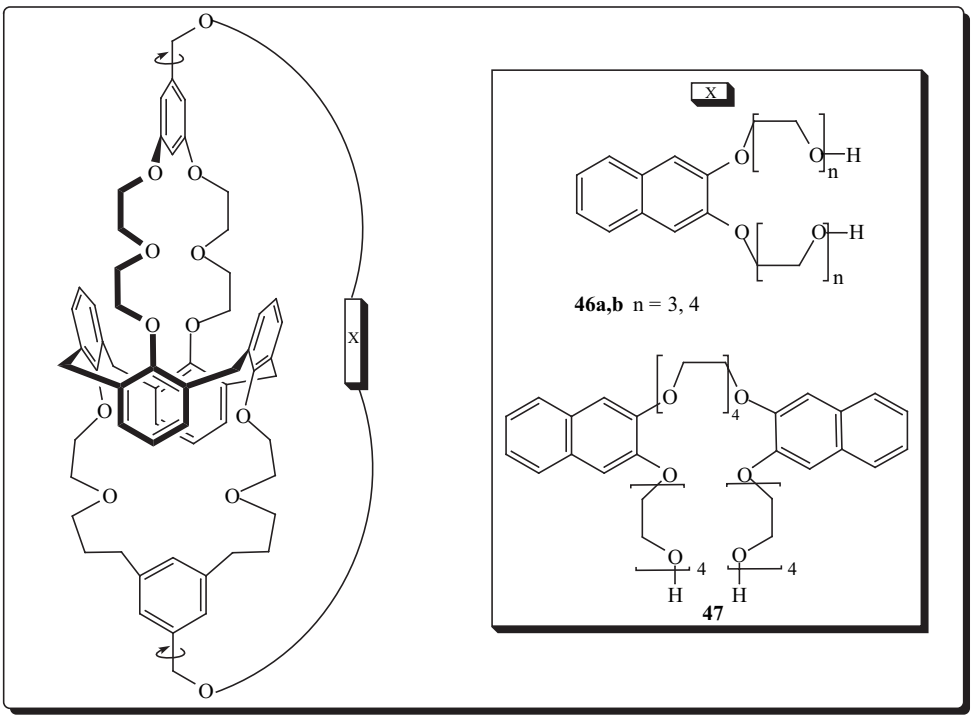
The calix[4]arene nanotube **44** containing three 1,3-alternate calix[4]arene units was prepared but no metal (Ag^+)



	R^1	R^2	R^3	R^4
41a	H	H	H	Br
41b	H	H	H	NO_2
41c	H	H	H	CO_2H
41d	H	H	H	$CONHSO_2CF_3$
41e	H	NO_2	H	NO_2
41f	H	H	NO_2	NO_2
41g	H	H	CHO	CHO
41h	H	H	CO_2H	CO_2H
41i	H	H	OH	OH
41j	H	NO_2	NO_2	NO_2
41k	Br	Br	Br	Br
41l	OH	OH	OH	OH
41m	NO_2	NO_2	NO_2	NO_2



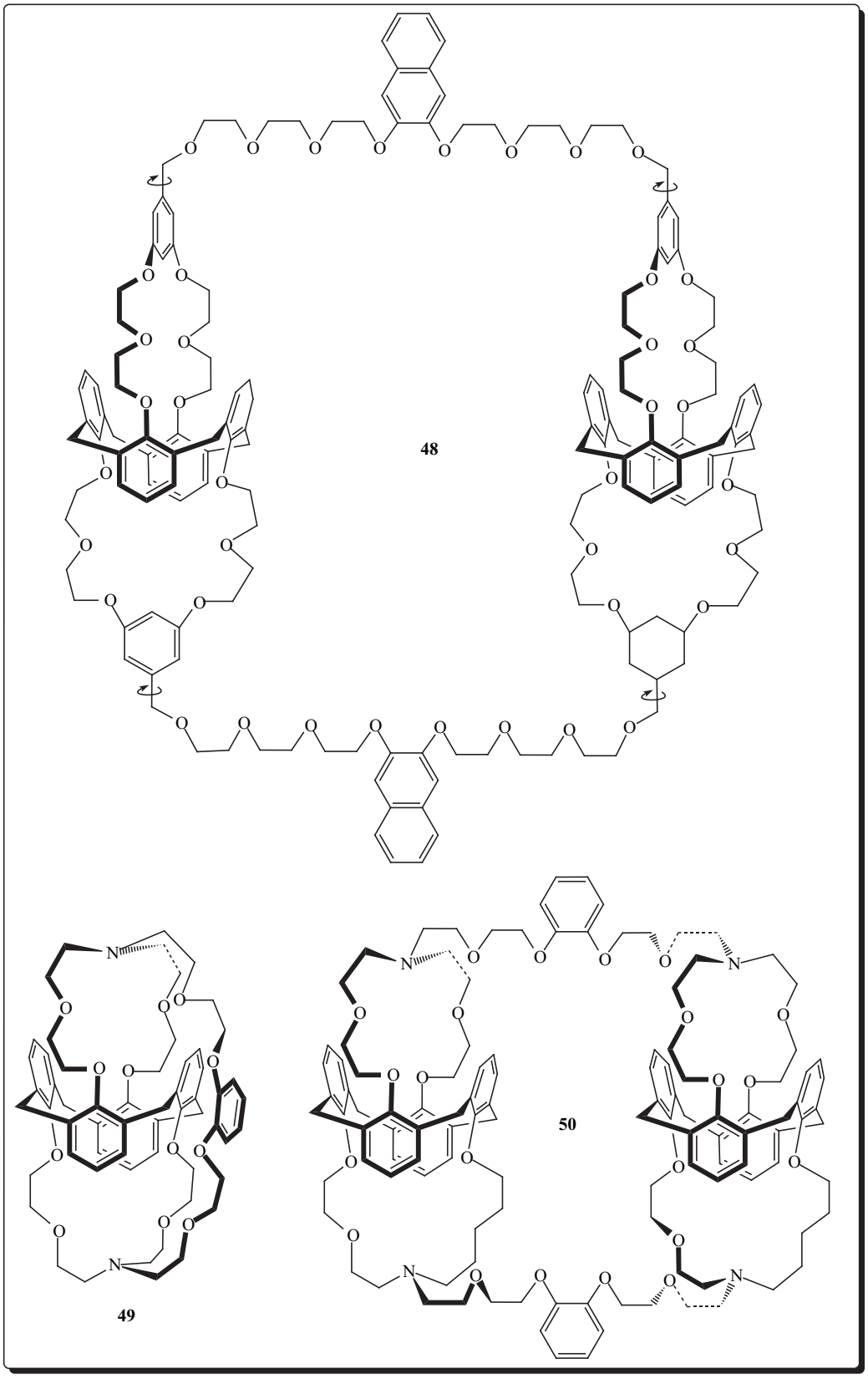
oscillation in the 1,3-alternate calix[4]arene tunnel of the silver complex was observed [114]. While this may indicate that there is possibly hindrance to a metal ion traversing longer tubes, the open tubular configuration of a multi-1,3-

