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The background of the cover features several calixarene molecules, which are macrocyclic compounds composed of four phenylene rings linked by methylene groups. These molecules are shown in a 3D ball-and-stick representation, with carbon atoms in grey, hydrogen in white, and oxygen in red. They are surrounded by a translucent, light blue electron density isosurface. Scattered throughout the light blue background are several small, dark red spheres and a few larger orange spheres, representing various ions or guest molecules.

Calixarenes:

DESIGNER LIGANDS FOR CHEMICAL SENSORS



DERMOT DIAMOND AND KIERAN NOLAN Dublin City University [Ireland]

These cup-shaped molecules can form inclusion complexes with a wide range of guest species.

The term “calixarene” was coined by Gutsche in the late 1970s to describe a new class of cyclooligomers formed via phenol–formaldehyde reactions. Each calixarene contains a repeating phenolic unit formed into a macrocycle via methylene bridges. The bridges function as points around which the phenolic groups rotate, leading to various rotamer conformations. Historically, calixarenes are related to resins, such as Bakelite, and those investigated by von Bayer in the 19th century. The calixarene “cups” have a vaselike form defined by an “upper rim, lower rim, and central annulus” (Table 1).

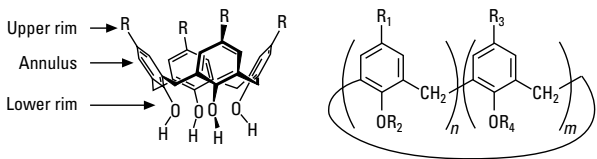
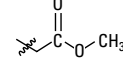
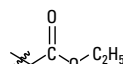
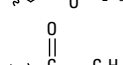
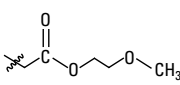
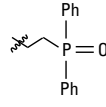
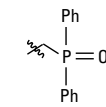
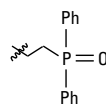
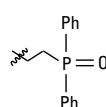
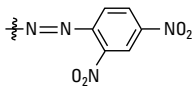
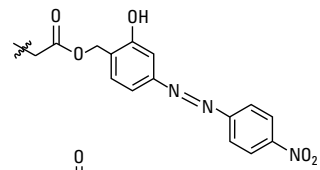
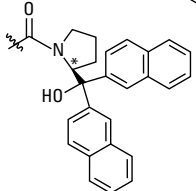
Analytical chemists are discovering calixarenes because they provide a route to molecules with well-defined cavities, which offer simultaneous polar (lower-rim) and nonpolar (upper-rim) features. Because of these properties, calixarenes can form inclusion com-

plexes with a wide range of guest species, depending on the binding groups substituted at each rim and the number of repeat units in the macrocycle. As such, they belong to a broad range of compounds, such as crowns, cryptands, and cyclodextrins, which are already well known for forming inclusion complexes with smaller guest species.

Although calixarenes with 3–20 repeat units are known, the majority with analytical activity have, to date, been tetramers (4 phenolic units) and, to a lesser extent, hexamers (6 phenolic units). The most commonly used form is the “cone” conformer, which has all phenoxy groups positioned at the lower rim. Because of intramolecular hydrogen bonding among the phenolic groups, this is the preferred conformer for the parent calixarenes. To reduce the number of rotamers, it is common practice to attach bulky *t*-butyl groups

**Calix: cup,
especially an
ecclesiastical
chalice.**

Table 1. Structure of calix[4]arene in the "cone" conformation and its derivatives.

			
Compound	Unique phenolic groups*		Substituents
	<i>n</i>	<i>m</i>	
1	4	0	<i>t</i> -butyl R_2, R_4 
2	4	0	<i>t</i> -butyl 
3	6	0	<i>t</i> -butyl 
4	4	0	<i>t</i> -butyl 
5	4	0	<i>t</i> -butyl 
6	4	0	<i>t</i> -butyl 
7	6	0	<i>t</i> -butyl 
8	5	0	<i>t</i> -butyl 
9	4	0	<i>t</i> -butyl $-\text{CH}_2\text{C}(\text{S})(\text{C}_2\text{H}_5)_2$
10	4	0	<i>t</i> -butyl $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_2\text{SCH}_2$
11	3	1	$R_1 = \text{H}$ $R_2 = R_4 = \text{H}$ $R_3 =$ 
12	4	0	<i>t</i> -butyl 
13	4	0	<i>t</i> -butyl 

at the upper rim because these substituents cannot pass through the annulus of the smaller tetrameric calixarenes.

