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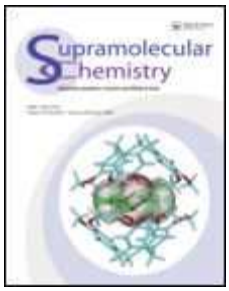

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Development of a calix[4]arene sensor for soft metals based on nitrile functionality.

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Abstract

The current work is amongst the first to examine the potential usefulness of the nitrile functional group in potentiometric analytical sensors for soft metals. Nitrile functionality has hereby been incorporated into a calix[4]arene skeleton to give a series of new cation selective hosts. The analytical sensing behaviour of these hosts was examined by Ion Selective Electrode (ISE) based potentiometry. In all cases a preference for soft metals was observed, explained primarily in terms of soft-soft compatibility between calix[4]arene nitrile hosts and metal guests in combination with a classical 'lock and key' best fit mechanism. Hosts **2**, **3** and **4** showed very strong responses towards Hg(II) ions, with Ag(I) being the main interferant. The introduction of electron delocalising aromaticity proximal to the nitrile functionality was thought to reduce the availability of negative charge for cation coordination, apparently affecting the Hg(II) cation in particular. An acute fall in Hg(II) response coupled with the emergence of Ag(I) as the primary ion was observed for **7** and **8**.

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Keywords: Calixarene, nitrile, mercury, silver, Ion Selective Electrodes (ISE), potentiometry.

Introduction: Calixarenes are a class of supramolecular receptor, synthesised by phenol-formaldehyde condensation reaction, to give oligomers comprising a central

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macrocycle of varying repeat phenolic units linked by methylene groups at the o position. Since their description by Gutsche in the 1980s[1], many calixarene derivatives have been described, due to the ease of modification of the so called upper and lower rims of the calixarene's central annulus[2-7]. The most noteworthy achievement of these structural modifications has been the advent of many cation selective host compounds. The *t*-butylcalix[4]arene family substituted at the lower rim have proven especially popular for this purpose, yielding highly preorganised and symmetrical supramolecular structures, often restricted to a cone conformation due to upper rim bulky *t*-butyl groups. The properties and characterisation of the calix[4]arene scaffold are well established[1,8].

The quintessential calix[4]arene host is the symmetrically substituted tetraester type compound like **1**[9]. This neutral host offers a polar cavity on its lower rim with localised negative charge provided by four ester carbonyls and four phenoxy oxygens. This represents a host providing an ideal 'lock and key' fit for the sodium ion as well as providing hard donor oxygens to coordinate effectively with the sodium ion. The sodium selectivity of the tetraester may be considered a kind of default for calix[4]arenes with extensive potentiometric investigations on these calix[4]arens already published[10]. Because of their excellent binding characteristics (selectivity, reversibility and rapid kinetics), their potential as active agents in chemical sensors was recognised at an early stage and in particular, several derivatives have provided the basis for successful ion-selective electrodes[3,9-11]. Similar but somewhat less celebrated success was achieved when soft donor groups are used. Selectivity has been observed for softer cations (e.g. transition metals, lanthanides and heavy metals)[12-14].

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The synthesis of the asymmetric tetranitrile calix[4]arene **2** was previously described[15]. Initial potentiometric screening of **2** confirmed the absence of sodium selectivity. This prompted the screening of **2** and related alkyl nitrile calix[4]arenes **3** and **4** by potentiometry for response towards a comprehensive range of hard and soft cations.

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In previous cases where nitrile groups have been incorporated into a molecular backbone such as a calixarene or a bis-calixarene, these compounds have been used (in monomeric form or attached to a polymer backbone), to perform multiphase extraction experiments of metals[16-20]. Hg(II) in particular was found to be extracted well in most cases. The best Hg(II) selectivity was observed for the alkyl nitrile substituents[21]. Aryl nitrile substituents enabled a delocalisation of nitrile electrons over the proximal π-electron cloud leading to less pronounced selectivity.

The early work on Hg(II) coordination involved solvent extraction experiments using macrocyclic polythiaether ligands[22-25]. These studies revealed Ag(I) as the main co-extractant (equivalent to interferant in sensor terms). Furthermore, recent developers of Hg(II) sensitive compounds often implicate silver (I) as a major co-analyte[26-30].

Electrochemical Hg(II) sensors developed recently include an ISE of a calix[4]crown based on imine[30], an ISE of a mercapto based system with it's soft nitrogen and sulphur donors[31] and a more classical thia-crown ether based ISE[32] amongst others[33,34]. Several charged compounds used in electrodes for Hg(II) detection have also been reported[35-37].

Relatively little reference is made in the literature to the cation coordinating ability of the soft nitrile functional group in analytical sensors. The use of nitrile functionality in calixarene (or other scaffolds) based Ion Selective Electrodes (ISEs) has not been reported to date to the best of our knowledge.

