Di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 ligands in the cone conformation: Effect of acidic side arm length for solvent extraction of divalent metal ions

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ABSTRACT

Several new di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 compounds were prepared in the cone conformation. For comparison with reported ligands, the systematic structural variation was a change of the pendent acidic groups from two adjacent -OCH₂CO₂H or -OCH₂C(O)NHSO₂Z (with Z = -Me, -Ph, -C₆H₄-4-NO₂, -CF₃) units to two adjacent -O(CH₂)₄CO₂H or -O(CH₂)₄C(O)NHSO₂Z groups. Competitive solvent extractions of alkaline earth metal (AEMC) cations from aqueous solutions into chloroform by these ligands were performed. Also single species solvent extractions were conducted for the divalent heavy metal cations of Pb²⁺ and Hg²⁺. Comparison of the extraction data for the new ligands with those reported reveal that the ligands with shorter proton-ionizable side arms are more effective divalent metal ion extractants.

Calixarenes, Proton-ionizable, Selective binding, Solvent extraction

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1. Introduction

Calix[4]crown ethers are a combination of a calix[4]arene and a cyclic polyether. They continue to receive attention for their metal ion complexation properties.¹⁻⁶ Attachment of the polyether segment to two distal phenolic hydroxyl groups of the calix[4]arene unit produces a calix[4]arene-1,3-crown ether. On the other hand, connection of two proximal hydroxyl groups forms a calix[4]arene-1,2-crown ether.^{7,8} Of these two possibilities, calix[4]arene-1,3-crown ethers are more commonly encountered. Partially this is due to difficulties often encountered in the preparation of calix[4]arene-1,2-crown ethers. More importantly, low metal cation binding ability and poor selectivity have been generally observed for 1,2-crown calix[4]arene ligands.⁹⁻¹¹

Recently we discovered that certain calix[4]arene-1,2-crown ether ligands in the cone conformation (Figure 1) exhibit high Ba^{2+} binding efficiency and selectivity for competitive solvent extractions of alkaline earth metal cations (AEMC) from aqueous solutions into chloroform.¹² In these cone conformation ligands, the 1,2-crown ether unit is flanked by two side arms with acidic functional groups. This forms a pocket in which a complexed divalent metal ion can perch on the polyether oxygens while being sandwiched between the crown ether unit and the two ionized side arms.¹²⁻¹⁴ **In agreement, the high binding efficiency and selectivity observed for the ligands shown in Figure 1, do not extend to the crown-3 and crown-6 analogues.**^{14,15}

Fig. 1. Di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-4 and -crown-5 ligands in the cone conformation (**1** and **2**, respectively)

For the ligands shown in Figure 1, the acidic side arms were $-\text{OCH}_2\text{C}(\text{O})\text{Z}$ with a single methylene group between the phenolic oxygen and the carbonyl carbon of the ionizable group. To probe the effect of lengthening the acidic side arms, we undertook the synthesis and evaluation of di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 ligands **3a-e** (Figure 2) with

four carbons separating the phenolic oxygen and carbonyl group in each acidic side arm. In addition, we prepared **4**, a “hybrid” di(carboxylic acid) calixcrown-5 ligand with one short side arm and one long side arm.

Fig. 2. Structures of di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 ligands **3a-e** with elongated side arms and “hybrid” di(carboxylic acid) ligand **4**

The ligand syntheses and complexation of selected divalent metal ions as assessed by solvent extraction from aqueous solutions into chloroform are now reported.

2. Results and discussion

2.1. Synthesis of di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 ligands **3**

Synthesis of di-ionizable *p*-*tert*-butylcalix[4]-1,2-crown-5 ligands **3a-e** is depicted in Scheme 1. Reaction of *p*-*tert*-butylcalix[4]arene, tetraethylene glycol ditosylate, and NaH in DMF gave *p*-*tert*-butylcalix[4]arene-1,2-crown-5 (**5**) in 56% yield. Diester **6** was obtained in 40% yield by refluxing **5**, ethyl 5-bromopentanoate, and Cs_2CO_3 in MeCN. Diester **6** was hydrolyzed to di(carboxylic acid) **3a** in quantitative yield with Me_4NOH (TMAOH) in aqueous THF. By reaction with oxalyl chloride in refluxing benzene, di(carboxylic acid) **3a** was converted into the corresponding di(acid chloride), which was used without further purification. Reaction of commercially available sulfonamides with NaH in THF at room temperature was followed by addition of the di(acid chloride) in THF to give **3b-e** in 43-70% yields.