The nomenclature of these compounds gives the number of repeat phenolic units in enclosed square brackets (e.g., calix[4]-arene for a tetramer), with the upper- and lower-rim substituents being described before and after this stem, respectively. (A useful section on the nomenclature of calixarenes is included in the revised edition of Gutsche's book [1].) Interest in calixarenes has grown rapidly because of the numerous derivatives that can be created through relatively simple synthetic procedures and because of their appealing three-dimensional (3-D) symmetry. This article focuses mainly on the sensor applications of these intriguing molecules. There are several excellent texts and useful reviews that give more detailed information (1–6).

Cation-selective electrodes

McKervey and Svehla first recognized that calixarenes with cation-complexing groups attached to the lower rim would possess the molecular requirements for the type of ionophores used in ion-selective electrodes (ISEs). In particular, calixarenes possessed rigid cavities that are predisposed to selectively complex with cations; rapid complexation–decomplexation kinetics for fast, reversible transduction processes; and sufficiently high lipophilicity (especially with the attached *t*-butyl groups) to keep most derivatives and their cation-complexed analogues from leaching from nonpolar membranes into aqueous solutions. Extraction studies from an aqueous phase into chloroform had previously shown that the esters **1** and **2** (Table 1) were selective for sodium compared to other group I and II metal ions. The studies also showed that there was a size selective effect manifested by a peak extraction of cesium by the hexamer **3** (Table 1) (7).

Of these, **1** proved to be an excellent ionophore for sodium in liquid membrane and PVC membrane electrodes (8, 9), and electrodes based on **1** were soon shown to be capable of measuring sodium in blood (10). Calixarene tetraesters like **1** are now commonly used in commercial blood electrolyte analyzers for sodium determination.

Changing the nature of the ligating groups at the lower rim can produce dramatic changes in selectivity. For example, substituting the ester groups at the lower rim with soft donors such as thio and thioamide groups (**9** and **10** in Table 1) dramatically changes the selectivity from Na^+ to Ag^+ (11). Considerable research into the synthesis of phosphine oxide derivatives has also taken place, primarily to investigate the complexation of lanthanide and actinide ions for the selective extraction of radioactive elements from nuclear waste. However, screening experiments showed that electrodes based on the tetramer **5** had excellent selectivity for Ca^{2+} in the presence of a wide range of common interferents, including Na^+ and Mg^{2+} (12).

The histogram in Figure 1a shows estimated potentiometric selectivity coefficients for electrodes based on the calix[4]arene tetraester **4** and the corresponding calix[4]arene tetraphosphine oxide derivatives **5** and **6**. The tetraester derivative **4** has excel-

lent selectivity for Na^+ , which completely disappears with compound **5**.

However, comparing the selectivity behavior of the phosphine oxide derivatives **5** and **6** illustrates the difficulty of predicting the effect of minor structure changes on ion-binding properties. Compound **5** has two methylene spacers between the phosphine oxide and the phenoxy ligating groups, whereas **6** has one (Figures 1b and 1c). Intuitively, one would predict that the more elongated cavity in **5** would be less suitable for binding ions, because the cavity size would inhibit simultaneous interaction between a guest ion and all eight oxygens. This is true for most ions; however, for Ca^{2+} , it appears that the phosphine oxide groups can swivel upward to bring all eight oxygen atoms into proximity with the guest ion (Figure 1b) (13).