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The aims of the current work were, using potentiometry to (1) investigate the mode of binding towards metals of a series of nitrile calixarenes and compare selectivity patterns (2) change ISE membrane parameters like polarity and host structure and correlate these changes to an analytical signal (3) discuss viability of calix[4]arene nitriles for use in chemical *sensors* for soft metals by focussing particularly on reversible and selective analyte detection and (4) to allude to future work and structural tuning strategies for synthesising improved supramolecular hosts with nitrile functionality.

Results and Discussion: The synthesis of **3** and **4** were carried out according to Scheme 1 and Scheme 2 respectively. **1**, **2**, **7** and **8** were synthesised as described elsewhere (Figure 1).

Scheme 1. The synthesis of 3.

Scheme 2. The synthesis of 4.

Neutral hosts **3** and **4** are asymmetrically tetrasubstituted on the lower rim, each containing four alkyl groups. In each case, two of the alkyl chains terminate with nitrile groups. The two possible cation binding sites within each of these compounds are the four hard phenoxy oxygens just below the calixarene's annulus and the two soft nitrile groups, either of which may interact with cations. Host **3** contains the two possible binding sites in close proximity, thus allowing possible cooperative binding between the two sites. Host **4** contains the two sites at a greater distance from each other and so in contrast a cation guest is more likely to interact with one *or* the other. The other host calixarenes discussed in the current report are shown in Figure 1.

Figure 1. Structures of calixarenes 1, 2, 7 and 8.

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Figure 2 highlights some of the absolute ISE potentials observed when **2** was screened separately with a selection of cations in aqueous solution of specific activity, log a = -3.0.

Figure 2. Potentials of an ISE based on 2 screened with a selection of cations, each at log a = -3.0. The effect of changing membrane plasticizer is also shown.

It can be seen that **2** shows a strong response towards soft metals, in particular to Hg(II) and Ag(I). The selectivities of ISEs are expressed formally by selectivity coefficients, K_{IJ}^{pot}, based on the Nernst equation[38,39]. Activity values are calculated using activity coefficients as calculated by equations based on the Debye-Hückel theory and have been calculated previously for many common electrolytes[40,41]. In this way concentration values, although often numerically similar, can be presented as activities. Activity values are more applicable than concentration for determining selectivity values as seen in the Nernst based equation 1.

Using the Separate Solutions Method (SSM), the selectivities were calculated for **2**, **3** and **4**. The SSM method is based on establishing potential values in separate aqueous solutions, each containing the same activity of a different ion. By taking the difference of pairs of potentials into account (primary ion I and each interferant, J, in turn) selectivity values are determined, according to Equation 1, based on the Nernst equation.

$$\text{Log } K_{IJ}^{pot} = \frac{z_I F(E_J - E_I)}{2.303RT} + \log\left(\frac{a_I}{a_J^{z_I/z_J}}\right) \qquad \text{(Equation 1)}$$

E_J and E_I are the potential values for the interferant and primary ion respectively. The activities of the separate solutions are usually the same (a_I=a_J). Table 1 shows selectivity coefficients for a comprehensive range of cations tested.

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Table 1. Selectivity Coefficients, log $K^{pot}_{Hg^{2+}J}$, for 2, 3 and 4, calculated using the Separate Solutions Method (SSM).

The very strong selectivity towards silver (I) and mercury (II) is immediately apparent from Figure 2 and confirmed in Table 1. The soft metals in general show a better response than the harder group I and II metals. This indicates that perhaps the nitrile functionality of the current host series dictates the response rather than the phenoxy oxygen atoms, which is consistent with the predicted conformation from theoretical calculations (Figure 3).

The theoretical molecular models in Figure 3 reveal the classic calixarene cone conformation adopted, allowing the selective binding of sodium ions by tetraester **1**, involving phenoxy and ester carbonyl oxygens. Conversely, we speculated that **2** (and related calixarene nitriles) would bind cations by association with nitrile functional groups as seen in Figure 3. This example of **2** coordinating a cation shows a more peripheral cavity binding at a greater distance from the annulus, not significantly involving the calixarenes phenoxy oxygen atoms.

Figure 3. General modes of complexation of 1 and 2 with cations. Software and calculation details are in the Experimental section.

The cone conformation of calix[4]arene **2** was initially confirmed by its ^{1}H NMR spectrum[15]. A pair of doublets at 4.33 and 3.28ppm, correspond to the protons of the methylene groups linking the central benzenes. This suggests a cone conformation according to a method of determining calix[4]arene conformation described by Gutsche[1]. Furthermore the upper rim *p-tert*-butyl groups and lower rim substituents of **2** are likely to prevent significant deviation from the cone conformation by blocking free rotation of benzenes through the central cavity.