Scheme 1. Synthesis of side arm-elongated, di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-5 compounds **3a-e**. *Reagents and conditions:* a) Ts(OCH₂CH₂)₄OTs, NaH, DMF, 70 °C; b) BrCH₂(CH₂)₃CO₂Et, Cs₂CO₃, MeCN, reflux; c) TMAOH, aqueous THF, reflux; d) i) (COCl)₂, C₆H₆, reflux; ii) XSO₂NH₂, NaH, THF, r.t.

Selected ¹H and ¹³C NMR shifts for ligands **3a-e** are listed in the Table 1. Since few symmetry elements are present in the cone calix[4]arene-1,2-crown-5 ligands, many of the ¹H NMR signals were heavily overlapped.¹⁶ This made it difficult to deduce the conformation of the ligands from their ¹H NMR spectra and the conformational study relied on their ¹³C NMR spectra.¹⁶ For each ligand in the 1,2-crown-5 series, three carbon signals were observed for the bridge carbons of the calix[4]arene platform. The fact that those three carbon signals correlate to three pairs of AB patterns confirmed a 1,2-linkage for the crown ether moiety. The broad separation of the AB patterns confirmed the cone conformation for these compounds (Figure 3).

Table 1. Selected Proton and Carbon Chemical Shifts (ppm) for Ligands **3a-e** in CDCl₃

Ligand	NH /OH	ArCH ₂ Ar ^a	<i>t</i> -Bu
3a	---	30.61, 31.22, 31.26	1.07
3b	10.15	30.56, 30.68, 31.16	1.07
3c	10.30	30.53, 30.67, 31.08	1.06
3d	10.44	31.08, 30.93, 30.65	1.07
3e	---	30.57, 30.97, 31.06	1.07

^aCarbon chemical shifts for methylene bridge of calix[4]arene platform. **Fig. 3.** Portion of the ¹H-¹³C hetero cosy spectrum of ligand **3c** in CDCl₃

2.2. Synthesis of ‘hybrid’ calixarene ligand **4**

By reducing the equivalents of NaH used in the alkylation of **5** (Scheme 1) from 10 to 5, it was found that monoester **7** became the major product in 44% yield (Scheme 2). Monoester **7** was reacted with ethyl bromoacetate and NaH in THF to give the unsymmetrical “hybrid” diester **8** in 69% yield. Hydrolysis of the “hybrid” diester with TMAOH in aqueous THF gave the “hybrid” di(carboxylic acid) **4** in 90% yield.

Scheme 2. Synthesis of unsymmetrical “hybrid” *p*-*tert*-butylcalix[4]arene-1,2-crown-5 di(carboxylic acid) **4**. *Reagents and conditions:* a) $\text{BrCH}_2(\text{CH}_2)_3\text{CO}_2\text{Et}$, Cs_2CO_3 , MeCN, reflux; b) $\text{BrCH}_2\text{CO}_2\text{Et}$, NaH, THF, r.t.; c) Me_4NOH , aqueous THF, reflux.

Due to the two different side arm lengths in **4**, the ^1H and ^{13}C NMR spectra are even more complicated than those for **3a**. A portion of the ^1H - ^{13}C hetero cosy spectrum for **4** is shown in Figure 4. Three carbon signals (two of them overlapped) were observed for the bridge carbons and are related to 3 AB pairs of protons.

Fig. 4. Portion of the ^1H - ^{13}C hetero cosy NMR spectrum for ligand **4** in CDCl_3

2.3 Solvent extraction of divalent metal ions

With two mono-ionizable side arms, ligands **2a-e**, **3a-e**, and **4** are designed for complexation of divalent metal ions. Competitive solvent extraction of AEMC (Mg^{2+} , Ca^{2+} , Sr^{2+} , and Ba^{2+}) from aqueous solutions into chloroform was conducted. Single species solvent extractions were also performed for Hg^{2+} and Pb^{2+} . According to the Hard-Soft Acid-Base Theory,¹⁷ AEMC are hard metal ion species, whereas Pb^{2+} is intermediate, and Hg^{2+} is soft.^{17,18}

2.3.1. Competitive AEMC solvent extraction by di-ionizable *p*-tert-butylcalix[4]arene-1,2-crown-5 ligands **3a-e** with elongated side arms

From competitive solvent extraction of aqueous AEMC (10.0 mM in each) solutions by 1.0 mM solutions **3a-e** in chloroform, plots of metal ion loading of the organic phase vs. the equilibrium pH of the aqueous phase are presented in Figure 5. Poor extraction efficiency and weak metal ion selectivity are immediately evident.