Similarly, with **6**, all eight oxygen atoms interact with Ca^{2+} to produce a stable complex (Figure 1c). However, relatively minor rearrangements of the phosphine oxide groups result in a larger cavity into which K^+ can fit. Li^+ also produces a strong response in electrodes based on **6**, and therefore, this ion interacts strongly with the ligating groups. Although theoretical tools (and computational power) are steadily improving, ion selectivity is very difficult to predict on a molecular basis. Hence, a combinatorial approach to selectivity optimization is usually best.

As mentioned previously, increasing the number of repeat units in the macrocycle leads to larger cavities, which affects the selectivity. Recently, it has been demonstrated that the phosphine oxide hexamer **7**, corresponding to the tetramer **5**, can be used for electrodes with exceptional selectivity for Pb^{2+} and Hg^{2+} depending on the pH (Figure 2) (14). This, coupled with the tremendous stability of the phosphine oxides, makes these derivatives attractive agents for use in chemical sensors. Ester derivatives, on the other hand, are subject to hydrolysis at high or low pH.

Beer and others have investigated the synthesis of anion-selective calixarenes (15). Although some interesting results have been published, there do not appear to be any real analytical applications of these derivatives at present. However, this is a challenging objective, and there are currently no examples of really efficient anion sensors based on any type of ionophore that mirror the success achieved with cations. This is due, in part, to the fact that anions cannot be easily discriminated from each other on the basis of size. Yet, the main problem is discovering how to synthesize a 3-D cavity with groups capable of interacting strongly with anions. Despite these difficulties, there is considerable interest in developing anion sensors for environmental and biomedical applications, and this remains an active area of research (16).

Calixarene-based optical sensors

Visible transduction. The signal in potentiometric sensors is generated by the permselective exchange of cations into the membrane phase, which is mediated by the calixarene ligand. However, for optical transduction, an optically responsive mechanism

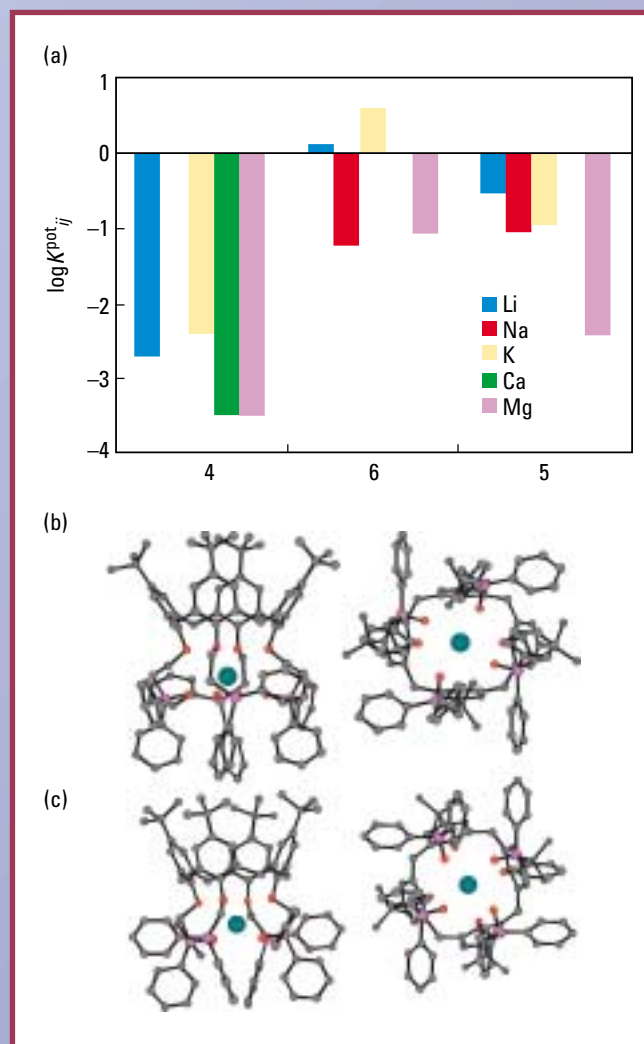


FIGURE 1. Selectivity and structure.