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The selectivity of an ISE can be modified by a number of strategies[38]. For example ISE membrane polarity can influence selectivity. Selectivity for divalent cations is generally enhanced in more polar membrane phases[42]. The polarity of the ISE membrane of 2 was changed by changing the plasticizer from NPOE (dielectric constant ε_r = 23.9) to DOS (ε_r = 3.9). This spans the majority of the polarity range of common ISE plasticizers. From Figure 2 it can be seen that the resultant ISE potentials observed were lower in general accompanied by somewhat more uniform selectivities as seen in Table 1. The NPOE membranes showed similar selectivities for Ag(I) and Hg(II), whereas for the DOS based ISE of 2, there is a considerable margin of selectivity of Ag(I) over Hg(II) (log $K^{pot}_{Hg^{2+}Ag^{+}}$ 2.2). However, the interference from group I metals like sodium and potassium is much greater with log K^{pot}_{IJ} values increasing by approximately six and five orders of magnitude respectively compared to NPOE based membranes. Similarly, proton interference was a greater factor with DOS membranes indicative of greater pH sensitivity. These observations are due to a much smaller margin of response between Ag(I)/Hg(II) and other cations when DOS plasticizer was used (Figure 2). In light of these observations, it was decided to use only NPOE for all further ISE work on Hg(II)/Ag(I) selective systems based on further receptors.

Table 2 reveals the ISE titration slopes obtained for Ag(I) and Hg(II) of the ISEs tested.

Table 2. Characteristics of ISEs based on 2, 3 and 4 for the indicated activities.

This ISE data was used to shed light on the complex formation process specifically. All slopes obtained for Hg(II) were super-Nernstian, except for the DOS membrane. Concurring with the slope values for mercury (II) is the abrupt Donnan failure (Figure 4) of the titration curves at higher concentrations of Hg(II) (log a ~ -2.0) .

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Figure 4. ISE titrations of 2, 3 and 4 showing Donnan failure occurring at higher cation concentrations.

Donnan failure is caused by the co-extraction of counter ions of measured ions and can be symptomatic of excessive affinities of an ISE towards the measured ion.

The complex formation process is known to be a major perpetrator causing Donnan failure with high analyte affinity or complex stabilities lowering the upper concentration limit at which the phenomenon takes place[43]. When developing a potentiometric sensor from a host compound, Donnan failure and its causes, as observed, would certainly impair the process of optimising the lower limit of detection (LOD) below the frequently observed classical LOD in the µM region. In addition, such a sensor would show poor reversibility[11,39,44].

Donnan failure and/or super-Nernstian slopes were observed for **2**, 3 and 4 in response to Hg(II) in all cases at log a ~ -2.0, regardless of membrane polarity. The phenomenon was further probed in the case of 2. Figure 5a shows the dynamic response when an ISE containing 2 was placed from water into a 10^{-2}M solution of Hg^{2+} and placed directly back into water. Even after 1.5 hours, the sensor had not recovered it's starting potential. Analogously, an ISE of 2 conditioned and filled with 0.01M $HgCl_2$ instead of 0.01M NaCl showed very little sensitivity towards mercury (II) over a large concentration range (Figure 5b). Therefore, in order to show *unbiased* selectivity coefficients, a non-primary salt, NaCl, was generally used for ISE filling and conditioning for the current work[39].

Figure 5. (a) The dynamic recovery of an ISE of 2 after exposure to 0.01M $HgCl_2$: Partial recovery after 1.5 hours. (b) The reduced sensitivity of an ISE of 2 with $HgCl_2$ filling and preconditioning .

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Another strategy therefore was to structurally modify the ionophore/host itself to modulate the interaction with guests. For example to lower the Hg(II) affinity or improve Ag(I) selectivity, strategies had to be applied to weaken the affinity of nitrile calix[4]arenes towards mercury (II) ions.

Hosts 3 and **4** contain only two instead of the previous four possible coordinating nitrile groups. It was thought that this would generally reduce complex stability. Furthermore, 3 has a smaller and more rigid lower rim cavity than **4**, which has longer alkyl nitrile appendages yielding a larger more flexible cavity.

The availability of somewhat more confined preorganised cavities in 2 and 3, with nitriles closer to the calix[4]arene annulus, may have resulted in the identical selectivities towards mercury (II) observed (Table 1), with marginal selectivity over silver (I) for both hosts. Conversely, **4** showed a modest selectivity for silver(I) over mercury(II). The larger silver ion may favour the greater flexibility of the two nitrile groups in the cavity of **4**. Table 3 compares the ionic radii of some selected cations[45].

Table 3. Ionic radii of selected cations.

Unlike with Hg(II), **2**, 3 and 4 yielded Nernstian or near Nernstian slopes for silver(I) and Donnan failure was not observed in the activity ranges of titrations carried out.

By and large, Hg(II) selectivity values over other cations are quite similar for **2**, 3 and 4 (Table 1). Lowering the number of nitriles from four to two did not yield a noticeably weaker Hg(II) interaction. As Hg(II) ions are known to preferably form two coordinate linear complexes[40], the tetrahedral arrangement of nitrile functionality offered by 2 may not necessarily lead to stronger complex formation compared to dinitriles 3 and **4**.

