Calixarene-Based Sensing Agents *

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Abstract. The well-known selective receptor properties and ease of structural modification makes calixarene derivatives attractive materials for use in chemical sensors. This review looks at the history of sensor-related calixarene research prior to 1994 and identifies current trends in sensor research which are influencing the types of derivatives being synthesised and methods of evaluation, such as the increasing popularity of optical modes of transducing host-guest interaction. Future possibilities are briefly discussed and the need for more fundamental studies highlighted.

Key words: Calixarenes, ion-selective electrodes, sensors, optrodes.

1. Introduction

The development of new and more efficient means of performing real-time monitoring of species by means of sensors is one of the most difficult challenges facing modern science. The problems involved are multifaceted, requiring a broad understanding of many areas of expertise (ranging from organic synthetic chemistry, to thin layer deposition and surface analysis technologies, to computer-based data acquisition and signal processing) and their solution therefore demands a multidisciplinary research effort. Central to determining the overall performance of any chemical sensor is the nature of the sensing component used to generate the analytical signal, as this will largely (but not absolutely) define the critical characteristics of the resulting device, namely the selectivity, lifetime and response time. However, despite a huge effort over the past 30 years or so, the number of really efficient individual sensors remains disappointingly small, mainly due to the *ad-hoc* nature of the design and synthesis of possible agents.

To be fair, the difference between a really efficient sensing agent and a hopeless one is very difficult to predict as, on a molecular basis, the processes which together define the overall preference of a host for a target guest in preference to all other interferents interact in subtle ways. However, recent improvements in the power of computer systems, and refinements in the algorithms used to minimise molecular energies have enabled more accurate predictions of 3-D structures to be made, and to probe in advance how a ligand might interact in a dynamic sense with certain guest species in different solvents. In addition, the large amount of information now

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* This paper is dedicated to the commemorative issue on the 50th anniversary of calixarenes.

available should perhaps enable statistical tools and pattern recognition techniques to give us more insight into the structural factors which influence selectivity.

2. Transduction Modes

The role of the sensing agent in a chemical sensor is to provide a transduction mechanism which enables an analytical signal to be obtained. The vast majority of calixarenes investigated as chemical sensors have employed an electrochemical transduction mechanism, either potentiometric or voltammetric/amperometric, although more recently there has been a move towards optical transduction. As the vast majority of working devices described have been potentiometric, this paper will focus mainly on these devices.

3. Electrochemical Transduction

POTENTIOMETRIC

In this case, spontaneous processes occur in the electrochemical cell leading to the generation of a cell potential which reaches a steady state when the net current flowing in the cell and measurement circuitry is zero, i.e. the processes occurring at the electrodes are at equilibrium.

AMPEROMETRIC

In this case, the electrochemical reactions are forced to happen at the working electrode under the influence of an externally poised potential controlled by a potentiostat.

Of these, calixarenes have been most extensively investigated as sensing agents for potentiometric sensors, that is, ion-selective electrodes (ISEs). This was perhaps inevitable, given the requirements of ideal sensing agents (ionophores, ligands) for these devices, which many of the early calix[4]arene derivatives such as the esters and ketones clearly possessed (see below). Pioneering work by Simon and coworkers [1] over a period of almost 30 years had demonstrated that neutral carriers were suitable ligands for use in potentiometric sensors aimed at cation analysis. Although most ISEs these days utilise PVC or some other support material to give a 'pseudo-solid' sensing membrane, the signal generation process still involves partitioning the primary ion into a nonpolar sensing liquid-membrane phase. Hence the role of the ionophore can be summarised as:

1. selectively complex the target or primary cation;
2. reject other cations and anions;
3. retain the complex within the membrane phase;
4. allow the complex to diffuse freely in the direction of the potential gradient; and finally,

5. the stability constant for the ion–ligand complex should not be too large.

Requirements 1 and 2 above are vital in determining the selectivity of the sensor, whereas 3 ensures an adequate lifetime. Requirement 4 (permselectivity) is necessary to provide a mechanism for charge transport through the membrane while 5 is a requirement for reversibility of the analytical signal (i.e. the signal should be able to return to baseline after being exposed to a more concentrated solution of the primary ion). In addition to these, the kinetics of complexation–decomplexation has to be sufficiently fast to guarantee an adequate response time to fluctuations in the primary ion concentration during continuous monitoring applications.

The above requirements define in turn the structural features needed by ligands which would render them possible contenders for use in ISE membranes. These can be summarised as:

(i) Polar ligating groups arranged spatially in such a manner that they would interact strongly with the target ion. The ions in question are usually alkali metals (or alkaline earth), with the commercial driving force over the past 30 years being the development of sensing technology for use in blood analysis. Suitable groups would be carbonyl oxygen atoms (as part of amide, ester or ketone functionalities) arranged so as to define a 3-D polar cavity which would give a best-fit with the target ion. The polar cavity would have to be sufficiently rigid to maximise selectivity and the ion–dipole interaction strong enough to ensure that the process represented by Equation (1) below favoured the right-hand side to the degree defined in Equation (2).

$$L_{(m)} + M^+_{(aq)} \rightleftharpoons LM^+_{(m)} \tag{1}$$

$$\beta = \frac{[LM^+_{(m)}]}{[L_{(m)}][M^+_{(aq)}]} \approx 10^5 \tag{2}$$

where L = ligand, M^+ is the metal ion, LM^+ is the complex, β is the stability constant and (m) and (aq) denote the sensor membrane and sample aqueous phases, respectively. From thermodynamics, we can predict from Equation (2) that;

$$\Delta G = -RT \ln \beta \approx -30 \, kJ \, mol^{-1}. \tag{3}$$

In other words, the ligating groups have to provide $30 \, kJ \, mol^{-1}$ surplus energy above that required to replace the water molecules of the hydrated ions.