(a) Selectivity of PVC membrane electrodes based on the calix[4]arene tetraester **4** and the tetraphosphine oxide derivatives **5** and **6**. (b) Side (left) and through the cavity (right) views of the Ca^{2+} complex of calix[4]arene tetraphosphine oxide **5** obtained from Monte Carlo conformational searches, which suggest that the Ca^{2+} ion is in the center of a cavity defined by the four phosphine oxide oxygen atoms and the four phenoxy oxygen atoms. Other ions (Na^+) are more loosely bound outside the cavity below the plane of the phenoxy oxygen atoms. (c) Similar views of the Ca^{2+} complex of calix[4]arene tetraphosphine oxide **6**. In this case, other ions (K^+ , Li^+) can be accommodated in the cavity, leading to a loss of calcium selectivity. (Calculations performed using the Merck Molecular Force Field, *Spartan* SGI version 5.0.1.)

must be coupled with the ion–ligand complexation process. One way to achieve this is to co-immobilize a lipophilic, acidochromic dye in the membrane with the ligand. The complexation of the metal ion by the ligand results in the expulsion of a proton from the dye to the sample phase, which maintains overall charge neutrality (Figure 3).

Using this approach, a series of optodes (ion-selective opti-

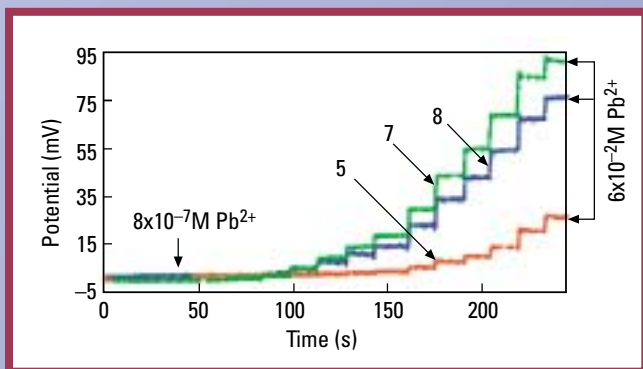


FIGURE 2. Response of PVC membrane electrodes based on the calix[4]arene tetraphosphine oxide derivatives 5, 7, and 8 to increasing concentrations of Pb^{2+} .

Pb^{2+} concentration increased from 8×10^{-7} M to 6×10^{-2} M in a background of 0.01 M Ca^{2+} . The selectivity of the tetramer 5 for Ca^{2+} is shown by the suppressed response to Pb^{2+} . However, with hexamer 7 and, to a lesser extent, pentamer 8, selectivity is reversed and a much more sensitive response to Pb^{2+} is evident.

cal sensors), based on the same calixarene ligands used in ISEs, has been created. A major benefit is that no synthetic modification of the ligand is required, and the same broad selectivity is observed, except with respect to pH due to the nature of the dye. Although commonly used to make these optically responsive membranes, lipophilic Nile Blue derivatives are, in fact, rather unstable. There are, however, alternative dyes, such as acridine derivatives, which can produce optode membranes with much longer lifetimes (17).

Calixarene-based bulk optodes have also been developed to detect small organic molecules. One recent example is low molecular weight aldehydes, which were detected by using Girard's reagent P derivative of butyraldehyde, the tetraester **2**, and the chromoionopore ETH5294 (18). PVC membranes containing this mix were coated on quartz glass plates mounted in a spectrophotometric cell. The detection limits for this technique were 0.5 μM . Calixarene optosensing of cationic surfactants has also been reported using the hexaester **3** and ETH5294 in a PVC film (19). In addition, calibration curves were reported for the detection of cetyltrimethylammonium bromide at concentrations of 3–40 μM .

It is also possible to attach acidochromic groups directly to the calixarene, either as part of the calixarene "cup" or through further elaboration of the substituent groups on the

upper or lower rims. An example is the chromogenic calixarene **11** (Table 1), which was reported by Shinkai and co-workers (20). This derivative had one of the phenolic groups of the annulus converted into an azophenol dye. It was found that upon coordination with specific alkali metals (Li^+ , in particular), the electron density at the azophenol hydroxy group was affected, resulting in a shift in the electronic spectrum. This type of chromogenic calixarene has recently been applied as a Na^+ -selective bulk optode sensor.