In order to maintain the selectivity of Ag(I)/Hg(II) over the other cations but to discriminate more between them, hosts **7** and **8** were synthesised. These introduce

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aromatic moieties proximal to the nitrile functionality (Figure 1), and, in addition, each lower rim benzene ring contains two nitrile groups, the idea being that one nitrile of each benzene ring would serve as guest coordinator whilst the other nitrile group and benzene ring would serve as electron withdrawing and delocalising agents respectively. It was hoped that the net effect would be to weaken the affinity for cations of these hosts by reducing the availability of negative charge. It was thought that this would suppress the excessive Hg(II) affinity previously observed and possibly induce discrimination between Ag(I) and Hg(II). With the large margin of selectivity of Hg(II)/Ag(I) previously enjoyed over the other cations for **2**, **3** and **4**, a modest loss in overall selectivity could be sustained.

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Table 4 shows the selectivity values obtained for **7** and **8**, from ISEs prepared in an identical fashion to the other receptors described.

Table 4. Selectivity Coefficients, log $K^{pot}_{Ag^+J}$, for 7 and 8, calculated using the Separate Solutions Method (SSM).

Immediately apparent was the suppression of the Hg(II) sensitivity but maintenance of the Ag(I) response. Interestingly, selectivities are more uniform in the case of **8** and the margin of selectivity of Ag(I) over the other cations is greater for **7** (e.g. log $K^{pot}_{Ag^+Hg^{2+}}$ of -5.1 and -3.3 for **7** and **8** respectively) . Perhaps this is due to the larger more flexible cavity of **8** discriminating less between cations than the more rigid preorganised cavity of **7**. The ISE characteristics of **7** and **8** (Table 5) confirmed that they are poor hosts for Hg(II) as response slopes went from previously observed super-Nernstian to sub-Nernstian (Typically >+40mV/decade for **2**, **3** and **4** compared to <+15mV/decade for **7** and **8**). Furthermore, Donnan failure is absent in the activity ranges examined. Slopes closer to Nernstian values were observed for Ag(I) in all cases.

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Table 5. Characteristics of ISEs of 7 and 8 at the indicated activities.

Conclusion: The current work describes calix[4]arene host systems based on nitrile functional groups, which display excellent Hg(II)/Ag(I) selectivity over other cations. In the course of the work described, an 'overtuning' of host structure led to the near suppression of a formerly excessive Hg(II) response, leaving Ag(I) as the primary analyte. In all cases changes in potentiometric ISE data could be correlated to the structural differences between hosts examined. ISEs were found to be an excellent tool for the design of host systems, as they conveniently served to evaluate the work of the organic chemist whilst representing an analytical technique known to be readily implementable in real life pratical sensors.

It was found that structural modifications of the host ionophore had a more dramatic effect on selectivity patterns observed than changing other ISE membrane components like membrane plasticizer (affecting polarity). The positioning of electron withdrawing groups and delocalising aromaticity proximal to the coordinating nitriles (**7** and **8**) led to a dramatic suppression of the Hg(II) response observed before and a corresponding Ag(I) selectivity. On the other hand, changing the number of nitrile groups available for binding and changing cavity dimensions (**2**, **3** and **4**) did not appear to dramatically change the high affinity for Hg(II). It is thought that Hg(II) forms a two coordinate complex with two nitrile groups per calixarene host, perhaps in a tweezer like fashion. This is in agreement with the theory suggesting Hg(II) ions ideally form linear two coordinate complexes.

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The structural fine tuning of present hosts is ongoing. In particular, efforts will focus on modifying the chemistry proximal to the nitrile groups in a way that could yield a practical and reversible Hg(II) sensor, by controlling the localisation of negative charge available for cation coordination. A further strategy will be to adorn other

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molecular scaffolds, apart from calixarenes, with cation coordinating nitrile groups for the purpose of soft metal sensor development.

Materials and methods: The synthesis of hosts **1**[3], **2**[15], **5**, **7** and **8**[46] was described elsewhere. NaH used was a 60% dispersion in mineral oil. All reactions were carried out under argon. The name *p-tert*-Butylcalix[4]arene was used instead of the IUPAC name for convenience: 5,11,17,23-tetra-*p-tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene.

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HPLC was carried out using a HP1100 with UV detection. For LC-MS and direct injection MS work, a Bruker/Hewlard-Packard Esquire system, using a positive ESI source and the software's default 'smart' settings were used. Mobile phase used was isocratic LC grade Acetonitrile with 0.25% formic acid content. This also served as the sample solvent. A Synergy 150.0 x 2.0mm, 4µm Fusion-RP column was used. Flowrate was 0.2ml/min. Detection wavelength was 210nm. Injections were 5µl of 0.5mg/ml sample.

Potentiometric membranes were prepared using 250mg 2-Nitrophenyl octyl ether, 125mg PVC, 6.5mmol Kg^{-1} host ionophore and 2.7mmol kg^{-1} potassium tetrakis(4-chlorophenyl) borate dissolved in dry THF and evaporated slowly.

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The electrochemical cell used consisted of a double junction reference electrode and a PVC membrane working electrode in the following arrangement:

Ag | AgCl | 3M KCl ‖ 0.1M LiOAc ‖ sample solution | PVC membrane | 0.01M NaCl | AgCl | Ag. Membranes were conditioned in 0.01M sodium chloride for 12 hours and deionised water for half an hour prior to ISE titrations. The potentiometric cell was interfaced to a PC using a National Instruments SCB-68 4-channel interface. All ISE measurements were performed in triplicate.

