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Efficient divalent metal cation extractions with di-ionizable calix[4]arene-1,2-crown-4 compounds

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Abstract—Di-ionizable calix[4]arene-1,2-crown-4 ethers in the cone conformation were synthesized and their conformation and regioselectivity verified by NMR spectroscopy. These new ligands exhibited high Ba^{2+} selectivity in competitive solvent extraction of alkaline earth metal cations from aqueous solutions into chloroform. The selectivity order was $Ba^{2+} >> Sr^{2+} > Ca^{2+} > Mg^{2+}$ with Ba^{2+}/Sr^{2+} selectivity exceeding 100. The ligands also exhibited high extraction ability for Pb^{2+} and for Hg^{2+} in single species extraction. With variation of proton-ionizable groups, which are oxyacetic acid moieties and *N*-(X)sulfonyl oxyacetamide units with X=methyl, phenyl, 4-nitrophenyl, and trifluoromethyl, 'tunable' ligand acidity was obtained.

1. Introduction

Calixarenes have been widely used as building blocks for the design of selective cation receptors and carriers. In the calixarene family, the tetrameric calix[4]arene is particularly well-suited for this purpose due to its ready accessibility, facile chemical modification, and binding properties toward cations. The parent calix[4]arene molecules are easily modified with functional groups at either the wide and narrow rims, or both, which not only greatly increases their solubility in organic solvents, but also enhances the binding ability and selectivity for guest molecules or ions.[1]

Crown ethers derived from calix[4]arenes, named calix[4]crowns, may exhibit very high binding affinity and selectivity in metal cation extractions.[2] However, the contributions come from only one of the two regioisomers of calix[4]crowns, the calix[4]arene-1,3-crown ethers. The other regioisomer, calix[4]arene-1,2-crown ethers, has been much less studied, probably due to difficulty in synthesis and their poor binding ability and selectivity toward metal cations.[3–6] The first example of a 1,2-bridged calix[4]crown compound was the 1,2-dimethoxycalix[4]arene-crown-5 synthesized by Ti(IV)-assisted proximal 1,2-bis-demethylation of tetramethoxy-*p*-*tert*-butylcalix[4]arene.[3] Later it was shown that 1,2-bridged calix[4]crowns can be obtained in good yields by direct condensation of calix[4]arenes and oligoethylene glycol ditosylates with a strong base, e.g., NaH or KH, in DMF.[4–6] The complexation properties of 1,2-bridged calix[4]crowns have been rarely reported. Pappalardo and co-workers synthesized *p*-*tert*-butylcalix[4]arene-1,2-crown-4, -crown-5, and -crown-6 ethers bearing pendant picolyl groups. The metal ion complexation abilities of these ligands were tested by extraction of metal picrates from water into dichloromethane. The results showed only low extraction levels of alkali, alkaline earth, and heavy metal picrates. Compared with their corresponding 1,3-linked counterparts, these ligands were much less efficient and selective.[6]

The complexed cation may be located in the polar cavities of the macrobicyclic calixcrowns.[7] Incorporating pendant proton-ionizable groups (PIGs) into calix[4]crowns can enhance their binding affinity toward metal cations compared with their non-ionizable analogues.[8] The other important function is that PIGs eliminate the need to transfer aqueous phase anions into the organic phase during liquid–liquid extraction by operating in a cation-exchange mode with the metal cation. This is essential for efficient extraction due to the low distribution coefficients of common anions, such as Cl^- and NO_3^-, between an aqueous phase and an organic phase.[9] The nature of the proton-ionizable group, particularly its acidity, controls the metal ion complexation properties of such ligands. In our earlier work, we have introduced the *N*-(X)sulfonyl carboxamide function, $–C(O)NHSO_2X$, as pendent proton-ionizable groups into crown ethers and calix[4]arenes.[10] The resulting proton-ionizable ligands exhibited high efficiency and selectivity in solvent extraction of metal cations. By variation of the electronic properties of X, the acidity of the macrocyclic ligand is 'tunable'. Recently, we incorporated these proton-ionizable groups into *p*-*tert*-butylcalix-[4]arene-1,2-crown-4 compounds and found that the newly formed ligands were efficient extractants with

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Keywords: Calixarenes; Crown compounds; Molecular recognition.