A series of calix[4]arenes with nitrophenolazophenol chromophores substituted at the lower rim (e.g., **12**, Table 1) have also been reported. These ligands exhibit a strong shift in their electronic spectrum upon coordination with Li^+ (21). The mechanism assumes that the complex will be a stronger acid than the free ligand, because of the electrostatic effect of the metal ion on the proximate acidic proton of the chromophore. A base must be present to accept the proton, but it must be carefully chosen so as not to deprotonate the free ligand—thus, deprotonation of the chromophore coincides with the complexation of the metal ion.

For example, a solution of the azophenolnitrophenol calix[4]arene derivative **12** (Table 1) in chloroform changes color upon addition of Li^+ in the presence of tri-*n*-dodecylamine (TDDA). On complexation of Li^+ , the labile dye proton is transferred to TDDA, and the color changes from a pale yellow to deep brownish red (absorbance maximum shifts from ~ 380 nm to ~ 530 nm).

Interestingly, it is possible to "reverse" this mechanism and use the complex as a "super-sensitive" chromophore for detecting bases. Interest in this idea arises not in the molecular recognition of the base, but because such complexes must be inherently more acidic than the free acidochromophore and therefore more sensitive reagents for the optical detection of bases. This has been demonstrated for ammonia detection using optical fiber probes coated with a PVC film containing **12** (Figure 4). A greatly enhanced response is evident, which has been shown to depend on both the cation-to-ligand mole ratio in the membrane and the cation used (21). The same approach has been used to produce a sensitive visual indicator of the presence of volatile bases, such as trimethylamine, which build up in the headspace of pack-

aged fish and are associated with the onset of spoilage (22).

Other chromogenic calixarenes have been reported but have yet to be used in bulk optodes. Some of these calixarenes are very novel and could have important analytical applications. An example is the "light-switchable" calixarene (**14**, Figure 5a), which is a derivative containing a fluorescent pyrene group in the 1-position and a *p*-nitrobenzyl quencher in the 3-position

Interest in calixarenes has grown rapidly because of the many derivatives that can be created and their 3-D symmetry.

(23). Fluorescence is absent in the cation-free form of the calixarene, but the presence of a cation guest in the cavity forces the lower rim into a more open conformation, with quencher and fluorophore spatially separated, thus allowing fluorescence to occur. These receptors are obvious candidates for use in fluorescence-based ion sensors. Similar ideas have been used to create calixarenes with their lower rim functionalized to contain luminescent ruthenium(II) trisbipyridal complexes (24). These compounds are potential amine sensors.

Chiral recognition

One of the most difficult molecular recognition tasks is to distinguish between enantiomers, because this must be achieved solely by a complementary spatial arrangement of binding groups in the host. In addition, the host must be chiral, and the selective binding of the guest must produce a signal.

The (*S*)-di-naphthylprolinolcalix[4]arene derivative (**13**, Table 1) has shown excellent chiral discrimination between the enantiomers of phenylglycinol, phenylethylamine, and norephedrine (25). Quenching experiments using (*S*)-di-naphthylprolinolcalix[4]arene with norephedrine have demonstrated that the enantiomeric composition of norephedrine at a 10-mM total concentration can be determined to ~2% accuracy, which is very encouraging considering it is a direct measurement.

The mechanism of recognition seems to hinge on the relative distances between the aryl group, the chiral center(s), and the hydrogen bonding sites in the guest molecule. For example, there is no discrimination observed between the enantiomers of phenylalaninol, which have an additional methylene spacer between the chiral center and the aryl group. Transduction of the binding event involves interaction between the naphthyl groups of the host and the aryl group of the guest, because no quenching is observed with cyclohexylethylamine. That stands in contrast to the structurally analogous phenyl-

lethylamine, which produces strong quenching.