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Energy minimised molecular models were generated using Chem3D pro v.8.0 software, using the MM2 forcefield method. **5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(cyanomethyl)-oxy]-26-28-bis[(butyl)-oxy]calix[4]arene (3)**. Calixarene **5** (2.0g, 2.76mmol) and NaH (0.22g, 5.52mmol) was stirred 1 h at room temperature in anhydrous DMF (100ml). 4-Bromobutane (0.82g, 5.52mmol) was added batch wise and the mixture was stirred at 75 ^{o}C for 24 h and a further aliquot of NaH and 4-bromobutane added as above. The reaction was monitored by HPLC-MS. After a further 24 h, the DMF was evaporated and the residue taken up in CH_2Cl_2 (200ml), washed with 1N HCl (100ml), H_2O (50ml), brine (50ml) and saturated NH_4Cl (50ml) and dried with Mg_2SO_4. After filtration the CH_2Cl_2 was removed to yield an oily solid. Upon washing with 20ml MeOH at 0°C, 0.84g of a white solid was obtained: yield 37%; mp 165-170 ^{o}C; IR (KBr) 2174cm^{-1} (CN); ^{1}H NMR δ 7.16 (s, 4H), 6.42 (s, 4 H), 5.01 (s, 4H), 4.39 and 3.24 (ABq, 4H, J = 13.0), 3.78 (t, 4H), 1.97 (m, 4H, J = 7.2), 1.49 (m, 4H, J = 7.6), 1.35 (s, 18H), 1.00 (t, 6H, J = 7.2), 0.79 (s, 18H); ^{13}C NMR δ 152.6 (s), 151.9 (s), 147.6 (s), 144.7 (s), 135.8 (s), 131.4 (s), 126.1 (s), 124.6 (s), 117.2 (s), 76.1 (s), 57.8 (s), 34.8 (s), 33.6 (s), 32.5 (s), 31.6 (s), 31.0 (s), 22.7 (s); 19.5 (s), ESI mass spectrum +m/e 861.4 ([M + Na^{+}], calcd 861.5); HPLC purity: 95.6%. Anal. Calcd for $C_{56}H_{74}N_2O_4$: C, 78.46; H, 8.94; N, 3.27. Found: C, 78.42; H, 9.18; N, 2.90.

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(cyanopropyl)-oxy]-26-28-dihydroxycalix[4]arene (6). *p-tert*-Butylcalix[4]arene (5.0g, 7.72mmol), K_2CO_3 (1.28g, 9.26mmol) and bromobutyronitrile (2.41g, 16.20mmol) was heated in CH_3CN (80ml) at 80 ^{o}C for 5 days. The reaction was monitored by LC-MS. The solvent was evaporated and the residue taken up in CH_2Cl_2 (300ml), washed with 1N HCl (100ml), H_2O (50ml) and brine (50ml) and dried with Mg_2SO_4. CH_2Cl_2 was

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evaporated and the residue was recrystallised from $CHCl_3$/MeOH yielding 3.7g of a white solid: yield 61%; mp 295-300 °C; IR (KBr) 2250 cm^{-1} (CN), 3406 cm^{-1} (OH) ; ^{1}H NMR δ 7.46 (s, 2H), 7.05 (s, 4 H), 6.86 (s, 4H), 4.16 and 3.37 (ABq, 4H, J = 13.0), 4.09 (t, 4H, J = 5.6), 3.05 (t, 4H, J = 7.2), 2.34 (m, 4H, J = 5.6), 1.27 (s, 18H), 1.00 (s, 18H); ^{13}C NMR δ 150.3 (s), 148.8 (s), 147.6 (s), 142.1 (s), 132.6 (s), 127.5 (s), 125.8 (s), 125.3 (s), 119.5 (s), 73.3 (s), 34.0 (d), 31.8 (d), 31.0 (s), 26.6 (s), 14.2 (s); ESI mass spectrum +m/e 805.5 ([M + Na^+], calcd 805.5); HPLC purity: 97.3%. Anal. Calcd for $C_{52}H_{66}N_2O_4$: C, 79.76; H, 8.50; N, 3.58. Found: C, 79.64; H, 8.44; N, 3.54.