Fig. 5. Percent metal loading vs. the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by di-ionizable *p*-tert-butylcalix[4]arene-1,2-crown-5 ligands with elongated side arms **3a-e**, a) **3a**, b) **3b**, c) **3c**, d) **3d**, and e) **3e**. ($\square = \text{Mg}^{2+}$, $\circ = \text{Ca}^{2+}$, $\triangle = \text{Sr}^{2+}$, $\nabla = \text{Ba}^{2+}$)

The total AEMC loadings for ligands **3a-e** are much lower than the maximum metal loading for a 1:1 (divalent metal ion)(di-ionizable ligand) extraction complex. Recall that for analogous extractions of AEMC by *p*-tert-butylcalix[4]arene-1,2-crown-5 ligands with two $-\text{OCH}_2\text{CO}_2\text{H}$ or

-OCH₂C(O)NHSO₂Z side arms, the metal loading was 95-100%.¹² Di(carboxylic acid) ligand **3a** exhibited some Ca²⁺ selectivity over the other AEMC. Ligands **3b-e** showed only weak selectivity in differentiating among extraction of the different AEMC. In contrast, pronounced Ba²⁺ selectivity was observed for di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5 ligands with -OCH₂CO₂H or -OCH₂C(O)NHSO₂Z side arms. Thus, elongation of the acidic side arms is found to seriously disrupt both the AEMC extraction efficiency and selectivity.

2.3.2. Competitive AEMC solvent extraction by “hybrid” di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5

Figure 6 shows competitive AEMC solvent extraction profiles for *p-tert*-butylcalix[4]arene-1,2-crown-5 di(carboxylic acids) **2a** and **4**. Taken together with the data for **3a** in Figure 5a, this provides a ligand series in which the acidic side arms are varied from two -OCH₂CO₂H groups, to one -OCH₂CO₂H and one -O(CH₂)₄CO₂H unit, to two -O(CH₂)₄CO₂H groups. As can be seen, the profile for **2a** changes markedly in going to “hybrid” ligand **4** and ligand **3a** with the two elongated carboxylic acid groups both in terms of AEMC extraction efficiency and selectivity. Replacement of one -OCH₂CO₂H side arm by -O(CH₂)₄CO₂H produces a change in extraction selectivity from Ba²⁺ to Ca²⁺. Replacement of the second -OCH₂CO₂H retains the Ca²⁺ selectivity, but decreases the extraction efficiency.

Fig. 6. Percent metal loading vs. the equilibrium pH of the aqueous phase for competitive extraction of alkaline earth metal cations into chloroform by *p-tert*-butylcalix[4]arene-1,2-crown-5 di(carboxylic acids) **2a** and **4**. ($\square$ = Mg^{2+} , $\circ$ = Ca^{2+} , $\triangle$ = Sr^{2+} , ∇ = Ba^{2+})

2.3.3. Single species solvent extraction of Pb^{2+} by di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5 ligands **3a-e**

Compared with hard alkaline earth metal cations, Pb^{2+} is an intermediate divalent metal ion species.¹⁷ Single species extractions of Pb^{2+} by ligands **3a-e** were conducted using 0.50 mM solutions of the di-ionizable ligands **3a-e** in chloroform to extract 1.0 mM aqueous Pb^{2+} solutions.

Previously we reported Pb^{2+} extractions by di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5 with $-\text{OCH}_2\text{C}(\text{O})\text{Z}$ side arms.¹⁹ For **2a-e**, 95-100% maximum Pb^{2+} loading was observed from acidic aqueous solutions.

Figure 7 presents the extraction profiles for Pb^{2+} extraction by ligands **3a-e** with longer acidic side arms of $-\text{O}(\text{CH}_2)_4\text{C}(\text{O})\text{NHSO}_2\text{Z}$. For the longer acidic side arm species **3a-e**, only **3a** and **3e** exhibited Pb^{2+} loading above 10%. The maximum Pb^{2+} loading for **3e** was about 45% and that for **3a** with two $-\text{O}(\text{CH}_2)_4\text{CO}_2\text{H}$ side arms was about 70%. Clearly the shorter acidic side arms ligands gave better Pb^{2+} extraction than the similar ligands with longer ionizable side arms.

Fig. 7. Percent metal loading vs. equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} into chloroform by di-ionizable *p*-tert-butylcalix[4]arene-1,2-crown-5 ligands **3a-e**. ($\square = \mathbf{3a}$, $\circ = \mathbf{3b}$, $\Delta = \mathbf{3c}$, $\nabla = \mathbf{3d}$, $\diamond = \mathbf{3e}$)

2.3.4. Single species solvent extraction of Hg^{2+} by di-ionizable *p*-tert-butylcalix[4]arene-1,2-crown-5 ligands **3a-e**

Compared with hard alkaline earth metal cations and Pb^{2+} with intermediate hardness, Hg^{2+} is a soft **metal ion**.^{17,18} For single species solvent extractions of Hg^{2+} by ligands **3a-e**, 0.25 mM aqueous solutions of Hg^{2+} were extracted with 0.25 mM solutions of the di-ionizable ligands in chloroform.