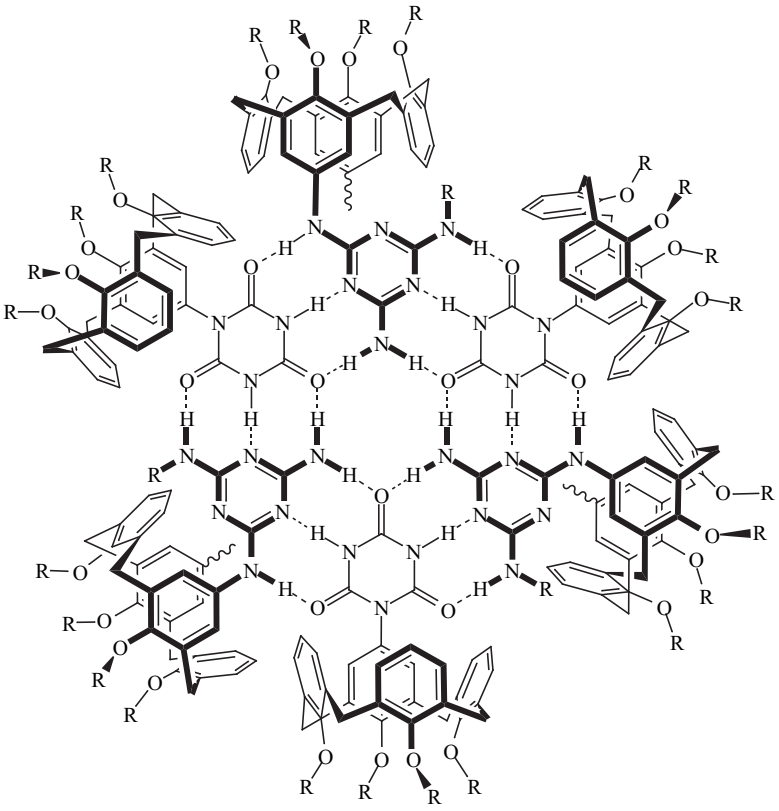


alternate calix[4]arene was confirmed by the X-ray crystal structure of double calix[4]arene **45**. This nanotube possessed a cross-section of 12 Å and a length of 28 Å. Its inside diameter varied between 4.1-4.5 Å and the two terephthaloyl units were parallel and separated by 3.3-3.9 Å [115].

STRAPPED 1,3-ALTERNATE CALIX[4]-*BIS*-CROWNS: AN APPROACH TO CALIX[4]ARENE MOTORS

Various efforts have been made to prepare "molecular machines" based on 1,3-alternate calix[4]crowns [12-14]. The





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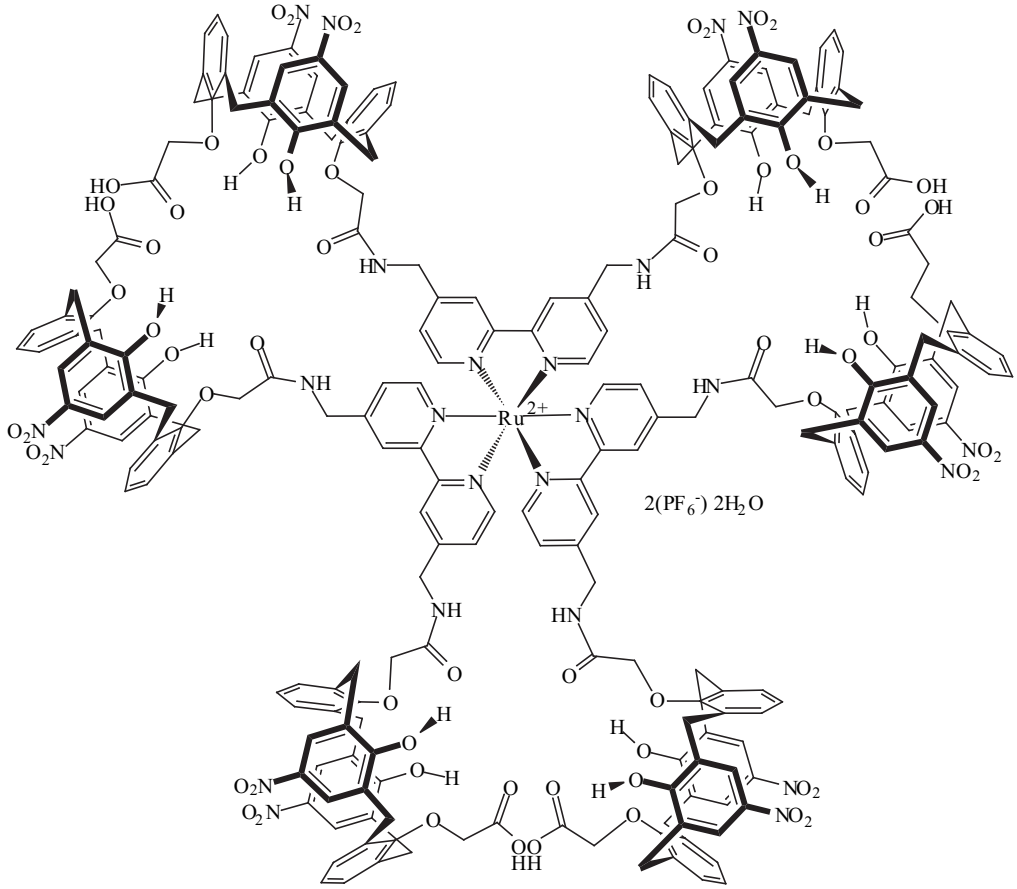