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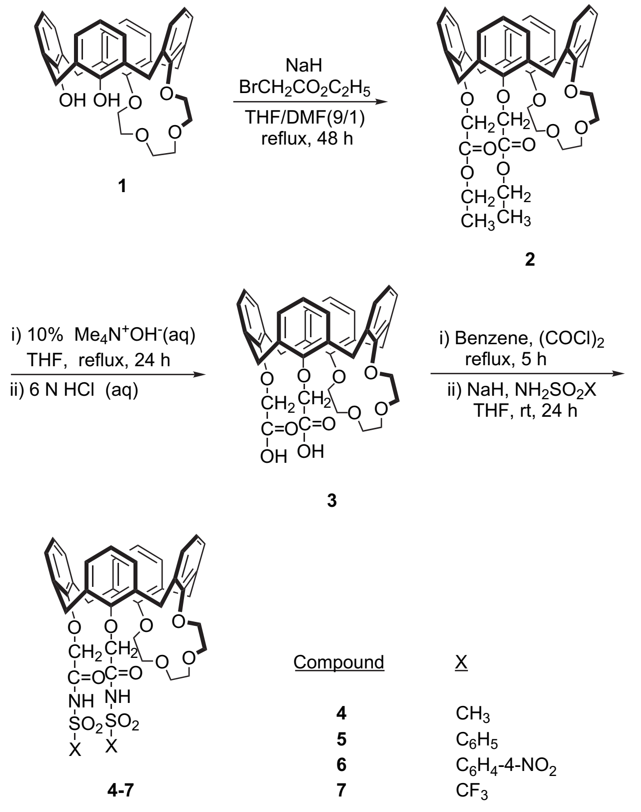
high selectivity for Ba^{2+} in competitive solvent extraction of alkaline earth metal cations from aqueous solution into chloroform.[11] To explore the influence of *p-tert*-butyl groups on the upper rim of the calix[4]arene scaffold on the efficiency and selectivity of the ligands in metal ion separations, we now report the synthesis of a series of di-ionizable calix[4]arene-1,2-crown-4 compounds in the cone conformation in which the four *p-tert*-butyl groups are replaced by hydrogen atoms and evaluation of their extraction abilities toward alkaline earth metal cations. In addition, the efficacy of both ligand sets for extraction of Hg^{2+} and Pb^{2+} has been assessed.

2. Results and discussion

2.1. Synthesis

Calix[4]arene-1,2-crown-4 (**1**) was synthesized by a reported procedure[4] and refluxed with ethyl bromoacetate and NaH in THF–DMF to give diester **2** in 88% yield (Scheme 1). Hydrolysis of diester **2** with Me_4NOH in aqueous THF gave diacid **3** in nearly quantitative yield. Diacid **3** was converted into the corresponding di(acid chloride) by refluxing with oxalyl chloride in benzene. Formation of the acid chloride was verified by IR spectroscopy with appearance of the strong carbonyl group absorption at 1810 cm^{-1} and the disappearance of the carbonyl group absorption at 1750 cm^{-1}. The di(acid chloride) was reacted with appropriate sulfonamide anions in THF to afford cone, di-ionizable calix[4]arene-1,2-crown-4 compounds **4**–**7** in 41–48% yield.



Compound	X
4	CH_3
5	C_6H_5
6	C_6H_4-4-NO_2
7	CF_3

Scheme 1. Synthesis of di-ionizable calix[4]arene-1,2-crown-4 compounds **3**–**7**.

2.2. Conformation

The conformation of the calix[4]arene unit for compounds **2**–**7** was verified by NMR spectroscopy. In the ^{13}C NMR spectra there were no absorptions between 36–40 ppm, revealing that all four benzene rings have *syn*-arrangements.[12]

2.3. Competitive solvent extraction of alkaline earth metal cations

Competitive solvent extraction of the alkaline earth metal cations Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} from aqueous solutions into chloroform by ligands **3**–**7** was performed. Results from competitive extractions of aqueous solutions containing 2.0 mM (in each) of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} with 1.0 mM chloroform solutions of ligands **3**–**7** are presented in Figure 1.