(ii) However, notwithstanding the above discussion, in order to comply with requirement 3, these ligands, and the resulting positively charged complex, would have to be preferentially retained in the nonpolar membrane phase of the sensor. This could only be achieved by combining large, nonpolar groups

internal electrolyte

M^+

$$E_m^{'}$$

$M^+ + L \longleftrightarrow L\ M^+$

E_d membrane phase

$M^+ + L \longleftrightarrow L\ M^+$

$$E_m^{''}$$

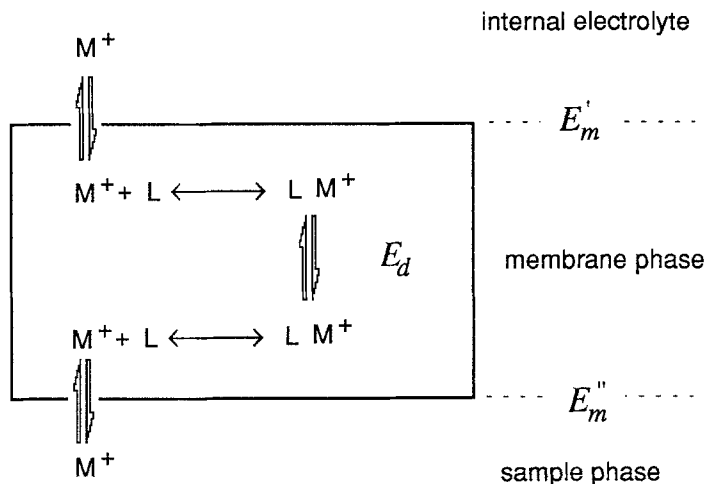M^+ sample phase

Fig. 1.   Processes occurring in an idealised ion-selective electrode membrane.

around the polar cavity, so as to shield the effect of the polar groups and charged complex from the nonpolar membrane environment. However, the molecule could not be made too bulky, or diffusion of the complex through the membrane would become a problem (requirement 4).

The processes occurring in an idealised ion-selective electrode (ISE) membrane are summarised in Figure 1. The aqueous analyte ions $(M_{(aq)}^+)$ are in equilibrium with the electrode membrane phase under the control of the ion–ligand complexation reaction, generating a boundary potential $(E_m^{''})$. The complexes generate a diffusion-migration potential (E_d) across the membrane phase which is normally constant, and an internal boundary potential $(E_m^{'})$ which is fixed, assuming that the concentration of the analyte ions on both sides of the internal boundary remains invariant. Hence fluctuations in the overall electrode potential arise from changes in the sample/membrane boundary potential $(E_m^{''})$ alone, which are related to the concentration (more correctly, activity) of the analyte ions in the sample phase.

4. Synthetic Ligands for ISEs

As mentioned above, Simon and coworkers led the way in the design of synthetic receptors for metal ions which would be suitable for use in ion-selective electrodes. Besides these systems (primarily based on amides), other workers were looking at alternatives in the various groups of neutral ligating families which were being developed during the 1970s, such as crowns and spherands. Given this activity, it was inevitable that calixarenes would eventually be examined, as their structural features met many of the requirements outlined above. This was recognised by McKervey and Svehla, who initiated the first investigation into the use of calixarenes as potentiometric sensors in 1985. Luckily as it turns out, the compounds

TABLE I.

Index	R	R'	n
1	CH_2CO_2Et	t-But	4
2	CH_2CO_2Me	t-But	4
3	CH_2CO_2Et	t-But	6
4	CH_2CO_2Et	H	6
5	$CH_2CO_2C_{10}H_{21}$	t-But	4
6	$CH_2CON(nC_4H_9)_2$	t-But	4
7	CH_2CO_2‑phenyl	t-But	4
8	$C_2H_5CO\text{-}But$	t-But	4
9	C_2H_5CO‑phenyl	t-But	4
10	$CH_2CO_2CH_2CH_2\text{-}N$(pyrrolidinone)	t-But	4
11	$CH_2\overset{S}{C}N(C_2H_5)_2$	t-But	4
12	$CH_2CO_2CH_2CH_2SMe$	t-But	4
13	$CH_2CO_2CH_2CH_2OMe$	t-But	4
14	$CH_2CO_2(CH_2)_3(SiO_2)SiCH_3$ with $CH_3\ CH_3$ / $CH_3\ CH_3$	t-But	4
15	$CH_2CH_2SCH_3$	t-But	4
16	$CH_2CH_2SC(S)N(C_2H_5)_2$	t-But	4
17	$CH_2CH_2OC(S)N(CH_3)_2$	t-But	4

chosen for the study included two tetrameric esters (Table I; **1** tetraethyl-*p-t*-butylcalix[4]arene tetraactetate and **2** tetramethyl-*p-t*-butylcalix[4]arene tetraacte-tate), which turned out to be excellent ionophores for sodium ions. Initial screening experiments carried out with liquid membrane sensors confirmed that excellent sensors for sodium could be produced with these ligands (Figures 2a and 2b, respectively), and that devices exhibiting caesium selectivity (Figures 2c and 2d) could be made with the hexamer esters (Table I; **3** tetraethyl-*p-t*-butylcalix[6]arene tetraactetate and **4** tetraethylcalix[6]arene tetraactetate). The results were present-ed at an international conference held in Dublin, Ireland, in June 1986, and were published as part of the proceedings of this meeting later the same year [2]. To this author's knowledge, this was the first reported use of calixarenes as sensing agents to appear in the literature. A second publication early in 1987 by Diamond and Svehla [3] again highlighted the excellent selectivity of ligand **2** for sodium against potassium and a range of other interferents which can affect the measure-ment of sodium in blood (the most important commercial application for sodium measurements). Detailed studies on the properties of PVC membrane ISEs based on the same compounds confirmed their usefulness as sodium and caesium sensors [4].