Another example of chiral discrimination is the interaction of calixarene **15** (Figure 5b) with the enantiomers of 1-phenylethylamine. In this case, the *R*-enantiomer causes a shift in the absorption of the calixarene to 538 and 650 nm, whereas the *S*-enantiomer causes a shift to 515 nm (26). This color change is attributed to the deprotonation of the indophenol on one side of the calixarene (long wavelength) and a hydrophobic interaction between the guest and the binaphthyl on the other side (short wavelength). It is the hydrophobic interaction between the guest chiral amine and the binaphthyl calixarene substituent that is enantiomer-dependent. The presence of the different enantiomers can therefore be detected through color changes.

These examples illustrate the broad potential of calixarenes

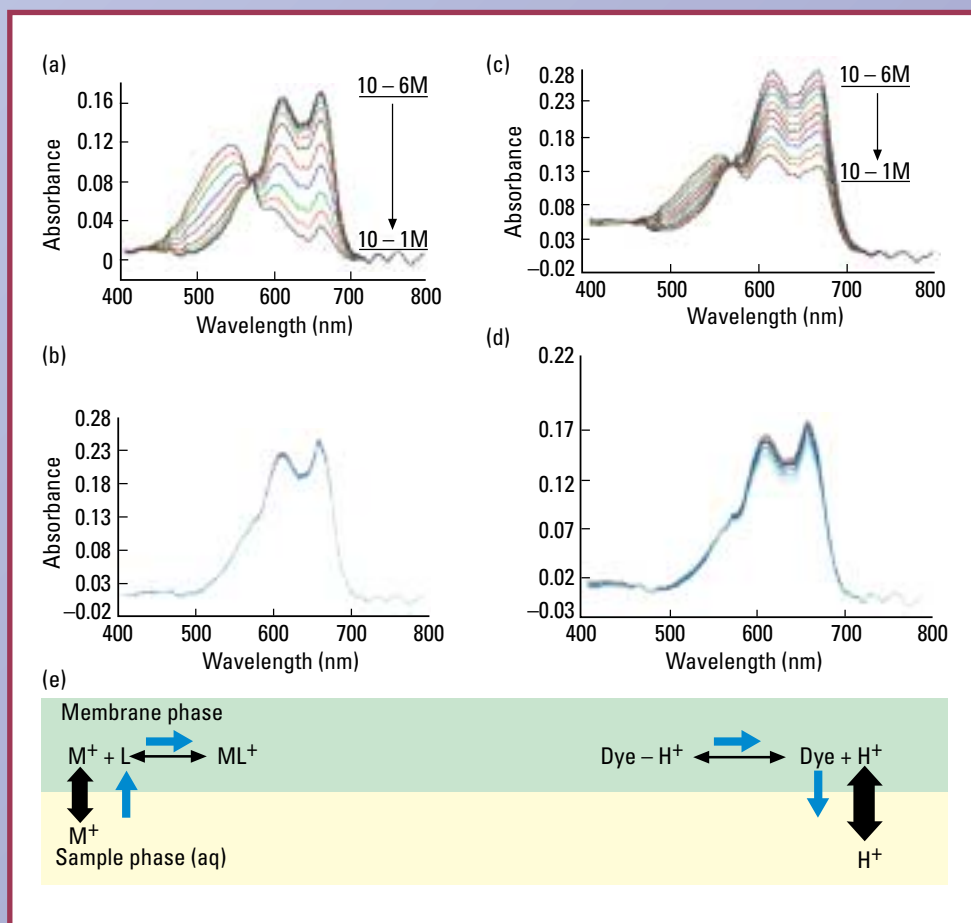


FIGURE 3. More NaCl and CaCl₂.

Optical response of PVC membranes based on the lipophilic analogue of Nile Blue and calix[4]arene tetraester **3** to increasing concentrations of (a) NaCl and (b) CaCl₂. The effect of replacing **1** with the tetraphosphine oxide calix[4]arene **5** on the optical response to (c) CaCl₂ and (d) NaCl are striking. (e) The optical transduction of the ion-complexation event is achieved by coupling ligand-mediated ion binding with deprotonation-protonation of the acidochromic dye. Charge compensation for metal ions (M⁺) drawn into the membrane phase from the sample through complexation with ligand (L) molecules is achieved by expulsion of protons into the same phase from dye molecules co-immobilized in the membrane.