In an earlier investigation, we determined the Hg^{2+} loading under these extraction conditions for ligands **2b-e** which have shorter side arms of $-\text{OCH}_2\text{C}(\text{O})\text{NHSO}_2\text{Z}$.¹⁹ The metal loadings were 90-100% with $\text{Z} = -\text{Me}$, $-\text{Ph}$, $-\text{C}_6\text{H}_4-4-\text{NO}_2$, and $-\text{CF}_3$. However, for di(carboxylic acid) **2a**, the maximum Hg^{2+} loading was only 70%.

Figure 8 shows the profiles for Hg^{2+} extractions by ligands **3a-e** with the longer $-\text{O}(\text{CH}_2)_4\text{C}(\text{O})\text{NHSO}_2\text{Z}$ side arms. The metal loading changed as Z was varied: $-\text{NHSO}_2\text{Ph}$ and $-\text{NHSO}_2\text{C}_6\text{H}_4-4-\text{NO}_2$ (~100%) > $-\text{NHSO}_2\text{Me}$ and $-\text{NHSO}_2\text{CF}_3$ (~80%), $-\text{OH}$ (~50%). For ligands

3b-e it should be noted that the metal loading percentage does not strictly follow the electron-withdrawing properties of the Z group in the $-\text{O}(\text{CH}_2)_4\text{C}(\text{O})\text{NHSO}_2\text{Z}$ side arm.²⁰

Fig. 8. Percent metal loading vs. equilibrium pH of the aqueous phase for single species solvent extraction of Hg^{2+} into chloroform by di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5 ligands **3a-e**. ($\square$ = **3a**, $\circ$ = **3b**, Δ = **3c**, ∇ = **3d**, $\diamond$ = **3e**)

3. Conclusions

For comparison with reported results for divalent metal ion extractions from aqueous solution into chloroform, several new di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-5 ligands were prepared in the cone conformation. The systematic structural variation was lengthening of the acidic side arm length from that reported for two adjacent $-\text{OCH}_2\text{CO}_2\text{H}$ or $-\text{OCH}_2\text{C}(\text{O})\text{NHSO}_2\text{Z}$ (with $\text{Z} = -\text{Me}$, $-\text{Ph}$, $-\text{C}_6\text{H}_4-4-\text{NO}_2$, and $-\text{CF}_3$) groups to two adjacent $-\text{O}(\text{CH}_2)_4\text{CO}_2\text{H}$ or $-\text{O}(\text{CH}_2)_4\text{C}(\text{O})\text{NHSO}_2\text{Z}$ groups. For competitive extraction of AEMC, this structural variation decreases the metal loading and changes the selectivity. For single species extractions of Pb^{2+} , and Hg^{2+} , lengthening the acidic side arms also decreases the divalent metal ion loading, but to a lesser degree with Hg^{2+} than Pb^{2+} . Thus the effect of lengthening the acidic side arms appears to lessen as the softness of the metal ion being extracted is increased.

It was also found for a “hybrid” di(carboxylic acid) **4** with one shorter and one longer acidic side arms that lengthening of one side arm for competitive extraction of AEMC produces a change from Ba^{2+} to Ca^{2+} selectivity. The Ca^{2+} selectivity is retained for **3a** with two long side arms, but with some decrease in extraction efficiency.

4. Experimental

4.1. General

Melting points were determined with a Mel-Temp melting point apparatus. Infrared (IR) spectra were recorded with a Nicolet IR100 FT-IR spectrometer as deposits from CH_2Cl_2 solution on NaCl plates. The ^1H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR spectrometer at 500 MHz and 126 MHz, respectively, in CDCl_3 , with Me_4Si as internal standard. Chemical shifts (δ) are given in ppm downfield from TMS and coupling constants values (J) are in Hz. Elemental analysis was performed by Desert Analytics Laboratory (now Columbia Analytical Services) of Tucson, Arizona.

Reagents were purchased from commercial suppliers and used directly unless otherwise noted. Acetonitrile (MeCN) was dried over CaH_2 and distilled immediately before use. Tetrahydrofuran (THF) was dried over sodium with benzophenone as an indicator and distilled just before use.