Kimura and coworkers published results on the related ligands **5–7** (Table I) as sodium sensors [5], and the effect of varying the substituent groups on the esters was examined for a series of compounds by Cadogan *et al.* in two papers for the tetramers [6] and the hexamers [7], respectively. The former were confirmed to be markedly sodium selective, while the latter group again showed peak selectivity for caesium. More recently, Cunningham *et al.* examined 12 tetramers and one hexamer as sensing agents in PVC membrane electrodes and reported the tetra-*p-t*-butylcalix[4] methoxymethyl ester (Table I, **13**) as producing the most selective sodium electrodes so far [8].

The obvious application of these sodium sensors was in the clinical analysis of sodium in body fluids. Although sodium is present in blood at elevated levels (typically 120–150 mM), the range of the sodium concentration is relatively limited, compared to potassium (1–4 mM). It follows that the signal obtained will have a limited range of a few mV over which the entire normal sodium distribution will occur. Hence, careful experimental design, and attention to sampling and signal processing is required in order to obtain acceptable accuracy and precision in the analytical results.

Initial studies on the performance of mini-PVC membrane electrodes for blood analysis were encouraging [9]. In this study, 44 plasma samples were analysed for sodium with the calixarene methyl tetraester-based PVC electrodes, and the results compared with those obtained with a SMAC-Technion Analyser. Good correlation was found ($r = 0.95$), but a systematic bias was apparent due to the calibration regime used in the study. A more detailed report of these investigations published the following year confirmed the utility of applying the sensors based on **2** to the analysis of sodium in blood [10].
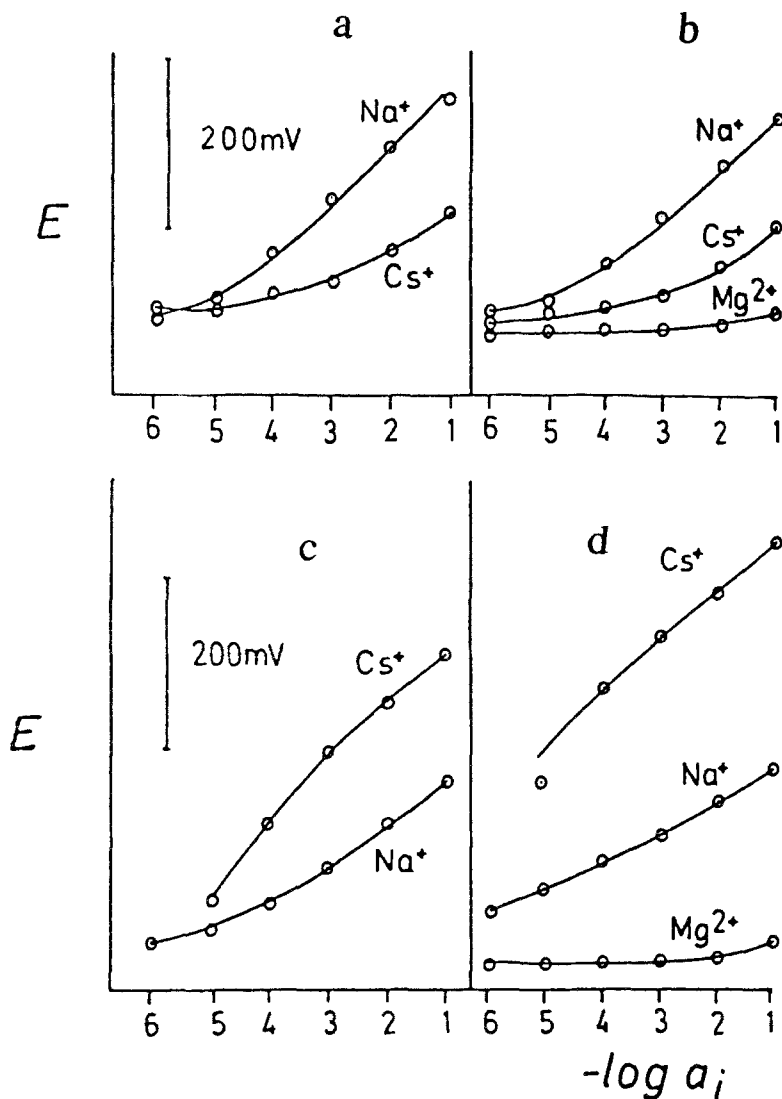
Fig. 2.   Response of liquid-membrane electrodes based on **1**(a), **2**(b), **3**(c) and **4**(d). These were the first results demonstrating the selectivity of ISEs based on calix[4]arene tetraester and calix[6]arene hexaester derivatives. The tetramers are clearly sodium selective and the hexamers caesium selective. Taken from reference [2] with permission.