Ligands **4**–**7** exhibit high selectivity for Ba^{2+} extraction over the other three alkaline earth metal ion species with 100% maximum metals loading (for formation of a 1:1 metal ion-di-ionized ligand complex). The extraction selectivity order is $Ba^{2+}>>Sr^{2+}>Ca^{2+}>Mg^{2+}$, the same order as the decreasing metal cation radii. The Ba^{2+}/Sr^{2+} selectivity reaches 116 under conditions of high loading. With variation of X groups in order of CH_3, C_6H_5, C_6H_4-4-NO_2, and CF_3, the ligand acidity is expected to increase as the electron-withdrawing power of the X group is increased. The pH for half loading, $pH_{0.5}$, is a qualitative measure of the ligand acidity. For compounds **4**–**7**, the $pH_{0.5}$ values are 6.4, 6.0, 5.9, and 3.4, respectively, which is in accord with the electron-withdrawing power of the X group. For compound **6** with X=4-nitrophenyl, the acidity is considerably less than what is expected. It is suggested that the lower than expected acidity of ligand **5** arises from inter- or intra-molecular NH⋯O=C hydrogen bonding or by conformational peculiarities of the compound that hinder metal ion complexation.[13] Diacid **3** is less efficient and selective than four sulfonyl amide ligands **4**–**7**, as shown in Figure 1a. Although it exhibited selectivity for Ba^{2+}, the extraction selectivity order of

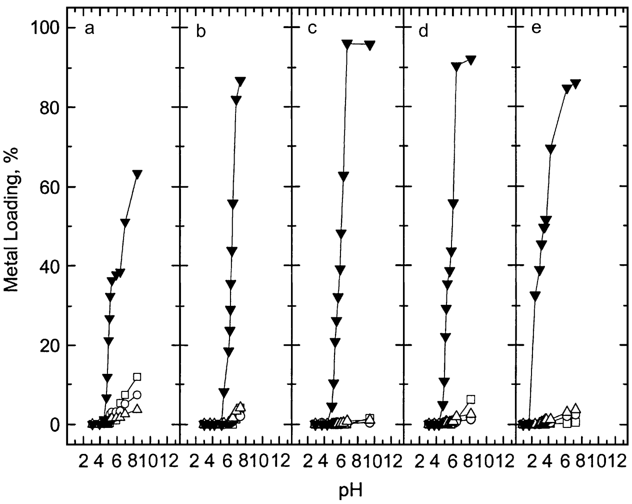


Figure 1. Percent metals loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by di-ionizable calix[4]arene-1,2-crown-4 ligands; (a) **3**, (b) **4**, (c) **5**, (d) **6**, and (e) **7** (□=Mg^{2+}; ○=Ca^{2+}; △=Sr^{2+}; ▼=Ba^{2+}).

$Ba^{2+}>Mg^{2+}>Ca^{2+}>Sr^{2+}$ is different from those for compounds **4–7**.

The crown ether ring size plays a critical role in the extraction of metal cations. We have reported that di-ionizable *p-tert*-butylcalix[4]arene-1,3-crown-5 ethers exhibited very high selectivity for Ba^{2+} among alkaline earth metal cations.[2e] It is known that calix[4]arene-1,3-crown-5 compounds are selective for K^+ due to good accommodation of the crown-5 ring toward K^+.[14] So the high selectivity of calix[4]arene-crown-5 ligands for Ba^{2+} can be attributed to the similar ionic radius of Ba^{2+} (1.49 Å) and K^+ (1.52 Å). In the cone conformation the two anionic centers required for electroneutrality of the extraction complex are oriented on the each side of the crown unit.[2d,e]

As for calix[4]arene-1,2-crown-4 ligands, upon ionization the new ligands **3–7** form alkaline earth metal ion complexes with two anionic centers over the same side of the crown unit (Fig. 2). Since the crown-4 ring is too small to accommodate Ba^{2+}, the metal ion is tightly clamped between the two anion centers on one side and the crown ring 'wall' on the other, as depicted in Figure 2. Compared with the corresponding analogues **8–12** with *tert*-butyl groups on the upper rim (Fig. 3), the di-ionizable calix[4]arene-1,2-crown-4 ligands **3–7** exhibit considerably higher Ba^{2+} extraction selectivities.[11]

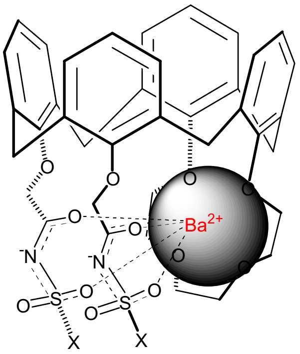
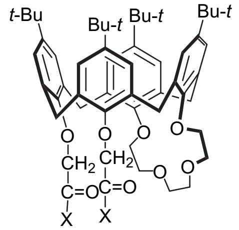


Figure 2. Depiction of spatial relationship between a crown-complexed divalent metal ion and the anionic centers formed by ionization of ligands **4–7**.