Tetraethyleneglycol ditosylate was prepared by the conventional aqueous THF method.²¹ *p*-tert-Butylcalix[4]arene-1,2-crown-5 (**5**) was prepared by a literature procedure.²²

4.2. Ligand synthesis

4.2.1. Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[(4'-ethoxycarbonyl)butoxy]-calix[4]arene-1,2-crown-5 (**6**)

A slurry of **5** (0.50 g, 0.62 mmol) and Cs_2CO_3 (1.03 g, 3.10 mmol) in MeCN (50 mL) was refluxed for 1 hour. Ethyl 5-bromopentanolate (0.52 g, 2.50 mmol) was added and the mixture was refluxed for 3 days. After removing the MeCN in vacuo, CH_2Cl_2 (25 mL) and 10% HCl (25 mL) were added slowly to the residue. The organic layer was separated and washed with water (2×50 mL), dried over MgSO_4 , and evaporated in vacuo. The crude product was

chromatographed on silica gel with hexanes-EtOAc (50:1 to 4:1 gradient) as eluent to give diester **6** (0.26 g, 40%) as a white solid with mp 138-140 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 1735 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.07 (s, 36H), 1.26 (t, 6H, *J* = 7.0 Hz), 1.71-1.80 (m, 4H), 2.04-2.12 (m, 4H), 2.38-2.50 (m, 4H), 3.09-3.14 (m, 4H), 3.72-3.75 (m, 8H), 3.82-4.16 (m, 16H), 4.33 (d, 2H, *J* = 12.5 Hz), 4.36 (d, 1H, *J* = 12.5 Hz), 4.50 (d, 1H, *J* = 12.5 Hz), 6.77 (s, 8H). ¹³C NMR (CDCl₃): δ 14.3, 21.6, 29.6, 30.6, 30.9, 31.2, 31.4, 33.8, 34.3, 60.2, 70.4, 70.6, 71.2, 73.5, 74.7, 124.9, 125.1, 133.6, 133.7, 133.8, 134.0, 144.4, 144.5, 153.4, 153.4, 173.6. Anal. Calcd for C₆₆H₉₄O₁₁: C, 74.58; H, 8.85 %. Found: C, 74.33; H, 8.81 %.

4.2.2. Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis(4'-carboxybutoxy)calix[4]arene-1,2-crown-5 (**3a**)

A solution of diester **6** (0.50 g, 0.47 mmol), 25 mL of 10% aqueous TMAOH, and 25 mL of THF was refluxed for 24 hours. After evaporation of the THF in vacuo, 20 mL of 6 N HCl was added to the residue. The aqueous mixture was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with water (2 x 50 mL) and dried over MgSO₄. Upon evaporation of the THF in vacuo, di(carboxylic acid) **3a** (0.48 g, quantitative yield) was obtained as a white solid with mp 92-94 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 2958 (CO₂H), 1709 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.07 (s, 36H), 1.71-1.87 (m, 4H), 2.50 (t, *J* = 7.0 Hz, 4H), 3.09-3.14 (m, 4H), 3.71-4.14 (m, 20H), 4.33 (d, 2H, *J* = 12.5 Hz), 4.39 (d, 1H, *J* = 12.5 Hz), 4.46 (d, 1H, *J* = 12.5 Hz), 6.77-6.78 (m, 8H). ¹³C NMR (CDCl₃): δ 21.7, 29.4, 30.6, 31.2, 31.4, 31.4, 33.8, 33.8, 34.3, 70.2, 70.3, 70.9, 73.3, 74.9, 124.9, 125.1, 133.6, 133.8, 134.0, 144.4, 144.6, 153.2, 153.3, 178.6. Anal. calcd for C₆₂H₈₄O₁₁•0.9CH₂Cl₂: C, 69.84; H, 7.99 %. Found: C, 69.96; H, 7.99 %.

4.2.3. General procedure for the synthesis of cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[4'-N-(X)sulfonyl carbamoylbutoxy]calix[4]arene-1,2-crown-5 ligands **3b-e**