In parallel with these studies, other ligands were assessed for use in sodium-selective electrodes, including the methyl, butyl, and adamantyl ketone tetramers of *p-t*-butylcalix[4]arene. However, only the methyl ketone derivative produced satisfactory PVC membrane electrodes [6]. These were subsequently applied to the analysis of sodium in plasma samples [11]. Excellent correlations ($r = 0.979$, $r = 0.987$ and $r = 0.951$, $n = 10$) were found in comparative tests with three reference

instruments (Hitachi 704 Analyser, Flame Photometer, SMAC Technicon Analyser, respectively). However, as before, a bias in the results was apparent in each case. Interestingly, in a paper by Kimura and coworkers, PVC electrodes based on 5 were also applied to the determination of blood sodium. Although only five samples were processed, a positive bias of around 2–3 mM was evident in all but one sample [12].

Obviously, when trying to establish a new analytical device in the face of existing technology, any bias in the results is unacceptable. Bias in analytical determinations commonly arises from systematic errors in calibration. In the above investigations, drift during the calibration and analytical measurements is a well-known problem. Its effect is further magnified by the very restricted range found in blood sodium samples, which leads to a narrow voltage range over which the measurements must be made, and, perhaps more importantly, significant 'bunching' of the concentration distribution in the samples. Hence most concentrations are focused in a very narrow range (135–140 mM) with a few outliers on either side which extend the range to perhaps 120–150 mM sodium. These outliers have a significant influence on the slope of the regression line, and must therefore be determined with particular care.

One way to reduce the effect of drift and to give very reproducible sample handling is to use flow-injection analysis (FIA). PVC membranes incorporating the methylketone and methyl ester derivatives were assessed as detectors in a FIA system for blood sodium analysis and the results demonstrated that the bias described above could be greatly reduced while still maintaining excellent correlation [13].

However, the best results were presented in a series of papers where the methylester tetramer was used as an element in an ISE array both in conventional dip-type measurements [14] and in a flow-injection analysis system [15, 16]. Using sophisticated calibration and sensor modelling techniques, these papers rigorously demonstrated that the methylester tetramer (Table I, 2) could be applied to blood sodium analysis with excellent results (Figure 3). Furthermore, the same ISE was shown to be suitable for the analysis of sodium in mineral water samples.

More recently, sodium selective PVC membrane electrodes incorporating the methylester tetramer have been assessed using batch injection analysis (BIA). This technique differs from FIA in that the sample is injected directly onto the sensor surface, and a dilution/mixing effect sweeps the sample quickly away, resulting in high-speed transient signals which can be used for analytical measurements. Initially, a single sodium electrode was investigated and shown to have excellent characteristics for this technique [17]. Subsequently, the electrode was used in a 3 × ISE array (Na, K, Ca) and successfully applied to the analysis of these ions in mineral water samples [18]. In the array study, the excellent selectivity of the calixarene–PVC membrane was apparent in carryover studies performed during the evaluation of the array, as virtually no response to the interfering ions was indicated.
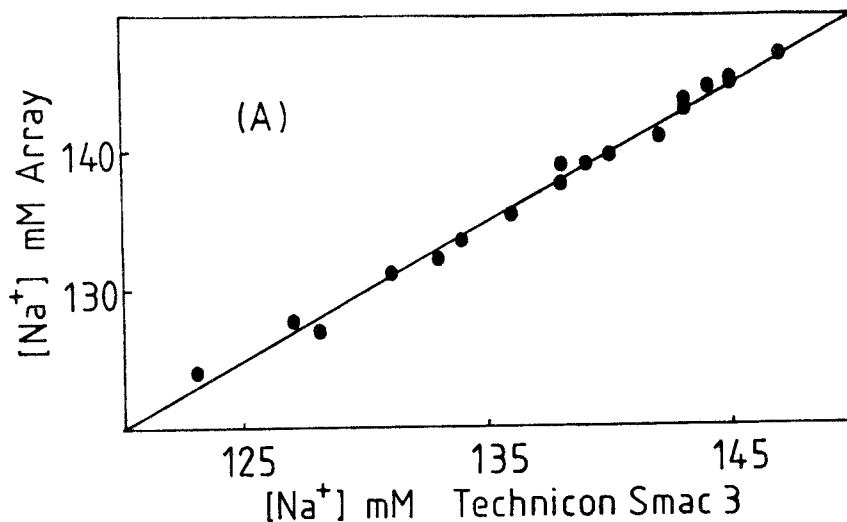
Fig. 3.   Plasma sodium analysis results obtained with a PVC membrane electrode based on
1 compared with a SMAC analyser. The electrode was part of an array of ISEs which were
carefully calibrated before use. Bias in the results was eliminated through the use of a flow-
injection analysis (FIA) approach which enabled the entire sample handling and analysis to be
automated. These results demonstrate clearly the successful application of calix[4]arene-based
ISEs to this important assay (from reference [15] with permission).

From the above, it is clear that the tetraesters and close derivatives can form the
basis of excellent sodium ISEs. Studies on device lifetime showed that the sensors
could be expected to be used for months at a time [19], and could analyse several
thousand blood samples before the signal would become unacceptably affected by
membrane coating or leaching of membrane components [20].