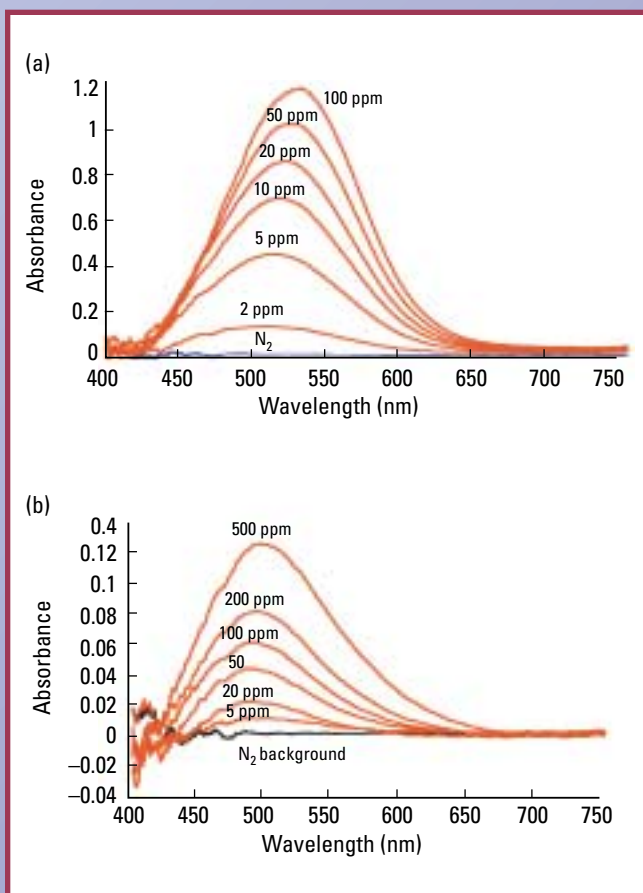


FIGURE 4. Response of a fiber-optic probe coated with a PVC film containing compound 12 to ammonia is greatly enhanced for (a) the lithium complex compared to (b) the free ligand.

to provide useful host molecules on the basis of a modular approach to molecular design, which incorporates selective recognition and a transduction mechanism to signal the binding event. An additional factor to consider for sensor applications is the immobilization mode. Calixarenes are attractive in this regard, as groups suitable for covalent attachment to surfaces or polymers may be substituted at the upper rim, leaving the host-guest activity at the lower rim relatively unaffected.

Future work

Up to now, calixarenes have been used most successfully for the development of cation sensors, and recently, neutral molecules. Reported improvements in ISE detection limits will generate fresh interest in the synthesis of new cation receptors with much greater selectivity than before (27).

For example, direct monitoring of heavy metals in water may require ISEs with selectivity over common ions such as Ca^{2+} and Na^{+} of least 5 or 6 orders of magnitude. Achieving this goal will be challenging, because the binding processes for continu-

ous monitoring sensors must be rather subtle if the guest is to reversibly bind with the host. Too strong an interaction may result in very sluggish decomplexation kinetics, leading to overlong recovery times and hysteresis. Other groups are continuing to work on the development of novel anion receptors to fill the need for simple, reliable sensors for a wide number of relatively common anions, such as PO_4^{3-} , NO_3^- , Cl^- , and SO_4^{2-} .

Calixarenes are also beginning to find applications as hosts for small molecules, as demonstrated with the systems developed by Umezawa and co-workers for dopamine recognition (28). This work elegantly demonstrates the flexibility of the calixarene template for solving recognition issues. In this case, a homoox-calix[3]arene was used as the sensing agent instead of the more usual tetramers. Homooxa calixarenes replace the methylene links with $-\text{CH}_2-\text{O}-$ bridging groups between the phenoxy units of the macrocycle. This approach provides a cavity of sufficient size to favor dopamine over other catecholamines, such as adrenaline and noradrenaline, and simultaneously drastically reduces interferences from alkali metal ions which occurs with equivalent calix[4]arenes.

