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Lower-rim versus upper-rim functionalization in di-ionizable calix[4]arene-crown-5 isomers. Synthesis and divalent metal ion extraction

Yanfei Yang, Gaurav Arora, Fernando A. Fernandez, Jennifer D. Crawford, Kazimierz Surowiec, Eun Kyung Lee, Richard A. Bartsch *

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

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ABSTRACT

Two series of di-ionizable calix[4]arene-crown-5 isomers in the cone conformation are synthesized to probe the effect of the pendant acidic group location on their metal ion extraction properties. In one series, the ionizable groups are attached to the lower rim of the calix[4]arene scaffold, which orients them near the crown ether cavity. In the second series, the ionizable groups are connected to the upper rim positioning them away from the crown ether ring, but close to the hydrophobic pocket of the calix[4]arene unit. The metal ion extraction behaviors of the two series of ligands are compared in extractions of alkaline earth metal cations, Hg^{2+}, and Pb^{2+}.

1. Introduction

In calixarene-crown ethers, also known as calixcrowns, two phenolic oxygens of a calixarene scaffold are connected with a polyether chain.[1–6] Most common are calix[4]arene-1,3-crown ethers in which a calix[4]arene platform is connected with a polyether fragment bridging two distal phenolic oxygens. The first example of this type of ligand, *p-tert*-butylcalix[4]arene-1,3-crown-6 (**1**) as reported by Ungaro and co-workers[7] is shown in Fig. 1

Of particular interest to our metal ion separations research program has been calix[4]arene-crown ether ligands with two pendant acidic groups attached to the remaining phenolic oxygens. Such ligands provide efficient extractions of divalent metal ions from aqueous solutions into organic diluents. The extraction proceeds by an ion-exchange mechanism to form electroneutral di-ionized calixcrown-divalent metal ion complexes in the organic phase. This avoids the need for concomitant transfer of anions from the aqueous phase into the organic phase, a very important factor when highly hydrophilic anions like chloride, nitrate, and sulfate are involved. The first example of such a di-ionizable calixcrown compound, *p-tert*-butylcalix[4]arene-1,3-crown-5 dicarboxylic acid **2** (Fig. 1) was described by Ungaro and co-workers who found that this ligand exhibited enhanced metal ion extraction ability compared to non-ionizable analogues.[8]

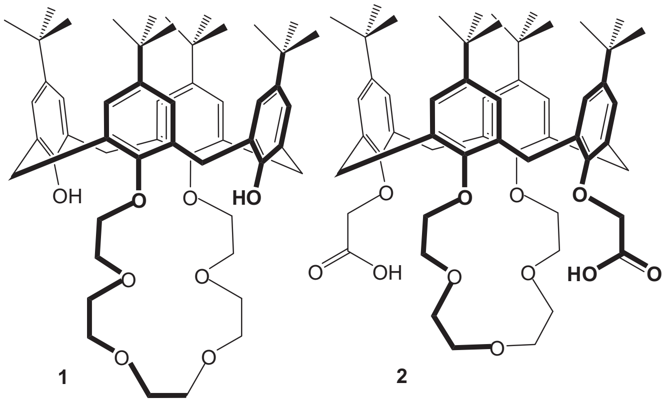

Fig. 1. Structures of the first-reported calixcrown **1** and di-ionizable calixcrown **2**.

Since 2005, we have been engaged in a systematic structural variation of di-ionizable calix[4]arene-1,3-crown ether compounds.[9–14] Effects of the changes are evaluated in solvent extraction of divalent metal ions from aqueous solutions into chloroform. The structural variations have included changing: (i) the size of the crown ether ring from crown-4 to crown-5 to crown-6;[9–11,13] (ii) the conformation of the calix[4]arene scaffold from cone to partial cone to 1,3-alternate;[9–11,13] and (iii) the presence of substituents on benzene ring positions *para* to the phenolic oxygens in the calixarene unit.[9,11] Also evaluated was the effect of replacing one oxygen in the polyether fragment with sulfur.[12,14] The

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* Corresponding author. Tel.: +1 806 742 3069; fax: +1 806 742 1289; e-mail address: richard.bartsch@ttu.edu (R.A. Bartsch).

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proton-ionizable groups have included carboxylic acid and *N*-(X) sulfonyl carbamoyl, $-C(O)NHSO_2X$, in which the acidity may be 'tuned' by varying the inductive effects of X.

In the cone conformation of calix[4]arene (**3**), the phenolic oxygen-containing portion is called the lower rim and the aryl group region is termed the upper rim (Fig. 2).[15] To date, our investigations have involved di-ionizable calix[4]arene-1,3-crown ethers with pendant acidic groups attached to the lower rim. To provide for a comparison with ligands in which the ionizable groups have been moved to the upper rim, we undertook the synthesis and evaluation of two new series of di-ionizable calix[4]arene-1,3-crown-5 compounds **4** and **5** (Fig. 3). The two series are constitutional isomers with the same molecular formula for a given acidic function. In the former series, the two acidic groups are connected to the lower rim of the calix[4]arene unit. In the latter, the upper rim bears the two acidic functions. In Series **4**, the two ionizable groups are in close proximity to the crown ether ring. In Series **5**, the acidic groups are remote from the crown ether ring, but close to the π-electron rich cavity of the calixarene unit.

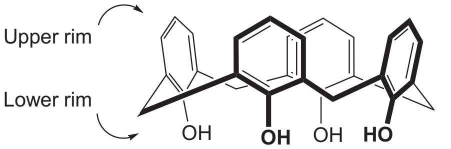

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Fig. 2. Upper and lower rims of calix[4]arene in the cone conformation.