5,11,17,23-Tetra-*p-tert*-butyl-25,27-bis[(cyanopropyl)-oxy]-26-28-bis[(butyl)-oxy]calix[4]arene (4). Calixarene 6 (4.0g, 5.12mmol) and NaH (0.41g, 10.21mmol) was stirred 1 h at room temperature in anhydrous DMF (100ml). 4-Bromobutane (1.52g, 10.21mmol) was added batch wise and the mixture was stirred at 75 °C for 24 h and a further aliquot of NaH and 4-bromobutane added as above. The reaction was monitored by HPLC-MS. After a further 24 h the DMF was evaporated and the residue taken up in CH_2Cl_2 (200ml), washed with 1N HCl (100ml), H_2O (50ml), brine (50ml) and saturated NH_4Cl (50ml) and dried with Mg_2SO_4. After filtration the CH_2Cl_2 was removed to yield an oily solid. Upon washing with 40ml MeOH at 0°C, 3.89g of a white solid was obtained: yield 85%; mp 190-195 °C; IR (KBr) 2244cm^{-1} (CN); ^{1}H NMR δ 7.06 (s, 4H), 6.52 (s, 4 H), 4.30 and 3.17 (ABq, 4H, J = 12.8), 4.06 (t, 4H, J = 7.2), 3.74 (t, 4H, J = 7.2), 2.64 (t, 4H, J = 7.6), 2.41 (m, 4H, J = 7.6), 1.86 (m, 4H, J = 7.6), 1.49 (m, 4H, J = 7.6), 1.28 (s, 18H), 1.02 (t, 6H, J = 7.6), 0.88 (s, 18H); ^{13}C NMR δ 153.4 (s), 152.3 (s), 145.5 (s), 144.3 (s), 135.1 (s), 132.1 (s), 125.6 (s), 124.7 (s), 119.9 (s), 75.7 (s), 72.7 (s), 34.1 (s), 33.7 (s), 31.7 (s), 31.2 (s), 30.9 (s), 25.9 (s); ESI mass spectrum +m/e 917.4 ([M + Na^+], calcd 917.5); HPLC purity:

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97.5%. Anal. Calcd for $C_{60}H_{82}N_2O_4$: C, 80.49; H, 9.23; N, 3.13. Found: C, 80.50; H, 9.41; N, 3.01.

Acknowledgements: Funding for BS was provided by Enterprise Ireland, grant code SC/2002/161**.** We also thank Science Foundation Ireland for support under the Adaptive Information Cluster award (SFI03/IN3/1361). Finally thanks to the Environmental Protection Agency, Ireland, funding code EPA2004-RS-AIC-M4.

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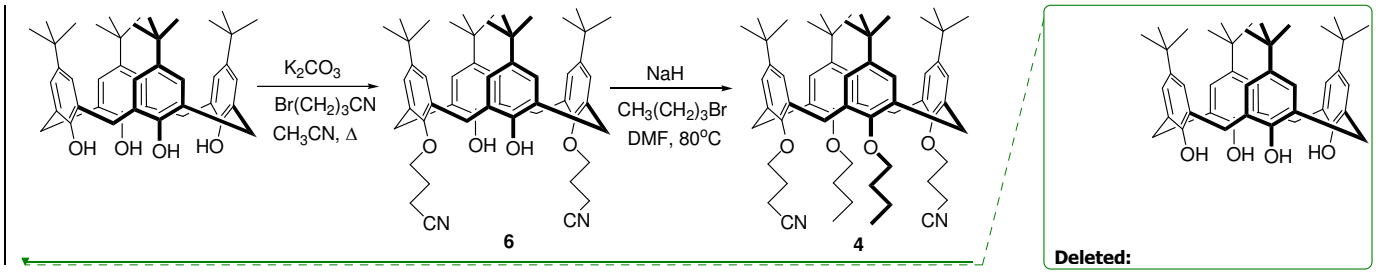
Scheme 2. The synthesis of 4.



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Host	2	4	3	2
Plasticizer	NPOE	NPOE	NPOE	DOS
Hg^{2+}	0	0	0	0
Ag^{+}	-0.19±0.07	0.95±0.14	-0.25±0.12	2.25±0.10
Pb^{2+}	-7.86±0.07	-7.20±0.00	-7.03±0.14	-3.02±0.02
Cu^{2+}	-7.00±0.09	-7.73±0.02	-6.56±0.19	-1.62±0.03
Co^{2+}	-8.21±0.10	-7.74±0.14	-8.03±0.07	n/a
Cd^{2+}	-9.41±0.07	-8.64±0.02	-8.84±0.12	-5.04±0.03
Zn^{2+}	-8.82±0.07	-8.88±0.02	-9.32±0.12	-4.75±0.02
H^{+}	-5.52±0.14	-5.02±0.02	-5.00±0.33	0.72±0.02
Mg^{2+}	-9.32±0.05	n/a	n/a	n/a
Ca^{2+}	-8.82±0.05	n/a	n/a	n/a
Li^{+}	-7.48±0.05	n/a	n/a	n/a
K^{+}	-3.91±0.07	-2.49±0.02	-3.45±0.24	0.72±0.02
Na^{+}	-6.23±0.08	-4.94±0.00	-5.31±0.19	-0.25±0.02

Note: I is the primary ion Hg^{2+} and J is the interferant specified. The Separate Solutions Method (SSM) was used where log a_I=loga_J=-2.3. Reproducibility based on three ISEs. n/a = Data not available.

Table 1. Selectivity Coefficients, log $K^{pot}_{Hg^{2+}J}$, for 2, 3 and 4, calculated using the Separa Solutions Method (SSM).