5. Solid-State Sodium-Selective Sensors

In addition to the traditional ISE configuration discussed above, researchers are
interested in solid-state designs of these sensors, such as ISFETs (ion-selective
field-effect transistors) or coated wire electrodes (CWEs), as these are expected
to be easier to mass produce and will be more compatible with the planar fab-
rication technologies used in the semiconductor and related industries. It is not
surprising, therefore, that studies on the performance of ISFETs incorporating cal-
ix[4]arene derivatives have recently appeared in the literature [21, 22]. One paper
[23] describes the characteristics of ISFETs based on the ketones 8 and 9 (Table I).
These gave Nernstian slopes and good selectivity against other Group I and Group
II cations. A well-known problem with these devices is the lack of a well-defined
internal boundary potential (i.e. E'_m in Figure 1 above) due to the lack of an internal
filling solution or compensating mechanism by which charge can be exchanged
across the internal boundary.

The same problem occurs with coated wire electrodes (CWEs), which differ from ISEs in that the sensing membrane is deposited directly onto a metallic conductor. This leads to a blocked internal interface between the membrane and the metal, as the former conducts only by means of ion movement, while the latter is an electronic conductor. Hence CWEs, while simpler in make up than equivalent ISEs, are generally much less stable, and exhibit greatly reduced effective lifetimes. The ISFET design proposed by Brunink *et al.* involved using a poly(2-hydroxyethyl methacrylate) (polyHEMA) hydrogel layer to help anchor the PVC membrane on the gate region of the device and simultaneously reduce the effect of interferents such as CO_2 which can diffuse through the PVC layer and affect the internal boundary potential. An alternative proposed by Tsujimura *et al.* [24] was to use calix[4]arenes bearing oligosiloxane moieties (e.g. **14**) in silicone rubber membrane ISFETs. These groups promoted the dispersibility of the ligands within the rubber membrane leading to more stable responses compared to similar devices based on the ethyl ester tetramer (**1**). However, no data are given on the performance of the device in real samples such as plasma.

One strategy which might overcome this limitation is to substitute a conductor of mixed character which is capable of transferring charge by means of either ion or electron movement. With this in mind, PVC membranes incorporating ligand **1** have been deposited on polypyrrole which was electrochemically formed on platinum substrates [25]. The resulting sodium-selective solid-state sensors were shown to be much more stable than CWE equivalents, and were unaffected by the presence/absence of redox active species in the sample solution which react on polypyrrole surfaces. Impedance studies confirmed a dramatic reduction in the charge transfer resistance through the device compared to CWE devices which had no polypyrrole layer between the Pt layer and the PVC.

6. Potentiometric Sensors for Other Ions

One of the main reasons for the great interest in calixarenes is the variety of possibilities for structural modification and elaboration. In particular, one can vary the dimensions of the polar cavity defined by the pendant ester, ketone and amide groups described for the sodium selective sensors discussed above. As the selectivity of these devices is determined by a best-fit mechanism which ideally gives a large difference in the Gibbs free energy of the primary ion complex compared to interfering ions, this ability to vary the cavity size raises the prospect of developing ligands suitable for use in sensors aimed at other ions.

An example of these are the caesium electrodes mentioned above based on the hexamers **3** and **4** (Table I). X-ray crystal structures [26] confirm that these ligands are much more open, and define larger polar cavities than the sodium selective tetramers. PVC membrane electrodes based on these ligands were found to be caesium selective against a wide range of possible interfering ions, with ligand **4** being the better of the two.
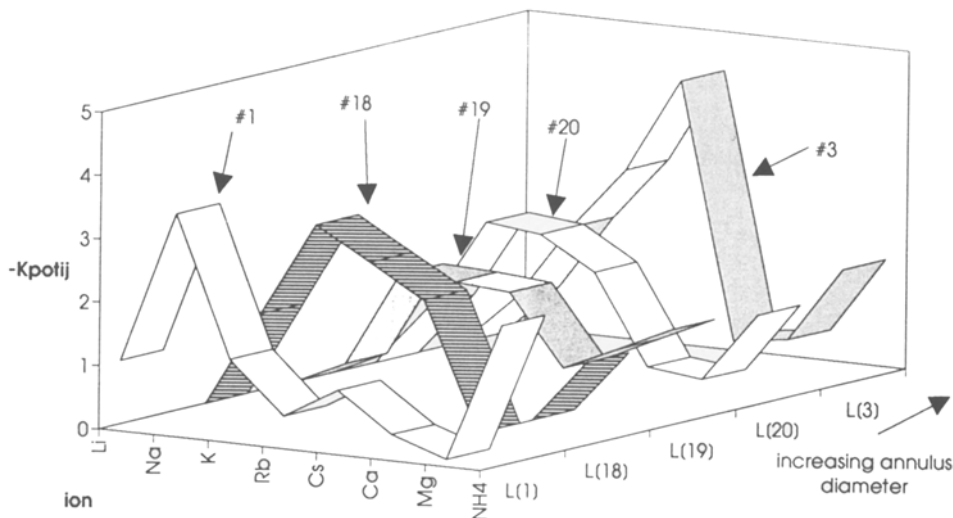
Fig. 4.   Variation in selectivity of PVC membrane ISEs as calixarene annulus size increases. The tetramer **1** is clearly sodium selective, while the three oxocalixarenes **18**, **19** and **20** have intermediate and rather poor overall selectivity. On the other hand, the hexamer **3** is obviously caesium selective.