Di(carboxylic acid) **3a** (0.50g, 0.50 mmol) was dried with a benzene azeotrope before addition of oxalyl chloride (0.63 g, 6.40 mmol) in benzene (50 mL). The solution was refluxed overnight. After conversion to the di(acid chloride) was confirmed by an IR shift of the C=O from around 1710 cm⁻¹ in **3a** to 1800 cm⁻¹ in the corresponding di(acid chloride), the benzene was evaporated in vacuo and the residue was dried under oil pump vacuum for 30 minutes. The

residue was dissolved in THF (20 mL) and the solution was added to a mixture of the appropriate sulfonamide (1.10 mmol) and NaH (0.12 g, 5.00 mmol) in THF (25 mL) under nitrogen at room temperature. The reaction mixture was refluxed for 3 days. The THF was removed in vacuo and CH₂Cl₂ (50 mL) and 10% HCl solution (50 mL) were added to the residue. The organic layer was separated, washed with water (2 × 50 mL), and dried over MgSO₄. Evaporation of the CH₂Cl₂ in vacuo gave the crude product, which was purified by column chromatography on silica gel.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[4'-(N-methanesulfonyl carbamoyl)butoxy]calix[4]arene-1,2-crown-5 (3b) was chromatographed on silica gel with CH₂Cl₂-MeOH (100:1 to 10:1 gradient) as eluent in 43% yield. It was a white solid with mp 116-118 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 1718 (C=O), 3230 (NH) cm⁻¹. ¹H NMR (CDCl₃): δ: 1.09 (br s, 36H), 1.74-2.25 (m, 12H), 2.61 (t, 4H, *J* = 8.0 Hz), 3.11-3.18 (m, 4H), 3.33 (s, 6H), 3.62-4.49 (m, 20H), 6.78 (br s, 8H), 10.15 (br s, 2H). ¹³C NMR (CDCl₃): δ 22.1, 30.1, 30.6, 30.7, 31.0, 31.2, 31.4, 31.7, 33.8, 36.8, 41.3, 70.0, 74.6, 124.8, 124.9, 125.2, 125.5, 144.9, 153.1, 153.3, 172.3. Anal. calcd for C₆₄H₈₆N₂O₁₃S₂: C, 66.52; H, 7.50; N, 2.42%. Found: C, 66.04; H, 7.94; N, 2.25%.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[(4'-N-benzenesulfonyl carbamoyl)butoxy]calix[4]arene-crown-5 (3c) was chromatographed on silica gel with CH₂Cl₂-MeOH (200:1 to 10:1 gradient) as eluent in 70% yield. It was a pale yellow solid with mp 126-128 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 3238 (NH), 1722 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.06 (br s, 36H), 1.56-1.74 (m, 4H), 1.90-2.05 (m, 4H), 2.47 (m, 4H), 3.03 (d, 1H, *J* = 12.5 Hz), 3.11-3.16 (m, 3H), 3.67-4.20 (m, 23H), 4.42 (d, 1H, *J* = 12.5 Hz), 6.76 (br s, 8H), 7.52 (t, 4H, *J* = 7.5 Hz), 7.60 (t, 2H, *J* = 7.5 Hz), 8.09-8.11 (m, 4H). ¹³C NMR (CDCl₃): δ 21.0, 21.8, 29.9, 30.5, 30.7, 31.0, 31.1, 31.4, 33.8, 36.7, 70.0, 70.1, 73.5, 74.5, 124.8, 125.1, 125.5, 128.3, 128.4, 128.9, 133.7, 139.1, 144.7, 144.9, 153.0, 153.4, 172.4. Anal. calcd for C₇₄H₉₄N₂O₁₃S₂•0.2CH₂Cl₂: C, 68.92; H, 7.28; N, 2.17 %. Found: C, 68.89; H, 7.76; N, 2.29 %.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[4'-(N-4-nitrobenzenesulfonyl carbamoyl)butoxy]calix[4]arene-1,2-crown-5 (3d) was chromatographed on silica gel with CH₂Cl₂-MeOH (200:1 to 10:1 gradient) as eluent in 64% yield. It was a yellow solid with mp 118-120 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 2957 (NH), 1724 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.07 (br s, 36H), 1.58-1.84 (br m, 8H), 2.51 (br s, 4H), 3.05-3.17 (m, 4H), 3.64-4.20 (m, 23H), 4.40 (d, 1H, *J* = 12.5 Hz), 6.77 (br s, 8H), 8.32 (d, 4H, *J* = 8.5 Hz), 8.38 (d, 4H, *J* = 8.5 Hz). ¹³C NMR (CDCl₃): δ 14.1, 21.7, 29.7, 30.0, 30.5, 30.6, 31.2, 31.4, 33.8, 36.7, 69.9, 74.3, 124.1,