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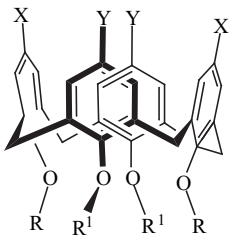
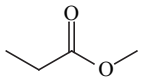
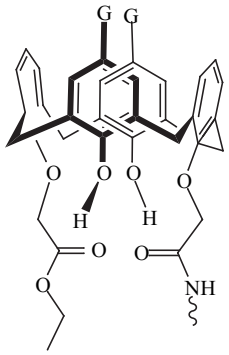
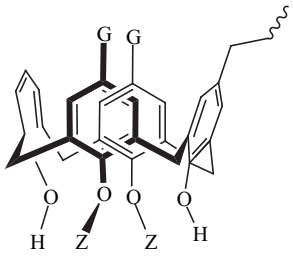
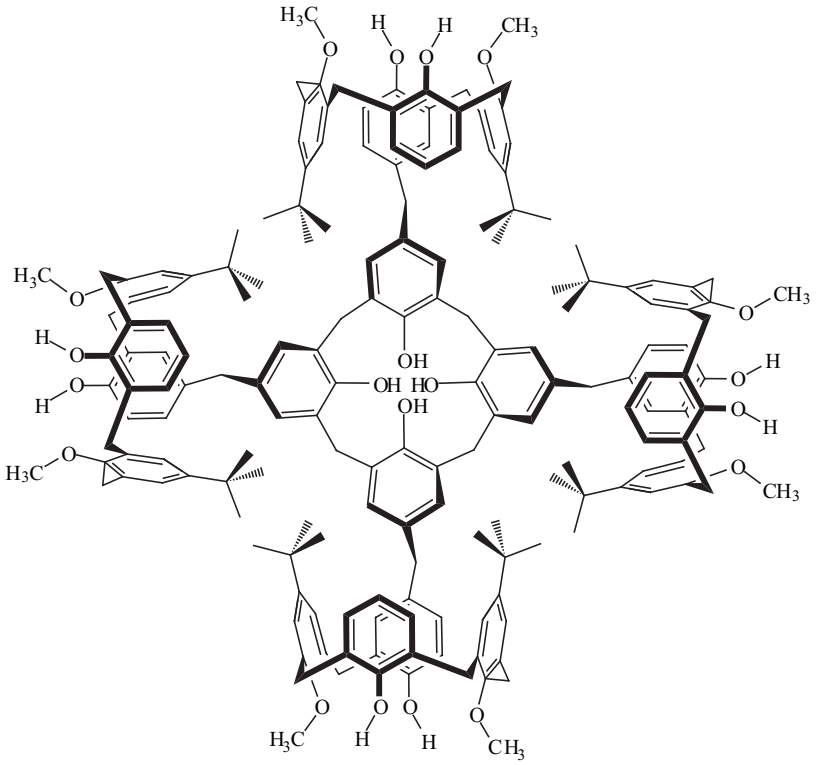
"mappemonde" molecules **46a, b** and **47** were designed with computer assistance and synthesized [12]. By ^{1}H NMR spectroscopy, it has been demonstrated that these globular calix[4]crowns spin about the axis both in the free and complexed forms [12]. A molecular "mill" **48** was also constructed and rotation of the calix[4]arene units again observed [14].



	R	R^1	X	Y
53		H	H	
54	Me	H	Bu'	