Compound	X
8	OH
9	$NHSO_2CH_3$
10	$NHSO_2C_6H_5$
11	$NHSO_2C_6H_4$-4-NO_2
12	$NHSO_2CF_3$

Figure 3. Di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-4 ethers **8–12**.

2.4. Single species solvent extraction of Pb^{2+} and Hg^{2+}

In previous studies, we found that calix[4]arenes with *N*-(X)sulfonyl carboxamide groups are not only effective in the extraction of hard metal cations, but also exhibit an high extraction efficiency and selectivity for some intermediate Pb^{2+} and soft Hg^{2+}.[2d,e,13,15] In this work, the single species solvent extractions of Pb^{2+} and Hg^{2+} by ligands **3–7** and analogues **8–12** were performed. The extraction results for Pb^{2+} are shown in Figure 4a and 4b, respectively. Both types of ligands exhibit high extraction ability toward Pb^{2+}. Similar results were obtained for the extraction of Hg^{2+}, as shown in Figure 4c and 4d, respectively. The maximum metals loadings in all four figures are over 90%, except for ligands with carboxylic acid groups with Hg^{2+}. The spatial relationship of ligand–Pb^{2+} complexes may be similar to that described in Figure 2. For ligand–Hg^{2+} complexes, some contribution to the complex stability may come from the π-interactions between Hg^{2+} and the electron-rich aromatic rings in the calix[4]arene framework.[15] The results are interesting since both types of ligands **4–7** and **8–12** exhibit high extraction efficiency and selectivity toward hard, borderline, and soft metal cations. Removal of *tert*-butyl groups from the upper rim of calix[4]arene scaffold significantly increases the extraction selectivity of ligands toward Ba^{2+},[11] while it has little apparent influence on the extraction ability of the ligands toward Pb^{2+} or Hg^{2+}.

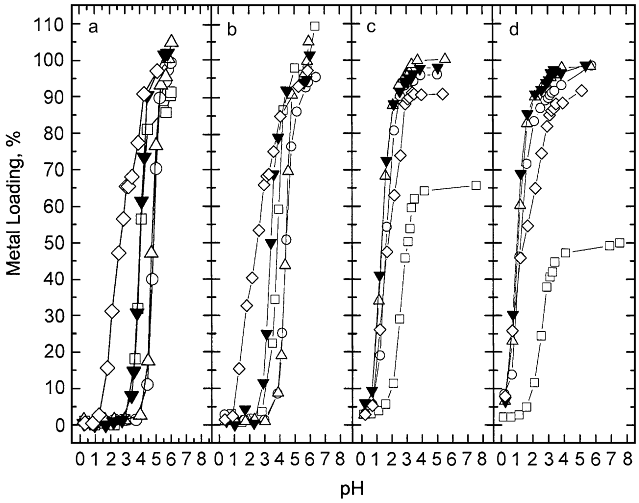


Figure 4. Percent metals loading of the organic phase versus the equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} by ligands: (a) **3** (□), **4** (○), **5** (△), **6** (▼), **7** (◇); (b) **8** (□), **9** (○), **10** (△), **11** (▼), **12** (◇); and single species solvent extraction of Hg^{2+} by ligands (c) **3** (□), **4** (○), **5** (△), **6** (▼), **7** (◇); (d) **8** (□), **9** (○), **10** (△), **11** (▼), **12** (◇).

3. Experimental

3.1. General

Reagents were obtained from commercial suppliers and used directly, unless otherwise noted. THF was dried over sodium wire with benzophenone ketyl as an indicator. DMF was stored over 4 Å molecular sieves. Infrared spectral analyses were performed with a Perkin–Elmer 1600 FTIR spectrophotometer by deposit from CH_2Cl_2 solution onto a NaCl plate. The absorptions are expressed in wavenumbers (cm^{-1}). NMR spectra were measured with a Varian Unity Inova FT-500 spectrometer at 296 K in $CDCl_3$ with TMS as an internal standard. Chemical shifts (δ) are expressed in parts per million downfield from TMS and coupling constant (J)

values are given in hertz. Melting points were determined with a Mel-Temp melting point apparatus. Elemental analysis was performed by Desert Analytics Laboratory of Tucson, Arizona.