An alternate strategy is to increase the annulus size by extending the methylene linking groups to dimethylene ether groups, rather than increasing the number of repeating calixarene groups. These so-called 'oxacalixarenes' have also been investigated for use in ion-selective electrodes for potassium [27]. While functioning electrodes have been made, the potassium selectivity is not comparable to that available with the well-established valinomycin electrode. It was found that introducing these spacer groups into the annulus, while it did lead to changes in the selectivity, also led to a drastic reduction in the ability of the ligand to discriminate [28]. The basis of the excellent selectivity of the tetramers discussed above lies in their rigid cone conformation, which does not allow ions larger or smaller than the optimum size (i.e. sodium ions) to interact strongly with the polar carbonyl ester, ketone or amide atoms. In contrast, although we see a shift in selectivity from sodium to potassium when one compares electrodes based on the tetraesters and tetraketones with their mono and, more clearly, their dioxa equivalents, the ability to discriminate between ions of different sizes is greatly reduced. This is clearly demonstrated in Figure 4, where the peak selectivity obtained for sodium and caesium with the tetraester **1** and hexaester **3** (Table I) contrasts strikingly with the relative lack of selectivity of the oxacalixarenes **18**, **19** and **20** (Table II). This is indicative of a much more flexible ligating process which is able to interact relatively strongly with cations of differing sizes. This in turn is a consequence of introducing the longer spacer groups between the calixarene units which enables them to swivel and presents a larger volume through which the ligating groups can move.

TABLE II.
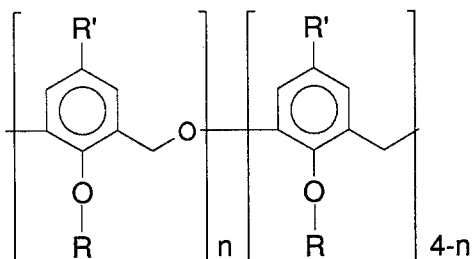
Index	R	R'	n
18	$CH_2CO_2C_2H_5$	t-but	1
19	$CH_2CO_2C_2H_5$	t-but	2
20	$CH_2CO_2C_4H_9$	t-but	2

7. Silver and Other 'Soft' Ions

O'Connor *et al.* have investigated the performance of ISEs based on calix[4]arenes containing silver and nitrogen atoms such as the amide, thioamide and thioester **10**, **11**, and **12** respectively (Table I). Of these, the thioester **12** gave the best results in terms of selectivity as this was the only one which produced electrodes selective for silver against sodium ions (log $K^{Pot}_{Ag,Na} = -1.16$) [29, 30]. A glassy carbon electrode coated with PVC containing **12** was subsequently successfully used to follow potentiometric titrations of mixtures of I^-, Br^-, and Cl^- [29].

Cobben *et al.* [31] have described calixarene-based ISFETs targeted at Ag^+, Cu^{2+}, Cd^{2+} and Pb^{2+}. Twenty-nine calix[4]arene derivatives were investigated in this study. The silver-selective ISFETs were based on PVC membranes doped with calix[4]arene derivatives with S-containing groups on the lower rim, such as **15**. On the other hand, ligand **16** resulted in devices more selective for Cu^{2+} (although limited data are given) and significantly none for the selectivity against Ag^+ or Hg^{2+}, which would be probable interferents for this type of membrane sensor. Preliminary data are also reported in this paper for Cd^{2+} selective ISFETs based on several ligands (e.g. **17**) and Pb^{2+} selective ISFETs based on similar oxamide derivatives. The behaviour of the oxamide based sensor is curious, giving a slope of nearly 60 mV/decade change in Pb^{2+} concentration (double the theoretical value) and the calibration curve shows a response linearly decreasing below 10^{-6} M, in contrast to that obtained with most conventional PVC membranes ISEs (and the other ISFETs reported in the paper), which generally level off around 10^{-5} M. Unfortunately, no data regarding the lifetime of the devices is given.

8. Voltammetric and Amperometric Sensors

Many ligands have been used as analyte accumulation agents for stripping analysis. The only publication in this area to date involving calixarenes has been the use of a linear polymeric form of a calix[4]arene tetraester for the preconcentration of Pb^{2+}, Cu^{2+} and Hg^{2+} [32]. In this study, the polymeric calixarene was dispersed in a carbon paste which was then packed into an electrode body. The polymer form of the ligand was used as this was not likely to diffuse into the aqueous sample phase, even when complexed to positively charged ions. The electrode was left at open circuit in the presence of the aqueous sample containing the analyte (accumulation cycle) for various times, and the accumulated metal subsequently stripped off by applying a voltammetric stripping waveform to the carbon paste electrode. Good sensitivity was obtained for Pb^{2+} in particular, with good analytical signals being obtained for 10^{-6} M samples after 3 min accumulation.
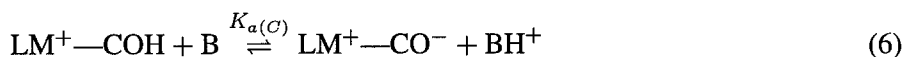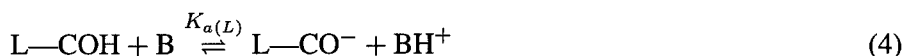
9. Sensors for Organic Guests

As is clear from the above discussion, calixarene derivatives have been thoroughly investigated as sensing agents for simple inorganic ions. However, calixarene-based sensors for organic amines have begun to appear in the literature. Both studies have involved the use of calix[6]arene esters as hosts for organic amines. The protonated amine is able to form a stable inclusion complex by formation of tripodal hydrogen bonds between the NH_3^+ group of the guest and the C=O groups of the host, resulting in good potentiometric signals from PVC membrane electrodes. Furthermore, the electrodes are selective for primary amines against secondary and tertiary amines [33]. Another study has revealed strongest potentiometric responses to primary amines bearing no substituent adjacent to the amino group such as 1-octylamine and dopamine [34].