G = NO_2 or NH_2

G = Bu' or H
Z = Me or H



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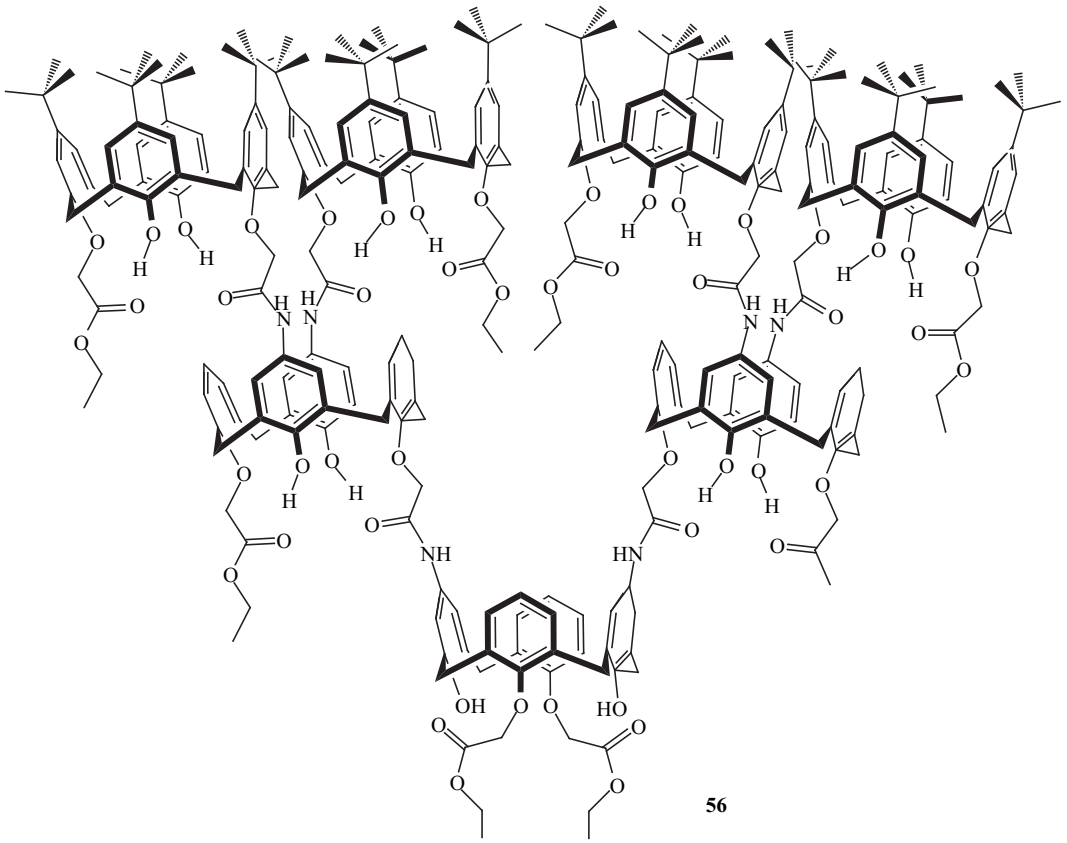

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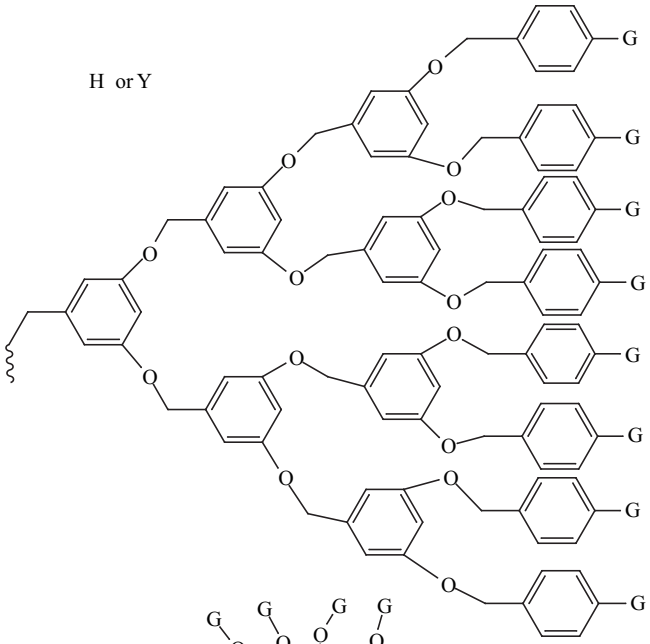
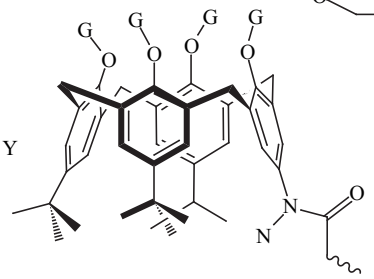
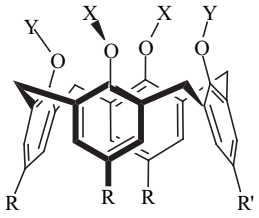
	R	R'	X	Y
57	BU^t	Bu^t	H or Y	
58	BU^t	H or NO_2	H or Y	