3.1.1. Synthesis of cone 25,26-bis[(ethoxycarbonyl)-methoxy]calix[4]arene-crown-4 (2). A solution of 25,26-dihydroxycalix[4]arene-crown-4 (**1**) (4.52 g, 8.39 mmol) in 100 mL of THF–DMF (9:1) was added dropwise to a mixture of NaH (2.01 g, 83.9 mmol) and 20 mL of THF–DMF (9:1) under nitrogen and the mixture was stirred for 1 h. Ethyl bromoacetate (7.44 mL, 67.13 mmol) in 10 mL of THF–DMF (9:1) was added over a 1-h period and the mixture was refluxed for 48 h. The reaction was quenched by addition of 1 N HCl (20 mL) at 0 °C. The organic solvent was evaporated in vacuo. The residual aqueous layer was extracted with CH_2Cl_2 (200 mL). The resulting organic solution was washed with H_2O (2×150 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a solid, which was chromatographed on silica gel with hexanes–EtOAc (1:1) as eluant to obtain 5.25 g (88%) of white solid with mp 126–128 °C. IR: 1757 (C=O), 1240, 1094, 1024 (C–O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=6.90–6.30 (m, 12H, ArH), 4.97 (d, J=13.1, 1H, ArCH_2Ar, ax), 4.76 (d, J=16.2, 2H, OCH_2C(O)), 4.73 (d, J=15.6, 1H, ArCH_2Ar, ax), 4.69 (d, J=16.2, 2H, OCH_2C(O)), 4.64 (d, J=13.4, 2H, ArCH_2Ar, ax), 4.35–4.19 (m, 6H, OCH_2), 4.19–4.10 (m, 2H, OCH_2), 3.94–3.77 (m, 6H, OCH_2), 3.77–3.67 (m, 2H, OCH_2), 3.24 (d, J=12.8, 1H, ArCH_2Ar, eq), 3.22 (d, J=13.2, 2H, ArCH_2Ar, eq), 3.13–3.11 (d, J=12.9, 1H, ArCH_2Ar, eq), 1.30 (t, J=7.1, 6H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ=170.1 (C=O), 156.1, 155.1, 135.8, 134.8, 134.5, 134.2, 128.5, 128.5, 128.3, 128.1, 122.8, 122.3 (Ar), 73.5 (OCH_2), 71.1 (OCH_2C(O)), 70.5, 70.2 (OCH_2), 60.5 (OCH_2CH_3), 31.3, 31.2, 29.8 (ArCH_2Ar), 14.2 (CH_3). Anal. Calcd for $C_{42}H_{46}O_{10}$: C, 70.97; H, 6.52. Found: C, 70.86; H, 6.76.

3.1.2. Synthesis of cone 25,26-bis(carboxymethoxy)-calix[4]arene-crown-4 (3). A solution of 25,26-bis[(ethoxycarbonyl)methoxy]calix[4]arene-crown-4 (**2**) (5.23 g, 7.36 mmol) in THF (65 mL) was mixed with 10% aq Me_4NOH (65 mL) and the resulting solution was refluxed for 24 h. After cooling to room temperature, the reaction was quenched by addition of 6 M HCl (35 mL). The mixture was stirred for 1 h. The organic solvent was evaporated in vacuo and the precipitate in the aqueous mixture was filtered. The precipitate was dissolved in CH_2Cl_2 (100 mL). The aqueous filtrate was extracted with CH_2Cl_2 (2×50 mL). The combined CH_2Cl_2 solutions were dried over $MgSO_4$ and evaporated in vacuo to provide 4.72 g (98%) of white solid with mp 178–180 °C. IR: 3400–2700 (br, CO_2H), 1750 (C=O), 1266, 1098, 1055 (C–O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=10.13 (br s, 2H, CO_2H), 6.96–6.53 (m, 12H, ArH), 5.23 (d, J=12.9, 1H, ArCH_2Ar, ax), 4.85 (d, J=16.1, 2H, OCH_2C(O)), 4.60 (d, J=16.1, 2H, OCH_2C(O)), 4.53 (d, J=13.9, 1H, ArCH_2Ar, ax), 4.49 (dd, J=11.5, 4.2, 2H, OCH_2), 4.34 (d, J=13.3, 2H, ArCH_2Ar, ax), 4.06 (t, J=9.4, 2H, OCH_2), 3.91–3.63 (m, 8H, OCH_2), 3.34 (d, J=12.9, 1H, ArCH_2Ar, eq), 3.31 (d, J=13.1, 2H, ArCH_2Ar, eq), 3.14 (d, J=13.1, 1H, ArCH_2Ar, eq). ^{13}C NMR (126 MHz, $CDCl_3$): δ=171.9 (C=O), 155.0, 154.8, 136.1, 134.2, 134.0, 133.6, 129.1, 129.0, 128.74, 128.37, 123.86, 123.15 (Ar), 74.82 (OCH_2), 71.62 (OCH_2C(O)), 69.89, 69.80 (OCH_2), 31.11, 29.4 (ArCH_2Ar). Anal. Calcd for $C_{38}H_{38}O_{10}\cdot0.4CH_2Cl_2$: C, 66.74; H, 5.72. Found: C, 67.02; H, 5.66.