10. Optical Transduction

One of the most striking trends in sensor research over the past five years or so has been the tremendous interest in optical methods of transduction. Optical-based sensing is attractive for many reasons, including inherent safety, less noise pick up in signal transmission over long distances, and the possibility of obtaining much more comprehensive information from a single probe (full spectrum vs. one channel of electrochemical information). While there have been many recent publications describing new calixarene derivatives capable of optically signalling the presence of metal ions, there are no functioning 'optodes' or optical equivalents of the electrochemical sensors described above. However, we can expect to see some of these systems being developed over the next few years.

The optically responsive ligands described in the literature contain either a chromophore or fluorophore which is either joined to or part of the calixarene backbone. On complexation, the environment of the chromophore or fluorophore is

sufficiently perturbed to produce a significant change in the UV-vis or fluorescence emission spectrum, respectively. In the case of the former, this is usually achieved by using an acidic chromophore in the presence of a base which is not strong enough to deprotonate the free ligand (i.e. the equilibrium in Equation (4) below favours the left-hand side). However, on complexation with a cation (Equation (5)), the additional positive charge residing in the calixarene cavity makes the chromophore a much stronger acid (i.e. $K_{a(C)} > K_{a(L)}$), and in the presence of the base, is deprotonated (i.e. the equilibrium in Equation (6) favours the right-hand side), shifting the UV-vis absorption to longer wavelengths (Figure 5). This shift in wavelength is easily monitored, and provided the selectivity of the parent calixarene is retained (not usually the case as the observed selectivity depends on three factors, the complexation of the metal ion, the effect of the metal ion on the acidity of the chromophore and the stability of the resulting deprotonated complex). These processes can be summarised as:

$$L\!-\!COH + B \overset{K_{a(L)}}{\rightleftharpoons} L\!-\!CO^- + BH^+ \tag{4}$$

$$L\!-\!COH + M^+ \rightleftharpoons LM^+\!-\!COH \tag{5}$$

$$LM^+\!-\!COH + B \overset{K_{a(C)}}{\rightleftharpoons} LM^+\!-\!CO^- + BH^+ \tag{6}$$

where L is the calixarene ligand, —COH is the acidic chromophore, B is the base, and M^+ is the metal ion. A variety of chromophores have been investigated, including nitrophenol [35, 36] and azophenol [37, 38] derivatives, and in most cases selective colour transduction on metal complexation has been achieved, although the selectivity is generally not as good as with the electrochemical equivalents (an exception is the chromogenic calixarene selective for potassium described by King et al. [39]). Further papers on similar systems are continuing to appear regularly in the literature [40].

Fluorescent derivatives have also been investigated for selective optical transduction of metal complexation [41–44]. Perturbation of the fluorophore is achieved through variation in the rigidity of the molecule accompanying complexation, or through the judicious positioning of fluorophores and quenching groups in such a way that the degree of quenching changes markedly due to conformational adjustments accompanying complexation. Once the effect of metal ion complexation on the emission spectrum is known, monitoring a responsive emission wavelength as a function of time enables transient changes in the concentration of metal ions to be detected (Figure 6).

11. Patents

A search of the patent literature has revealed 83 patents filed which include the use of the keyword 'calixarene'. These patents cover methods of preparation/synthesis
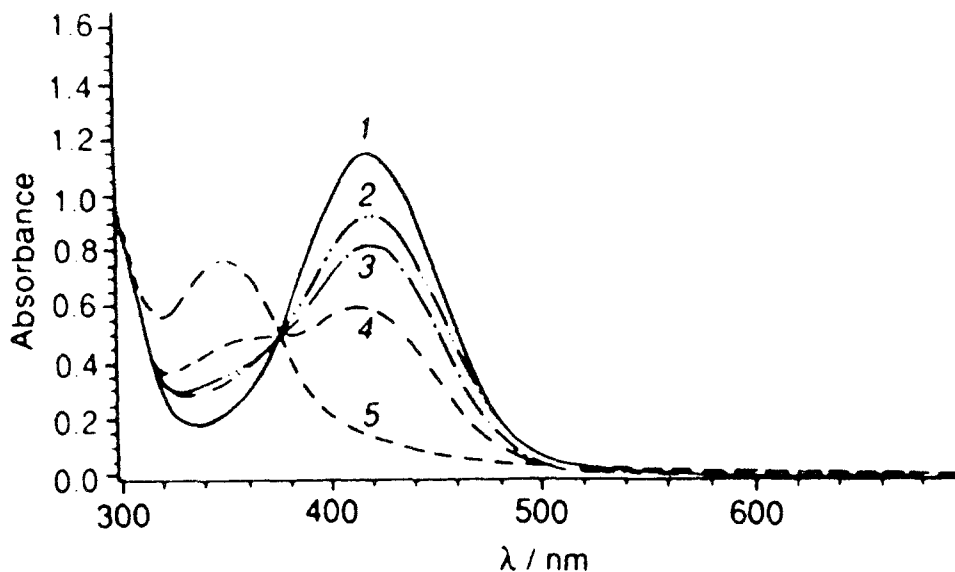
Fig. 5. Typical shifts in UV-vis absorbance accompanying complexation of a metal ion (in this case Li^+) by calixarene chromoionophore bearing acidic (ionisable) groups (in this case nitrophenyl-type moieties) in the presence of a base (0.1 M morpholine). The results show shifts brought about by additions of $LiClO_4$ to a 5×10^{-5} M solution of the ligand in THF containing 20 mm^3 morpholine to give final Li^+ concentrations of 0.1 M (1), 10^{-2} M (2), 4×10^{-3} M (3), 8×10^{-4} M (4), 2×10^{-5} M (5). Addition of the metal ions changes the solution from colourless to yellow. Data from references [35] with permission. Ligand: Tetramer as in Table I