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Host	Ion	Plasticizer	Range (log a)	Slope (mV/decade)	Donnan Failure (log a)
2	Hg^{2+}	NPOE	-4.0→-1.0	+49.7	-1.6
2	Hg^{2+}	DOS	-4.0→-1.0	+29.0	-1.6
3	Hg^{2+}	NPOE	-4.0→-1.0	+46.1	-1.6
4	Hg^{2+}	NPOE	-4.0→-1.0	+37.0	-1.6
2	Ag^{+}	NPOE	-4.0→-1.0	+56.9	NO
2	Ag^{+}	DOS	-4.0→-1.0	+54.8	NO
3	Ag^{+}	NPOE	-4.0→-1.0	+55.2	NO
4	Ag^{+}	NPOE	-4.0→-1.0	+53.4	NO

Note: NO=Not Observed. Theoretical Nernstian slopes are 59.6 and 29.3mV/decade for mono And divalent ions respectively.

Table 2. Characteristics of ISEs based on 2, 3 and 4 for the indicated activities.

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Ion	Radius (pm)	Coordination
K^+	138	VI
Na^+	102	VI
Hg^{2+}	102/69	VI/II
Ag^+	115/67	VI/II

Table 3. Ionic radii of selected cations.

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Host	7	8
Plasticizer	NPOE	NPOE
Hg^{2+}	-5.09±0.05	-3.26±0.02
Ag^{+}	0	0
Pb^{2+}	-4.50±0.02	-2.25±0.12
Cu^{2+}	-4.90±0.02	-3.07±0.14
Co^{2+}	-4.57±0.03	-2.80±0.11
Cd^{2+}	-4.96±0.04	-2.63±0.04
Zn^{2+}	-5.09±0.04	-2.80±0.06
H^{+}	-3.86±0.05	-2.29±0.06
Mg^{2+}	-6.66±0.10	-3.07±0.07
Ca^{2+}	-6.11±0.10	-2.49±0.02
Li^{+}	-4.00±0.01	-2.46±0.05
K^{+}	-1.78±0.03	-1.26±0.03
Na^{+}	-3.38±0.03	-2.09±0.01

Note: I is the primary ion Ag^{+} and J is the interferant specified. The Separate Solutions Method (SSM) was used where log a_I=loga_J=-2.3. Reproducibility based on three ISEs.

Table 4. Selectivity Coefficients, log $K^{pot}_{Ag^{+}J}$, for 7 and 8, calculated using the Separate Solutions Method (SSM).

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Host	Ion	Range (log a)	Slope (mV/decade)	Donnan Failure (log a)
7	Hg^{2+}	-4.0→-1.0	+14.8	NO
8	Hg^{2+}	-4.0→-1.0	+14.0	NO
7	Ag^{+}	-4.0→-1.0	+58.3	NO
8	Ag^{+}	-4.0→-1.0	+53.1	NO

Note: NO=Not Observed. Plasticizer used: NPOE.

Table 5. Characteristics of ISEs of 7 and 8 at the indicated activities.

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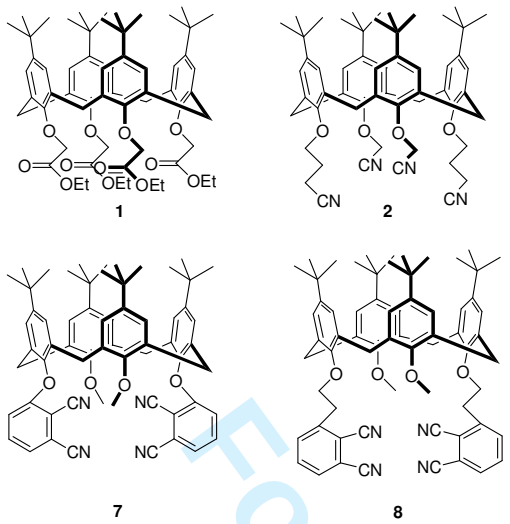
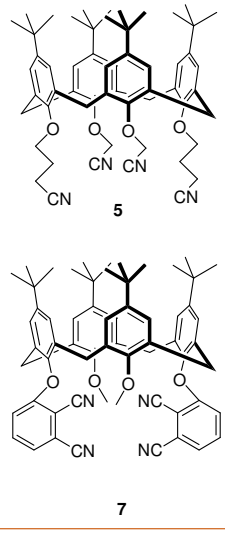


Figure 1. Structures of calixarenes 1, 2, 7 and 8.



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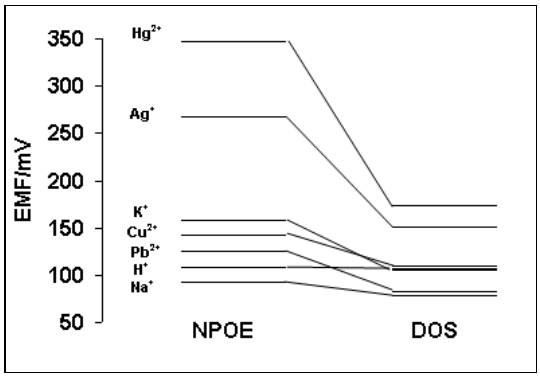

Figure 2. Potentials of an ISE based on 2 screened with a selection of cations, each at I activity (a) = -3.0. The effect of changing membrane plasticizer is also shown.