Another intriguing area of future application is nanomachines and devices. For example, calixarenes can be bridged at the upper rim with groups capable of changing length due to external photochemical or electrochemical stimuli. This expansion and relaxation of the upper-rim bridge generates a corresponding movement of groups at the lower rim through the methylene "hinges" to produce molecular tweezers, which could pick up or release single ions or molecules. Other developments could arise from fullerene-calixarene inclusion complexes, which have been published recently. Are these the first examples of nanodimensioned ball-and-socket joints (29)?

This article cannot pay appropriate attention to the many researchers that have contributed to calixarene chemistry during the past 20 years and brought it to its current vibrant state. Already, many hundreds of derivatives have been synthesized and characterized. We recommend reading the work of Shinkai, Atwood, Ungaro, McKervey, Beer, and Bohmer. For applications, Reinhoudt and Kimura have made important contributions, particularly with respect to calixarene-based ISE field-effect transistor sensors (30, 31). With the increasing demands for sensor-based information and the burgeoning developments in microfabrication technologies and surface characterization, calixarene receptors will provide a solid basis for generating new materials with properties tailored to the needs of microanalytical systems and sensors (32).

We would like to acknowledge our many co-workers who have contributed to our research into calixarenes over the years. We would also like to acknowledge funding for KN under the Irish Government Basic Research Program (grant number SC/99/131).

Dermot Diamond is associate director and Kieran Nolan is a senior research scientist at the National Centre for Sensor Research at

Dublin City University (Ireland). Diamond's research interests range from the design, characterization, and synthesis of molecular receptors to the development of sensing systems incorporating electrochemical and optical sensor arrays for rapid multicomponent analysis. Nolan's research interests include synthesizing new chemoreceptors. Address correspondence about this article to Diamond at National Centre for Sensor Research, Dublin City University, Dublin 9, Ireland (dermot.diamond@dcu.ie).

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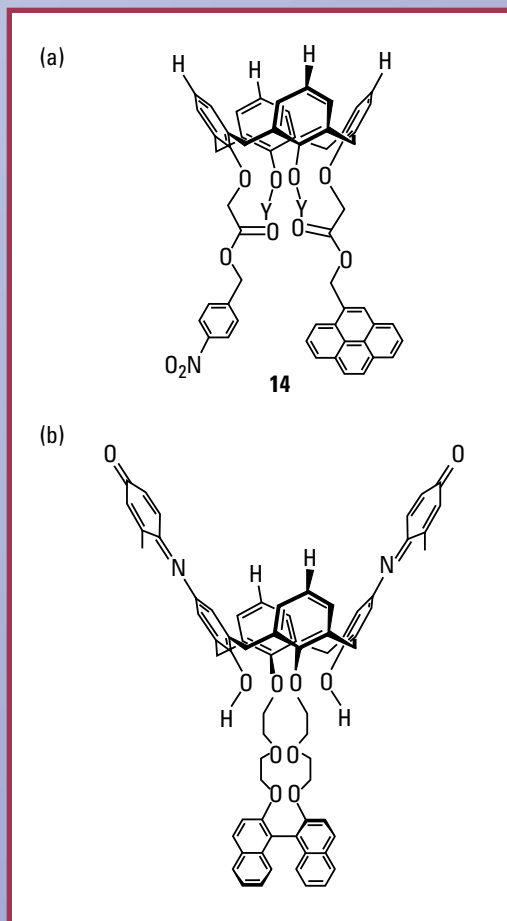


FIGURE 5. Designer molecules.

(a) The flexibility of free ligand 14 facilitates efficient quenching of the pyrene emission by the nitrobenzene group. However, Na^+ entering the cavity binds with the phenoxy and carbonyl oxygens and produces a much more rigid structure, in which pyrene and nitrobenzene are held far enough apart to inhibit quenching, and fluorescence is "switched on". (b) In 15, the enantiomers of phenylethylamine bind to produce differential shifts in the visible spectrum of the ligand (adapted from Ref. 27).