with R =
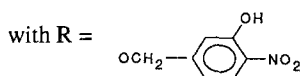
of certain calixarene derivatives, or their use in a wide variety of applications including corrosion inhibitors, fuel additives, hair dyes, charge controlling agents for developing electrostatic images, additives in epoxy resins and adhesives, developer solution for photographic negatives, extraction of uranium ions, deodorant additive, and stabilisers in rubbers. Very recently, the first chemical sensor related patents have begun to appear, and this trend will probably continue, given the obvious commercial importance of these devices. Of the four sensor patents, three relate to electrochemical sensors [45–47] for alkali metal ions, and one to the use of cation complexing dyes (chromoionophores) in optical sensors [48].

12. The Future

Sensing applications of calixarene derivatives are only beginning to develop. The potentiometric and other electrochemical sensors for metal ions can be regarded as the first generation of these sensors. Calixarenes capable of optically signalling complexation with metal ions, while valuable in their own right, could be the precursors of much more interesting sensing materials (see for example the fluorescence signalling of encapsulation of a flavin, pteridine, by calix[4]arene host
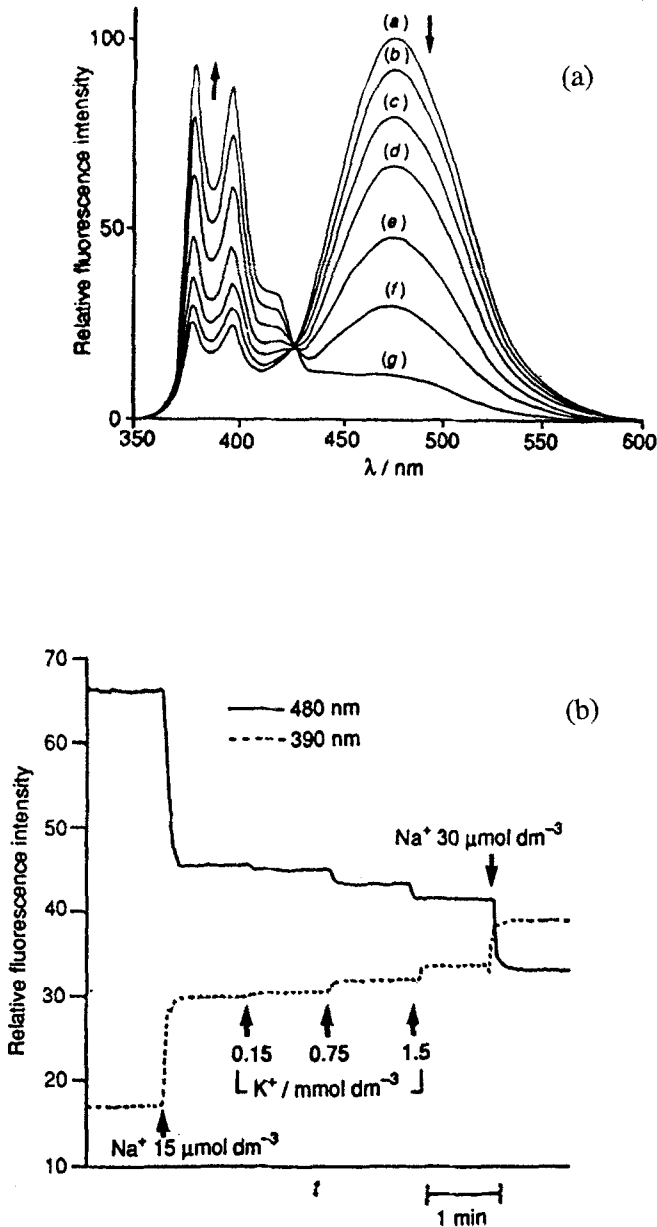
Fig. 6.   (a) Changes in fluorescence emission spectra obtained with fluorescent labelled calix[4]arene derivatives on addition of NaSCN and (b) selectivity of fluorescent response measured at 480 nm and 390 nm on addition of Na^+ and K^+ ions. Data from reference [43] with permission.

capable of changing from a 'closed' to an 'open' form [49]). It is now recognized that calixarenes can be used as building blocks of much more substantial structures which could be used to sense a huge number of potential hosts, ranging from neutral

gaseous molecules (e.g. toxic solvent vapours) to amino acids or more complex biological molecules. The key to achieving these new and exciting possibilities lies with a deeper understanding of the fundamental behaviour of these systems at the molecular level through detailed NMR and molecular modelling/molecular dynamics studies [50], and statistical analysis of the molecular basis of macroscopic properties [51]. Given the rapidly growing amount of basic information on calixarene host–guest behaviour, this will hopefully become a reality sooner rather than later.

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