124.8, 125.0, 125.1, 125.6, 130.0, 133.4, 144.4, 144.9, 145.0, 150.7, 152.9, 153.3, 172.5. Anal. calcd for $C_{74}H_{92}N_4O_{17}S_2$: C, 64.70; H, 6.74; N, 4.08 %. Found: C, 64.17; H, 7.00; N, 3.67 %. *Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26-bis[4'-(N-trifluoromethanesulfonyl carbamoyl)butoxy]calix[4]arene-1,2-crown-5 (3e)* was chromatographed on silica gel with CH_2Cl_2 -MeOH (100:1 to 10:1 gradient) as eluent in 56% yield. It was a pale yellow solid with mp 174-176 °C. IR (deposit from CH_2Cl_2 solution on NaCl plate): 1751 (C=O), 3265 (NH) cm^{-1} . 1H NMR ($CDCl_3$) δ : 1.07 (br s, 36H), 1.72-2.29 (m, 12H), 2.61 (br s, 4H), 3.10-3.19 (m, 4H), 3.62-4.43 (m, 20H), 6.77 (br s, 8H). ^{13}C NMR ($CDCl_3$): δ 21.6, 29.6, 29.7, 29.9, 30.5, 30.6, 31.0, 31.1, 31.4, 31.7, 33.8, 37.1, 69.8, 69.9, 74.4, 118.0, 120.5, 124.8, 124.9, 125.2, 125.6, 133.5, 144.9, 145.0, 152.9, 153.3, 171.8. Anal. calcd for $C_{64}H_{84}F_6N_2O_{13}S_2$: C, 61.11; H, 5.93; N, 2.23%. Found: C, 60.91; H, 6.37; N, 1.82%.

4.2.4 *Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25-[4'-(ethoxycarbonyl)butoxy]-26-hydroxy-calix[4]arene-1,2-crown-5 (7)*

A mixture of **5** (0.50 g, 0.62 mmol) and NaH (0.090 g, 3.75 mmol) in THF (50 mL) was stirred at room temperature for 30 minutes before the addition of ethyl 5-bromopentan-3-one (0.52 g, 2.50 mmol). The mixture was refluxed for 2 days. After removing the THF in vacuo, CH_2Cl_2 (25 mL) and 10% HCl (25 mL) were added slowly to the residue. The organic layer was separated, washed with water (2×50 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was chromatographed on silica gel with hexanes-EtOAc (50:1 to 4:1) as eluent to give monoester **7** (0.25 g, 44%) as a white solid with mp 93-94 °C. IR (deposit from CH_2Cl_2 solution on NaCl plate): 3456 (OH), 1734 (C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 0.76 (s, 9H), 0.85 (s, 9H), 1.25 (t, 3H, $J = 7.0$ Hz), 1.33 (s, 9H), 1.34 (s, 9H), 1.83-2.02 (m, 4H), 2.39 (t, 2H, $J = 7.5$ Hz), 3.16-3.25 (m, 4H), 3.66-4.07 (m, 14H), 4.13 (q, 2H, $J = 7.0$ Hz), 4.16-4.51 (m, 8H), 5.93 (s, 1H), 6.43 (s, 2H), 6.55 (d, 2H, $J = 2.0$ Hz), 7.05 (d, 2.0 Hz, 2H), 7.08 (d, 2H, $J = 2.0$ Hz), 7.14 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.8, 29.6, 30.8, 31.0, 31.2, 31.7, 31.8, 33.6, 33.7, 33.8, 34.1, 60.3, 68.5, 69.8, 70.0, 70.5, 71.0, 71.6, 72.0, 75.4, 76.2, 124.6, 124.8, 124.9, 125.0, 125.2, 125.6, 125.8, 128.6, 129.2, 131.7, 131.8, 132.3, 135.8, 136.0, 141.1, 144.8, 145.7, 145.8, 150.8, 151.0, 151.9, 153.6, 173.4. Anal. calcd for $C_{59}H_{82}O_9$: C, 75.77; H, 8.84 %. Found: C, 75.82; H, 9.01 %.

4.2.5 Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25-[4'-(ethoxycarbonyl)butoxy]-26-[ethoxycarbonyl-methoxy]-calix[4]arene-1,2-crown-5 (8)