3.2. General procedure for the synthesis of cone 25,26-di(*N*-(X)sulfonyl carbamoylmethoxy)calix[4]arene-crown-4 compounds 4–7

A solution of 25,26-bis(carboxymethoxy)calix[4]arene-crown-4 (**3**) (1.80 g, 2.75 mmol) in benzene (90 mL) was refluxed with a Dean–Stark trap for 2 h during which 50 mL of benzene was removed. Oxalyl chloride (3.84 g, 30.24 mmol) was added to the flask with a syringe and the mixture was refluxed for 5 h under nitrogen. The benzene was evaporated in vacuo to give the corresponding di(acid chloride), which was used directly in the next step. The sulfonamide salt was prepared under nitrogen by adding over a 10-min period to a mixture of the appropriate sulfonamide (6.05 mmol) in THF (35 mL) NaH (0.66 g, 27.49 mmol) and THF (35 mL). The mixture was stirred for 1.5 h followed by addition of a solution of the di(acid chloride) in THF (10 mL). The reaction mixture was stirred for 24 h after which H_2O (10 mL) was added and stirring was continued for 0.5 h. The THF was evaporated in vacuo. CH_2Cl_2 was added to the residue and the resulting solution was dried over $MgSO_4$. After purification by chromatography on silica gel, the product was dissolved in CH_2Cl_2. The solution was shaken with 6 M HCl, dried over $MgSO_4$, and evaporated in vacuo to give the product as a solid.

3.2.1. Cone 25,26-bis(*N*-methanesulfonyl carbamoyl-methoxy)calix[4]arene-crown-4 (4). Compound **4** was chromatographed on silica gel with CH_2Cl_2–MeOH (19:1) as eluant to give 0.98 g (44%) of white solid with mp 304–305 °C. IR: 3173 (N–H), 1744 (C=O), 1346, 1154 (SO_2), 1265, 1130, 1065 (C–O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=10.24 (br s, 2H, NH), 6.80–6.40 (m, 12H, ArH), 5.14 (d, J=15.7, 2H, OCH_2C(O)), 4.93 (d, J=13.7, 1H, ArCH_2Ar, ax), 4.85 (d, J=13.3, 1H, ArCH_2Ar, ax), 4.35 (d, J=15.7, 2H, OCH_2C(O)), 4.28 (d, J=14.2, 2H, ArCH_2Ar, ax), 4.27–4.15 (m, 2H, OCH_2), 3.98–3.86 (m, 6H, OCH_2), 3.86–3.73 (m, 4H, OCH_2), 3.38 (s, 6H, CH_3), 3.34 (d, J=14.3, 2H, ArCH_2Ar, eq), 3.25 (d, J=14.0, 1H, ArCH_2Ar, eq), 3.22 (d, J=14.9, 1H, ArCH_2Ar, eq). ^{13}C NMR (126 MHz, $CDCl_3$): δ=170.4 (C=O), 156.2, 155.6, 135.3, 135.0, 133.8, 132.7, 129.4, 128.7, 128.6, 128.6, 123.1, 123.0 (Ar), 73.7 (OCH_2), 73.3 (OCH_2C(O)), 70.4, 70.1 (OCH_2), 41.3 (CH_3), 31.6, 29.6 (ArCH_2Ar). Anal. Calcd for $C_{40}H_{44}O_{12}N_2S_2$: C, 59.40; H, 5.48; N, 3.46. Found: C, 59.27; H, 5.37; N, 3.44.