G = H, CO_2CH_3 or CO_2H



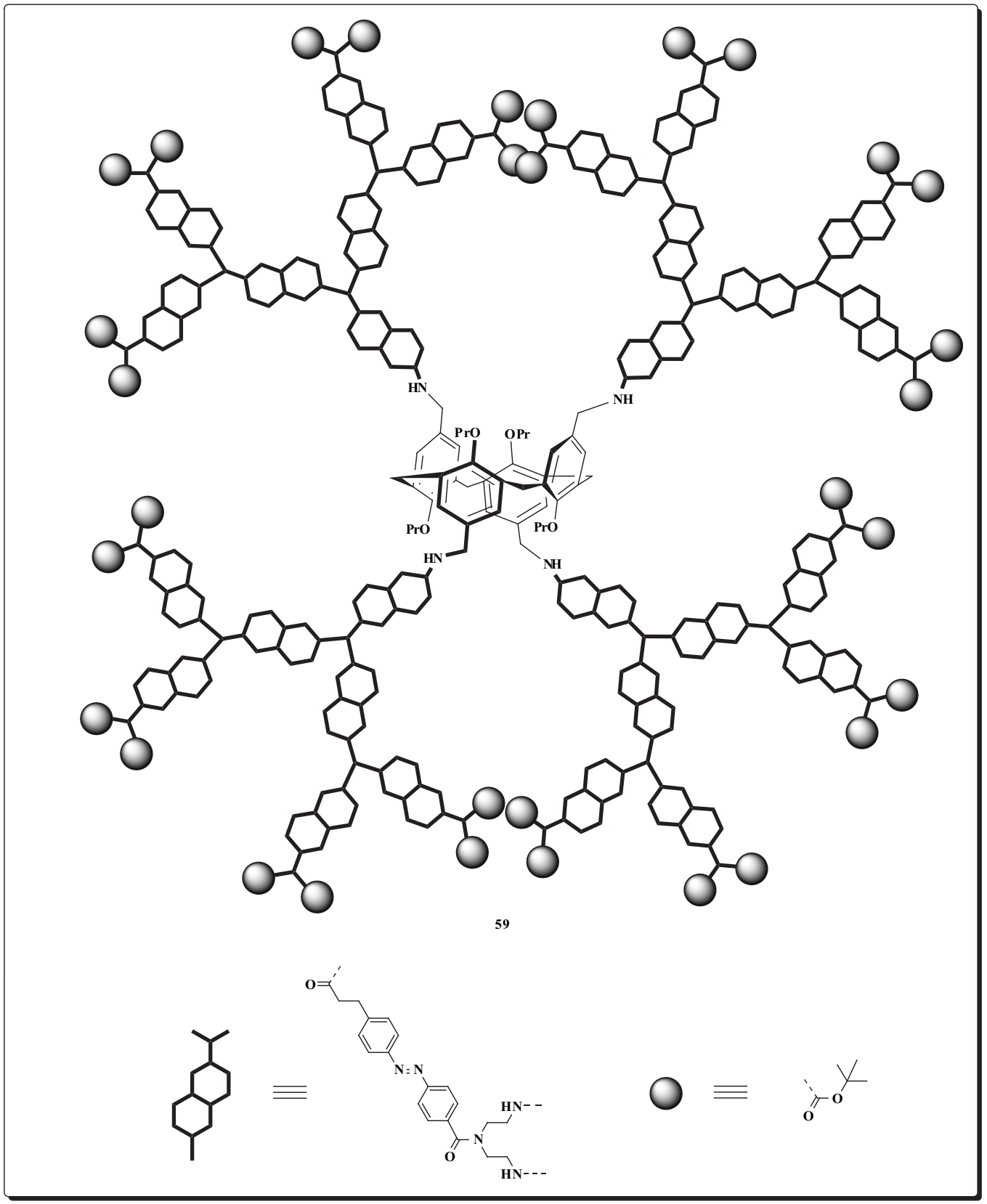
G = C_5H_{11} or $CH_2CO_2C_2H_5$



Second generation "mappemonde" and "mill" molecules **49** and **50** were prepared from a 1,3-alternate calix[4]-bisazacrown (see p. 1). In these molecular architectures, no spinning about the axis was observed [13].

CALIX[4]ARENE-BASED DENDRIMERS: THE SMART NANOSTRUCTURAL MATERIALS

Dendritic molecules (dendrimers) have been the focus of much interest over the past two decades due to their singular



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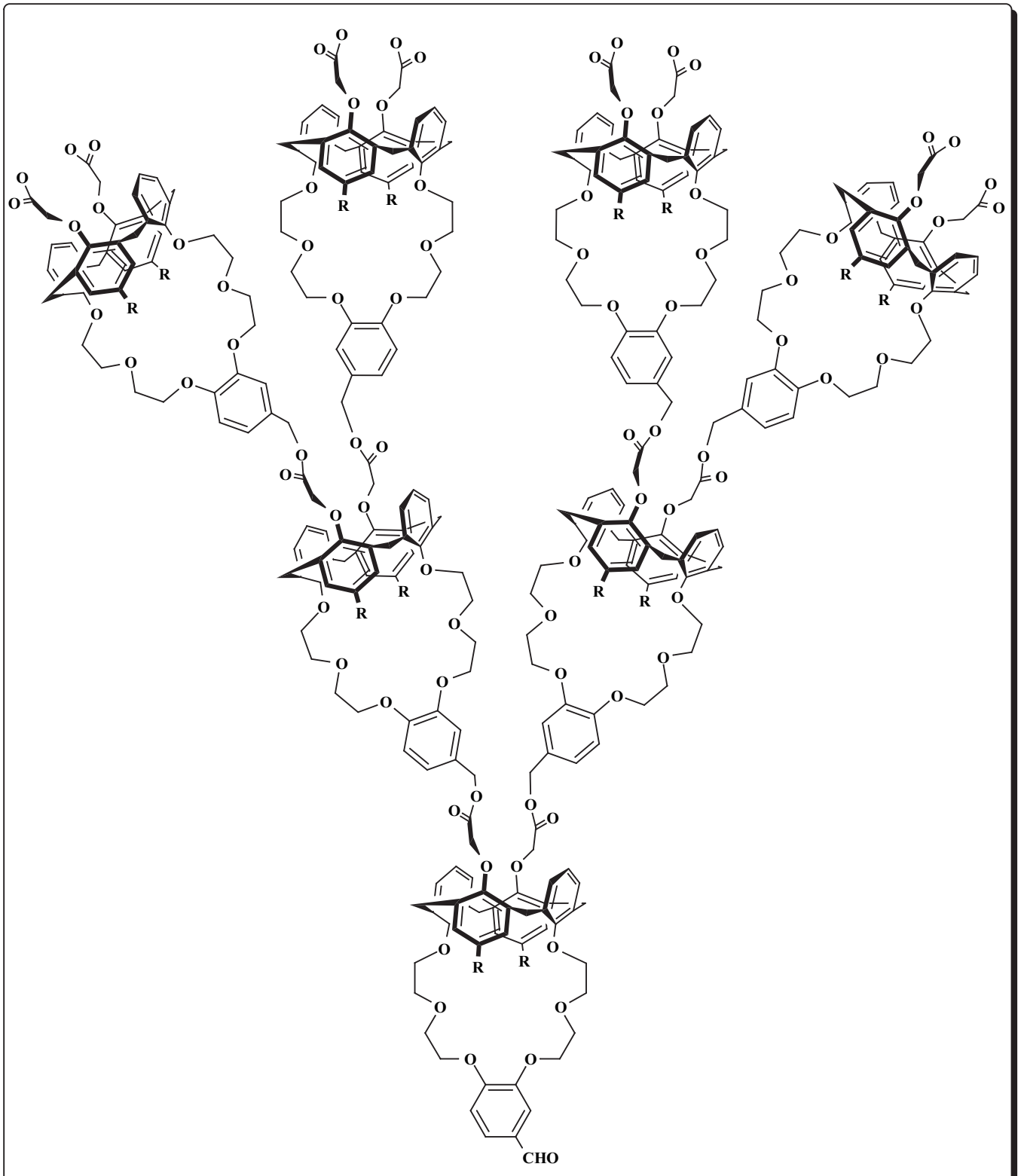
properties that distinguish them from linear polymers. These include their monodispersity, their globular, symmetric geometry and the high density of peripheral functionality. As artificial receptors, dendrimers are expected to be especially efficient. Due to their multiple sites for substitution and their different conformations, calixarenes are attractive as all components of a dendrimer, its cores, branches and peripheries [116-127]. As a core, cone calix[4]arene must generate tree-like structures [116,117,122-124], whereas 1,3-alternate calix[4]arene can give rise to