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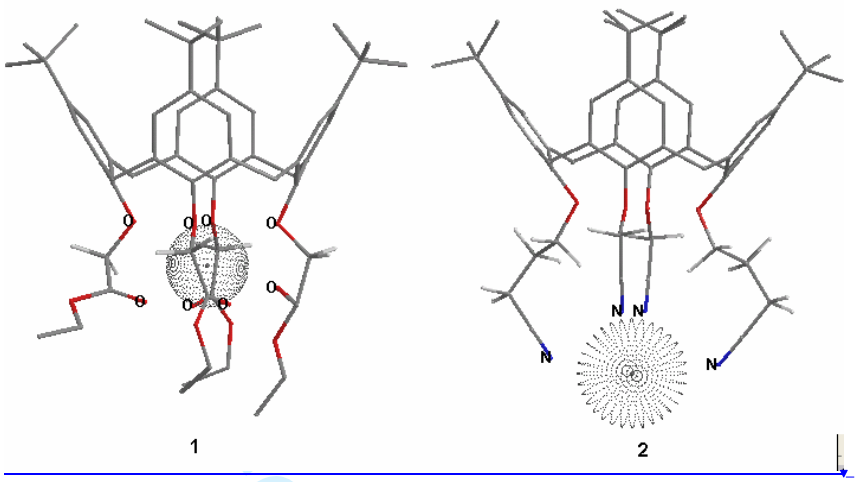

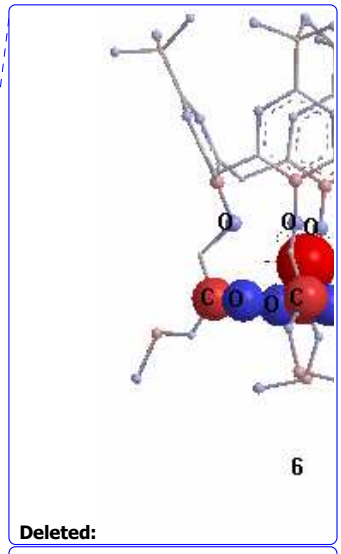

Figure 3. General modes of complexation of 1 and 2 with cations. Software a calculation details are in the Experimental section.

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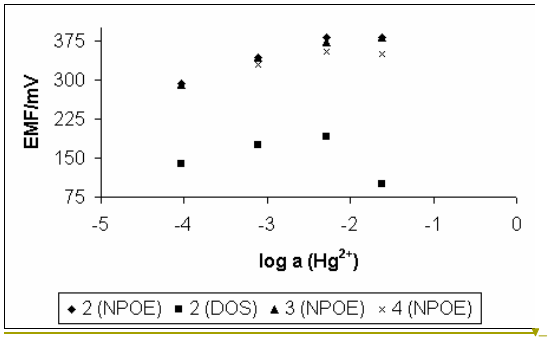

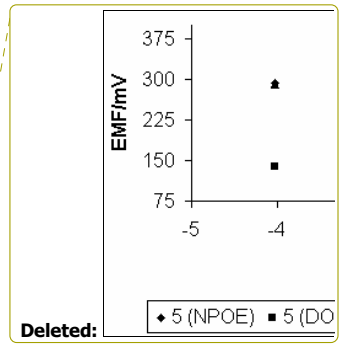

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Figure 4. ISE titrations of 2, 3 and 4 showing Donnan failure occurring at higher cation concentrations.

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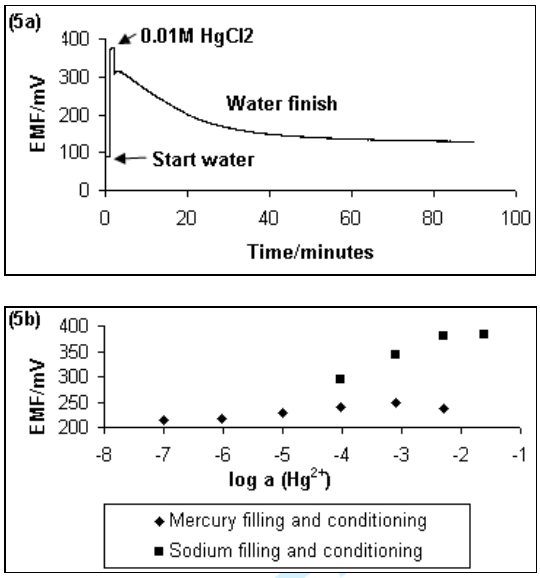

Figure 5. (a) The dynamic recovery of an ISE of 2 after exposure to 0.01M $HgCl_2$: Part recovery after 1.5 hours. (b) The reduced sensitivity of an ISE of 2 with $HgCl_2$ filling a preconditioning .

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