3.2.2. Cone 25,26-bis(*N*-phenylsulfonyl carbamoyl-methoxy)calix[4]arene-crown-4 (5). Compound **5** was chromatographed on silica gel with EtOAc as eluant to give 1.23 g (48%) of white solid with mp 151–153 °C. IR: 3253 (N–H), 1712 (C=O), 1348, 1154 (SO_2), 1264, 1088, 1051 (C–O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=10.45 (br s, 2H, NH), 8.18 (dd, J=8.0, 1.2, 4H, ArH), 7.62 (t, J=7.6, 2H, ArH), 7.52 (t, J=8.0, 4H, ArH), 6.80–6.20 (m, 12H, ArH), 5.05 (d, J=14.8, 2H, OCH_2C(O)), 4.86 (d, J=13.2, 1H, ArCH_2Ar, ax), 4.49 (d, J=13.7, 1H, ArCH_2Ar, ax), 4.33–4.24 (m, 2H, OCH$_2$), 4.22 (d, *J*=14.8, 2H, OCH_2C(O)), 4.20 (d, *J*=14.0, 2H, ArCH_2Ar, ax), 3.96–3.71 (m, 10H, OCH$_2$), 3.25 (d, *J*=14.2, 2H, ArCH_2Ar, eq), 3.17 (d, *J*=13.2, 1H, ArCH_2Ar, eq), 2.63 (d, *J*=13.8, 1H, ArCH_2Ar, eq). ^{13}C NMR (126 MHz, CDCl$_3$): δ=168.6 (C=O), 156.1, 155.8, 138.5, 135.1, 134.8, 133.9, 133.7, 132.6, 129.3, 128.9, 128.7, 128.5, 128.5, 128.4, 122.9, 122.8 (Ar), 73.9 (OCH$_2$), 73.8 (OCH_2C(O)), 70.2, 69.6 (OCH$_2$), 31.5, 31.4, 29.5 (ArCH_2Ar). Anal. Calcd for $C_{50}H_{48}O_{12}N_2S_2$: C, 64.36; H, 5.18; N, 3.00. Found: C, 64.04; H, 5.33; N, 2.95.

3.2.3. Cone 25,26-bis(*N*-*p*-nitrobenzenesulfonyl carbamoylmethoxy)calix[4]arene-crown-4 (6). Compound **6** was chromatographed on silica gel with CH$_2$Cl$_2$–MeOH (19:1) as eluant and then recrystallized with CH$_2$Cl$_2$ to give 1.15 g (41%) of yellow solid with mp 183–185 °C. IR: 3241 (N–H), 1728 (C=O), 1532, 1312 (NO$_2$), 1350, 1184 (SO$_2$), 1266, 1143, 1050 (C–O) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ=10.82 (br s, 2H, NH), 8.41 (d, *J*=7.1, 4H, ArH), 8.36 (d, *J*=8.79, 4H, ArH), 6.95–6.10 (m, 12H, ArH), 5.16 (d, *J*=14.9, 2H, OCH_2C(O)), 4.81 (d, *J*=13.2, 1H, ArCH_2Ar, ax), 4.51 (d, *J*=13.4, 1H, ArCH_2Ar, ax), 4.32 (br s, 2H, OCH$_2$), 4.20 (d, *J*=15.1, 2H, OCH_2C(O)), 4.17 (d, *J*=15.0, 2H, ArCH_2Ar, ax), 4.06–3.92 (m, 4H, OCH$_2$), 3.92–3.68 (m, 6H, OCH$_2$), 3.30 (d, *J*=14.0, 2H, ArCH_2Ar, eq), 3.22 (d, *J*=13.2, 1H, ArCH_2Ar, eq), 2.60–2.37 (m, 1H, ArCH_2Ar, eq). ^{13}C NMR (126 MHz, CDCl$_3$): δ=169.2 (C=O), 156.0, 155.7, 150.8, 143.8, 134.8, 134.7, 133.6, 132.5, 130.2, 129.5, 128.6, 128.3, 124.2, 123.1, 123.0 (Ar), 73.7 (OCH$_2$), 73.6 (OCH_2C(O)), 70.2, 69.3 (OCH$_2$), 31.5, 29.5 (ArCH_2Ar). Anal. Calcd. for $C_{50}H_{46}O_{16}N_4S_2$: C, 58.70; H, 4.53; N, 5.48. Found: C, 58.46; H, 4.31; N, 5.48.