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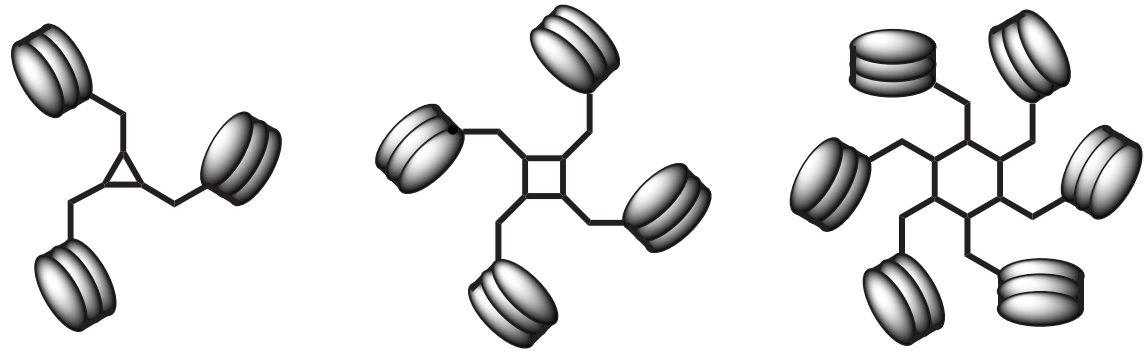
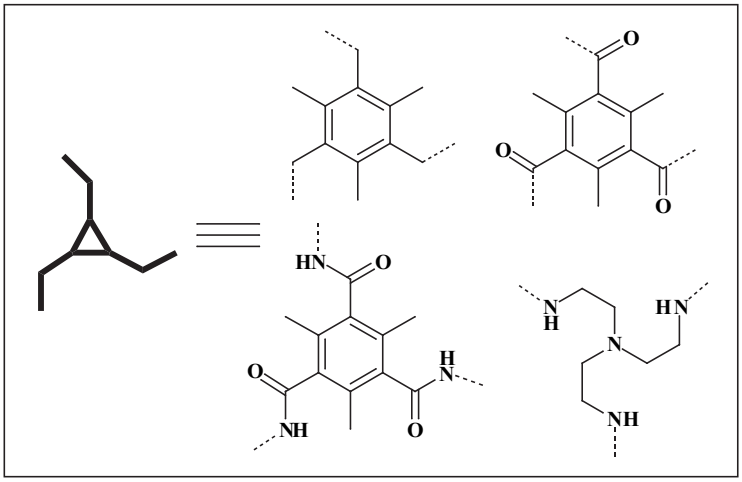
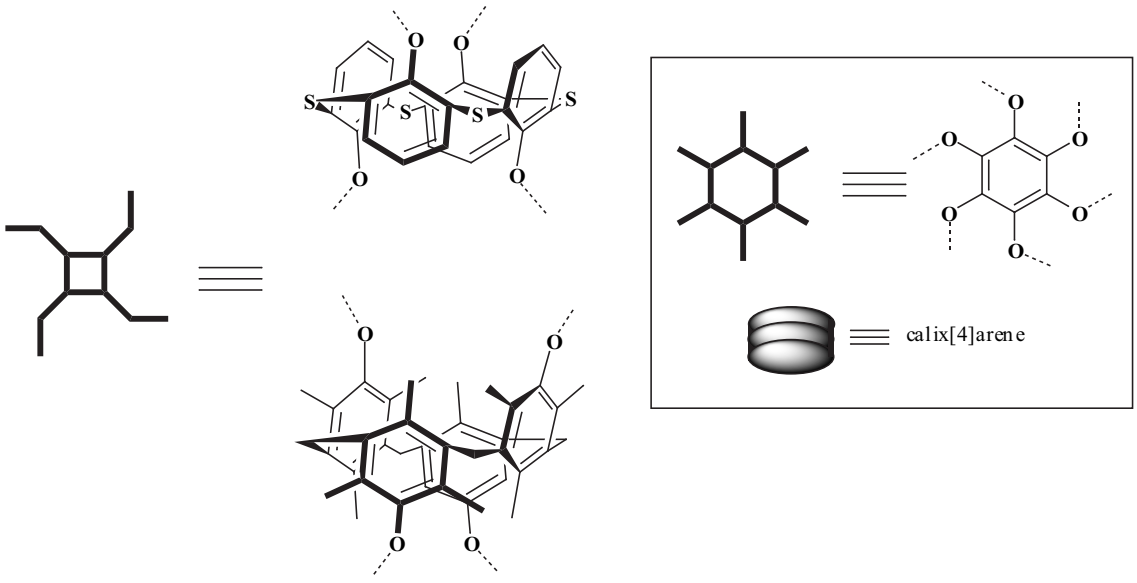
hourglass-like forms [118,126,127]. Calixarenes may be used in both divergent [118,121,124,127] and convergent [120,121,123,125,126]dendrimer syntheses.