A mixture of monoester **8** (0.20 g, 0.21 mmol) and NaH (0.026 g, 1.05 mmol) in THF (30 mL) at room temperature was stirred for 30 minutes before addition of ethyl bromoacetate (0.071 g, 0.42 mmol). After stirring for 24 hours at room temperature, the THF was removed in vacuo and CH₂Cl₂ (25 mL) and 10% HCl (25 mL) were added slowly to the residue. The organic layer was separated, washed with water (2 × 50 mL), dried over MgSO₄, and evaporated in vacuo. The crude product was chromatographed on silica gel with hexanes-EtOAc (50:1 to 4:1) as eluent to give “hybrid” diester **8** (0.15 g, 69%) as a white solid with mp 90-92 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 1759 (C=O), 1735 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 0.97 (s, 9H), 1.00 (s, 9H), 1.17 (s, 9H), 1.18 (s, 9H), 1.24-1.28 (m, 6H), 1.75-1.82 (m, 2H), 2.02-2.08 (q, 2H, *J* = 7.5 Hz), 2.40-2.44 (m, 2H), 3.09-3.20 (m, 4H), 3.70-4.31 (m, 22H), 4.34 (d, 1H, *J* = 12.5 Hz), 4.44 (d, 1H, *J* = 12.5 Hz), 4.53 (d, 1H, *J* = 12.5 Hz), 4.69 (d, 1H, *J* = 16.5 Hz), 4.84 (d, 1H, *J* = 12.5 Hz), 5.08 (d, 1H, *J* = 16.5 Hz), 6.63-6.66 (m, 4H), 6.90-6.91 (m, 4H). ¹³C NMR (CDCl₃): δ 14.2, 14.3, 21.7, 29.5, 30.6, 31.0, 31.2, 31.3, 31.5, 31.7, 33.7, 33.9, 34.3, 60.2, 70.4, 70.5, 70.7, 71.4, 72.8, 74.2, 74.9, 124.6, 124.8, 124.9, 125.1, 125.2, 125.4, 125.5, 132.7, 133.0, 133.1, 133.2, 133.7, 134.5, 134.6, 134.7, 144.2, 144.5, 144.9, 153.0, 153.1, 153.5, 153.6, 170.8, 173.7. Anal. calcd for C₆₃H₈₈O₁₁•0.4CH₂Cl₂: C, 72.09; H, 8.41 %. Found: C, 72.16; H, 8.09 %.

4.2.6 Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25-[carboxybutoxy]-26-[carboxymethoxy]-calix[4]arene-1,2-crown-5 (4)

A solution of **7** (0.50 g, 0.50 mmol), 25 mL of 10% aqueous TMAOH, and 25 mL of THF was refluxed for 24 hours. After evaporating the THF in vacuo, 20 mL of 6 N HCl was added to the residue. The aqueous mixture was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed with water (2 x 50 mL) and dried over MgSO₄. Upon evaporation of the THF in vacuo, the “hybrid” di(carboxylic acid) **4** was collected (0.43 g, 90% yield) as a pale yellow solid with mp 74-76 °C. IR (deposit from CH₂Cl₂ solution on NaCl plate): 3209 (CO₂H), 1756 (C=O), 1712 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 0.81 (s, 9H), 0.83 (s, 9H), 1.33 (s, 9H), 1.34 (s, 9H), 1.82-1.97 (m, 4H), 2.46-2.51 (m, 2H), 3.14 (d, 1H, *J* = 12.5 Hz), 3.19 (d, 1H, *J* = 13.0 Hz), 3.24 (d, 2H, *J* = 12.5 Hz), 3.67-4.00 (m, 15H), 4.08-4.29 (m, 4H), 4.34 (d, 1H, *J* = 12.0 Hz), 4.45-4.50 (m, 1H), 4.56-4.60 (m, 2H), 4.73 (d, 1H, *J* = 16.5 Hz), 6.48-6.52 (m,

2H), 6.58-6.60 (m, 2H), 7.12-7.13 (m, 2H), 7.16 (s, 2H). ^{13}C NMR (CDCl_3): δ 14.1, 22.0, 22.7, 29.6, 29.7, 30.3, 30.4, 30.8, 31.6, 31.7, 33.7, 33.9, 34.1, 34.2, 69.1, 70.4, 70.4, 70.6, 70.6, 71.6, 73.5, 76.0, 124.7, 124.8, 125.2, 125.3, 125.5, 125.6, 126.0, 131.4, 132.4, 133.1, 134.8, 135.0, 135.7, 145.0, 145.3, 145.4, 147.3, 150.5, 151.0, 151.7, 153.9, 171.2, 175.38. Anal. calcd for $\text{C}_{59}\text{H}_{80}\text{O}_{11} \cdot \text{C}_6\text{H}_{14}$: C, 74.28; H, 8.95 %. Found: C, 74.28; H, 9.12%.

4.3 Extraction Procedures

Procedures for competitive AEMC extraction and single species extraction of Pb^{2+} and Hg^{2+} were described previously.²³

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Graphical Abstract

- $\underline{Z}$
a $-\underline{OH}$
b $-\text{NHSO}_2\text{Me}$
c $-\text{NHSO}_2\text{Ph}$
d $-\text{NHSO}_2\text{C}_6\text{H}_4-4-\text{NO}_2$
e $-\text{NHSO}_2\text{CF}_3$