3.2.4. Cone 25,26-bis(*N*-trifluoromethanesulfonyl carbamoylmethoxy)calix[4]arene-crown-4 (7). Compound **7** was chromatographed on silica gel with CH$_2$Cl$_2$–MeOH (19:1) as eluant and then recrystallized with hexanes–EtOAc (1:1) to give 1.09 g (43%) of white solid with mp 222–224 °C. IR: 3400–2200 (br, N–H), 1754 (C=O), 1390, 1198 (SO$_2$), 1234, 1131, 1050 (C–O) cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ=10.46 (br s, 2H, NH), 6.66 (s, 12H, ArH), 5.17 (d, *J*=16.0, 2H, OCH_2C(O)), 4.82 (d, *J*=13.1, 1H, ArCH_2Ar, ax), 4.81 (d, *J*=13.3, 1H, ArCH_2Ar, ax), 4.59 (d, *J*=16.5, 2H, OCH_2C(O)), 4.33 (d, *J*=16.2, 2H, ArCH_2Ar, ax), 4.28 (br s, 2H, OCH$_2$), 4.06–3.72 (m, 10H, OCH$_2$), 3.36 (d, *J*=14.2, 2H, ArCH_2Ar, eq), 3.26 (d, *J*=13.6, 1H, ArCH_2Ar, eq), 3.25 (d, *J*=13.1, 1H, ArCH_2Ar, eq). ^{13}C NMR (126 MHz, CDCl$_3$): δ=168.6 (C=O), 155.9, 155.7, 134.9, 133.7, 132.5, 129.5, 128.7, 128.7, 128.6, 123.4, 123.1 (Ar), 120.4, 117.9 (CF$_3$), 73.7 (OCH$_2$), 73.0 (OCH_2C(O)), 70.3, 69.4 (OCH$_2$), 31.8, 31.5, 29.5 (ArCH_2Ar). Anal. Calcd for $C_{40}H_{38}O_{12}N_2S_2F_6$: C, 52.40; H, 4.18; N, 3.06. Found: C, 52.68; H, 4.31; N, 3.01.

3.3. Procedure for competitive extraction of alkaline earth metal cations

An aqueous solution of the alkaline earth metal chlorides with hydroxides for pH adjustment (2.0 mL, 2.0 mM in each alkaline earth metal cation species) and 2.0 mL of 1.0 mM ligand in chloroform in a capped, polypropylene, 15-mL centrifuge tube was vortexed with a Glas-Col Multi-Pulse Vortexer for 10 min at room temperature. The tube was centrifuged for 10 min for phase separation with a Becton–Dickinson Clay Adams Brand® Centrifuge. A 1.5-mL portion of the organic phase was removed and added to 3.0 mL of 0.10 M HCl in a new, 15-mL, polypropylene centrifuge tube. The tube was vortexed for 10 min and then centrifuged for 10 min. The alkaline earth metal cation concentrations in the aqueous phase from stripping were determined with a Dionex DX-120 Ion Chromatograph with a CS12A column. The pH of the aqueous phase from the initial extraction step was determined with a Fisher Accumet AR25 pH meter with a Corning 476157 combination pH electrode.

3.4. Procedure for single species extraction of Pb(II)

The procedure used for competitive extraction of alkaline earth metal cations was modified, as follows. The organic phase was a 0.50 mM solution of the ligand in chloroform. The aqueous phase contained 1.0 mM Pb(NO$_3$)$_2$ with the pH adjusted using either HNO$_3$ or tetramethylammonium hydroxide (TMAOH) solutions. For stripping of the extracted Pb^{2+} from the chloroform phase, 1.0 M HNO$_3$ was utilized. The Pb^{2+} concentrations in the aqueous stripping solutions were determined with a Perkin–Elmer Model 5000 atomic absorption spectrophotometer.

3.5. Procedure for single species extraction of Hg(II)

An aqueous solution (3.0 mL) of 0.25 mM Hg(NO$_3$)$_2$ with HNO$_3$ or TMAOH for pH adjustment and 3.0 mL of 0.25 mM solution of the ligand in chloroform were placed in a capped, polypropylene, 15-mL centrifuge tube. The mixture was vortexed for 10 min at room temperature. The tube was centrifuged for 10 min for phase separation. A 0.50-mL sample of the aqueous phase was removed and diluted to 5.0 mL with water. A 1.5-mL aliquot of the diluted solution was shaken for 10 min with 3.0 mL of 14 ppm solution of dithizone in chloroform and 1.5 mL of 1.0 M citric acid solution for which the pH had been adjusted using NaOH. The mixture was centrifuged for 10 min. The organic phase was then analyzed by using the absorbance at 496 nm for mercury dithizonate complex with a Shimadzu Model 260 UV–vis spectrophotometer. The pH of the remaining aqueous phase from the initial extraction step was determined with a Fisher Accumet AR25 pH meter with a Corning 476157 combination pH electrode.

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