The first calixarene-based dendrimers were prepared, in 1991, by Newkome and co-workers [116] who attached nine hydroxyl groups *via* three amide bonds to a calix[4]arene to form silvanols, water soluble calixarene dendrimers. Four years latter, Shinkai *et al*. [128] reported the synthesis and properties of oligo-calix[4]arenes and provided new impetus to the field of calixdendrimers. Along with these dendritic calixarenes, a few non-covalently bonded dendrimer-liked multicalix[4]arenes were also reported. Aggregation between *p-bis*-(melamine) calix [4] arenes and isocyanuric acid derivatives provided double rosette architectures **51** [129]. Another dendrimer-like multicalix[4]arene was prepared by complexation of *bis*(calix[4]arene)-bipyridine with ruthenium-blue, affording the ruthenium tris(dicalix[4]arene-





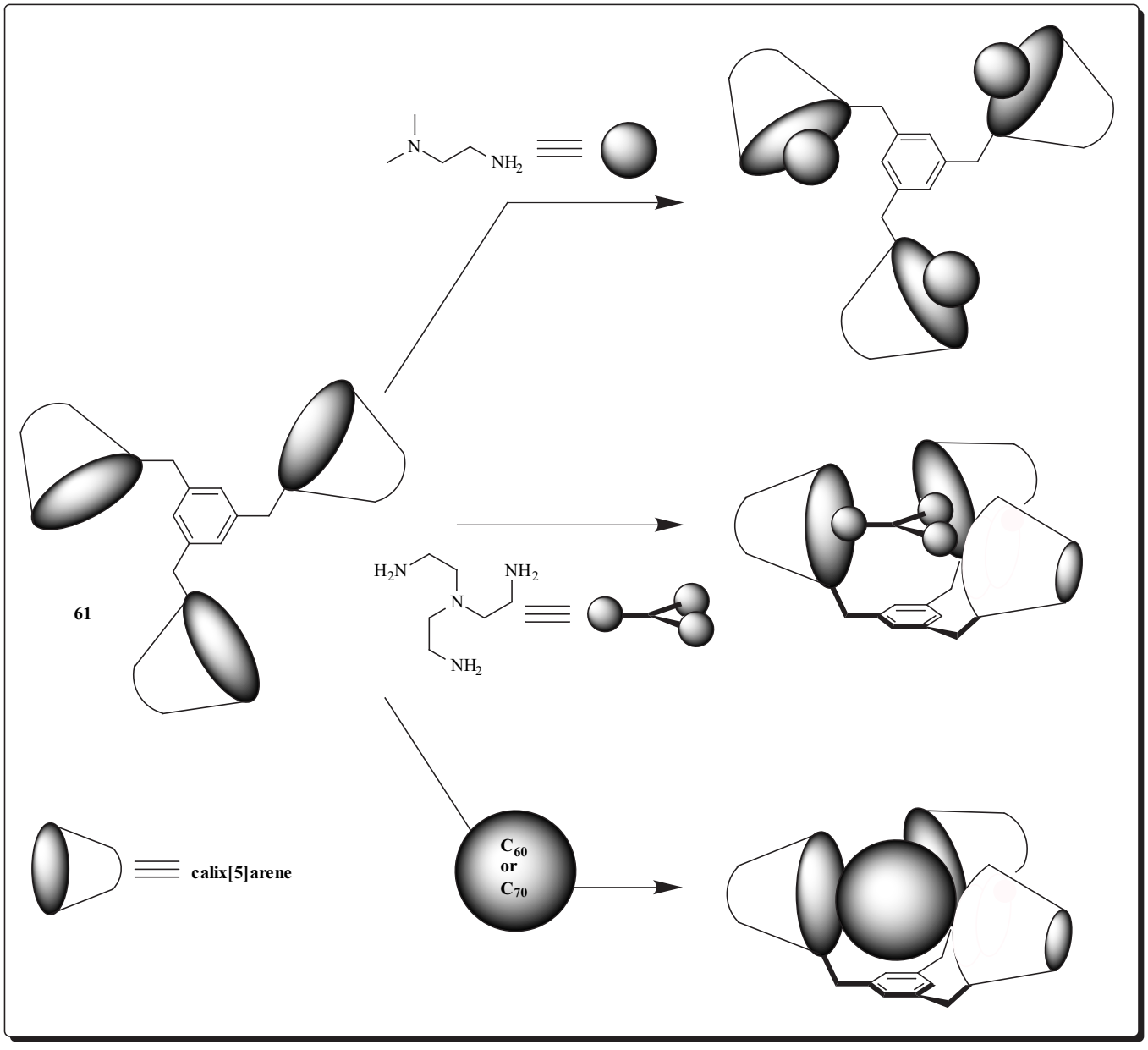


bipyridine) complex **52**. It was able to coordinate to Nd^{3+}, Eu^{3+} and Tb^{3+} ions, which quenched the luminescence of ruthenium. This complex also showed improved photophysical properties, compared to related ruthenium complexes containing only one or two calix[4]arene units, in terms of its luminescence emission lifetime (=560 ns) and quantum yield value (f = 0.028). This was attributed to the greater number of bound Ln(III) ions (at least five) [130].

As calix[4]arenes can be functionalized at the *para* positions (upper rim) or the hydroxyl groups (lower rims) of phenolic units and the degree of substitution, mono- to tetrasubstitution, can be selected, different dendritic forms can be obtained. With disubstitution of calix[4]arene synthons at the *para* positions, the linear trimer calix[4]arenes, **53** [123] and **54** [124], were obtained, while tetrasubstitution provided a starlike pentamer calix[4]arene **55** [124]. **53** can be reacted further to give a second generation (G2) dendrimer **56** [123].

When polyether wedges [117] or calix[4]arene moieties [122] were linked to the lower rim of calix[4]arenes in the cone conformation, dendritic calix[4]arenes **57** and **58** were obtained. Though the lower rim of a cone calix[4]arene, is usually narrower than the upper rim, both 1,3-disubstitution and tetrasubstitution with high encumbering polyether wedges or calix[4]arene units gave similar yields [117,122].

The use of 1,3-alternate calix[4]arene as a core is not only suitable for reduction of repulsions at the periphery since the 1,3-alternate conformer has a pseudo-tetrahedral structure but also affords hourglass-like geometrical dendrimers [118] or cone-shape dendrimers [127]. The photochromic 1,3-alternate calix[4]arene dendrimers containing BOC-4-[*N,N-bis*(2-aminoethyl)amino]carbonyl-4'-carboxyazobenzene as branches (**59**) and a higher generation (G4) were prepared by a convergent method. Study of their photochromism showed the isomerisation induced by visible or ultra-violet light to be thermally reversible. These dendrimers were intended for use in a photoresponsive drug delivery system [118].



Recently, the 1,3-alternate conformation has been used to built the second generation of a dendrimer made of 1,3-calix[4]crowns-6 **60** and their use in removal of cesium can be anticipated [127].

When the appropriate cores are used, different numbers of calixarene-based peripheries could be attached at lower rim or upper rim. Several connecting-point cores such as three connecting-point core; 1,3,5-tris(bromomethyl)-2,4, 6-trimethylbenzene [119], 1,3,5-tricarbonylbenzene [125], 1,3,5-tricarboxamidobenzene [122] and *tris*(aminoethyl) amine (tren) [121], four connecting-point cores; calix[4] mesitylene [122] and thiacalix[4]arene [126]; or six connecting-point core; hexakis(bromomethyl)benzene were condensed with three, four or six calix[4]arene units to create calixarene-peripheral dendrimers.

The peripheral calixarenes in dendritic architectures have the potential for encapsulation either independently or cooperatively. It has been demonstrated that the tricalix[5]arene dendrimer **61** can form both 1:1 and 1:3 complexes with *N,N*-dimethylethylenediamine (DMED) and that the peripheral calix[5]arene entities can cooperatively accommodate tris(aminoethyl)amine (tren), C60 and C70. The analogous tricalix[4]arene dendrimer does not complex these guests [125].

PERSPECTIVES

Although application of 1,3-alternate calix[4]crowns has already been found in the treatment of nuclear waste, opportunities still exist for the improvement of these known systems, in particular through immobilisation of the calixarenes on polymers or silica surfaces. Understanding of the nature of metal ion interactions with calixarenes is important here, as it is in analysing metal ion movements in calix tubes, and study of these systems may aid in interpreting the cross-membrane transport of metal ions in biological systems. The STM technique used to look at macromolecules as a simple object allows the chemists to think that, as an example, the complexation of a cation in a marocycle can be 'touched and revealed as a real image' at the molecular level.

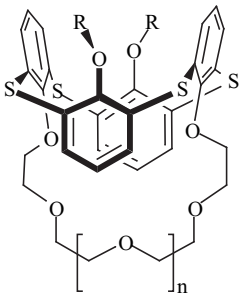
Continuing developments of the calixarene family extend to the analogous platforms that contains sulfide, sulfoxide or sulfone bridges, *viz.* thiacalixarenes, sulfinylcalixarenes and sulfonyl calixarenes [131]. As yet, there are few examples other than of calix[4]arene analogues in particular but even here possibly significant dimensional and electronic differences are apparent [132,133, 134]. For example, the bridging methylene carbon atoms in a calix[4]crown are ~5.1 Å apart, whereas the bridging S atoms in its thiacalixarene analogue are ~5.5 Å distant from one another. An illustration of the chemical consequences of these differences is that the extraction abilities of the 1,3-alternate thiacalix[4]arene-monocrowns **62a-c** were lower than those of the conventional 1,3-alternate calix[4]arene-monocrowns. This was explained by weaker electrostatic interaction of polyether ring oxygen atoms with metal ions and diminished π-metal interaction between metal ions and the aromatic rings of thiacalix[4]arene, as evidenced by X-ray crystal structure determinations and ^{1}H NMR spectroscopy [135]. Metal ion shuttling was found in 1,3-alternate thiacalix[4]arene-biscrowns **63a-d** and appears to be more facile than in the conventional 1,3-alternate calix[4]arene-biscrowns, presumably again because of the weaker binding in the crown units [135].

In the case of sulfone bridges, 1,3-alternate sulfonylcalix[4]arene-biscrowns **63e-f** show slightly inferior extraction abilities but slightly superior selectivities for alkali metal ions when compared to their calix[4]biscrown analogues [136].

These sulfur-containing bridge calix[4]arenes families open more opportunity for the chemists to create more realistic ion channels, nanotubes, dendrimers as well as molecular devices.

CONCLUSIONS

The numerous examples cited above point to the particular utility of the 1,3-alternate form of calix[4]arene as a basis for synthetic receptor molecules. Its provision of two divergent sites connected by a partially restrictive tube formed by the basic calixarene macrocycle, with both sites conveniently subject to an enormous variety of functionalsation, is the essence of its remarkable utility.



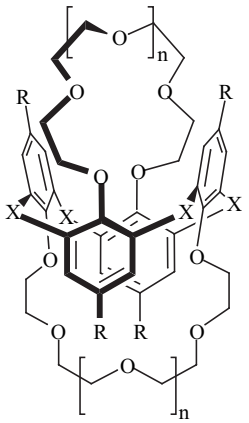
62a n = 1, R = Me

62b n = 2, R = Me

62c n = 1, R = Pr

62d n = 2, R = Pr

62e n = 3, R = Pr



	R	X	n
63a	Bu^t	S	1
63b	H	S	1
63c	Bu^t	S	2
63d	H	S	2
63e	Bu^t	SO_2	1
63f	H	SO_2	1

ACKNOWLEDGMENTS

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