We now report the synthesis of ligands **4a**–**e** and **5a**–**e** and evaluation of their metal ion binding propensities in solvent extraction of divalent metal ions.

2. Results and discussion

2.1. Synthesis of cone calix[4]arene-crown-5 ligands 4a–e with two lower rim acidic side arms

Preparation of di-ionizable calix[4]arene-crown-5 ethers **4a**–**e** in the cone conformation is depicted in Scheme 1. In adaptation of a reported method,[16] calix[4]arene (**3**) was reacted with iodomethane and K_2CO_3 in refluxing MeCN to give dimethoxycalix[4]arene **6** in 51% yield. For this reaction, it was found that if the amount of K_2CO_3 was more than 1 equiv, a mixture of mono-, di-, and trimethoxycalix[4]arenes resulted and the yield of the desired dimethylated product decreased. The dimethoxycalix[4]arene **6** remains in the cone conformation due to the hydrogen bonding between the two remaining hydroxyl groups. The dimethoxycalix[4]arene-crown-5 **7** was realized in 73% yield by a modified literature procedure[17] under high dilution conditions with tetraethylene glycol ditosylate and excess Cs_2CO_3 as the base. This base was utilized because of the template effect of Cs^+ in forming the crown ether unit. Due to elimination of the intramolecular hydrogen bonding and the presence of the two small methoxy groups on the lower rim, compound **7** is conformationally mobile in the solution. Demethylation of **7** with trimethylsilyl iodide by adaptation of a reported procedure[17] gave 25,27-dihydroxycalix[4]arene-crown-5 (**8**) in 78% yield. Diester **9** was realized in 50% yield by reaction of **8** with NaH and ethyl bromoacetate in THF at room temperature. Refluxing diester **9** with tetramethylammonium hydroxide in aqueous THF overnight followed by acidification gave diacid **4a** in 84% yield. Diacid **4a** was transformed into the corresponding di(acid chloride) by reaction with oxalyl chloride in refluxing benzene. Commercially available sulfonamides were converted into their sodium salts by reaction with NaH in THF. Subsequently the di(acid chloride) was added and the reaction was allowed to proceed at room temperature overnight to give the desired products **4b**–**e** in 48–65% yields.

The conformation of ligands **4a**–**e** was readily elucidated from their ^1H and ^{13}C NMR spectra using the 'de Mendoza' rule.[18] A pair of widely separated AB patterns was observed for the bridge protons and both of these protons correlated with a carbon signal at δ 31 ppm, confirming that the ligands are in the cone conformation.

2.2. Synthesis of cone upper-rim di-ionizable calix[4]arene-crown-5 ligands 5a–e

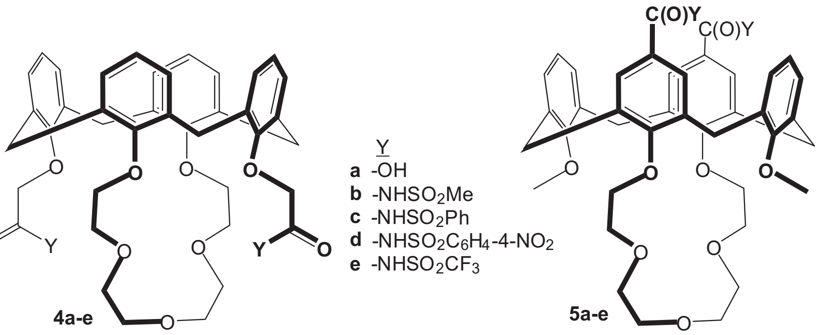
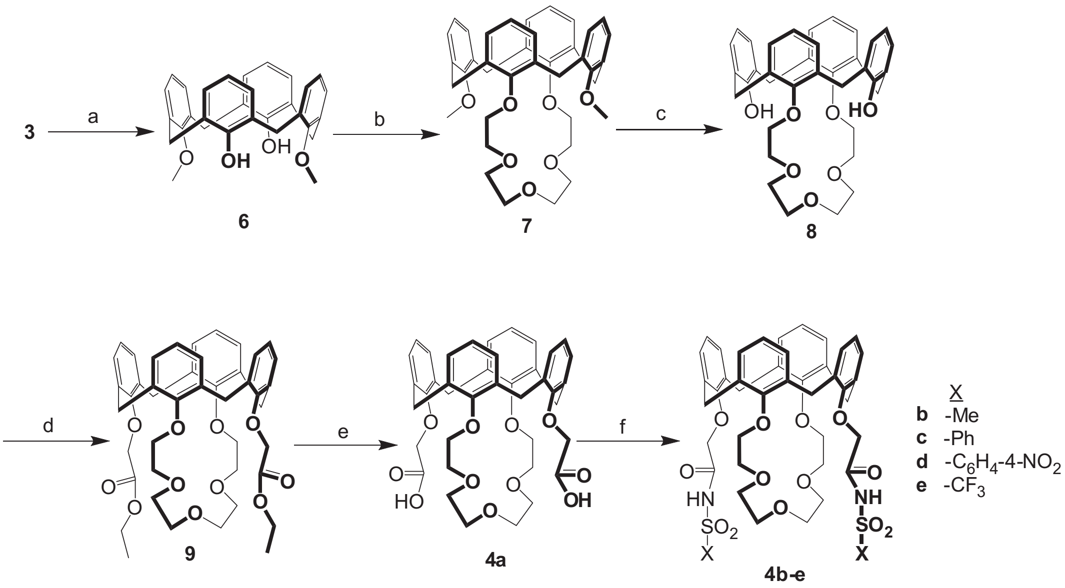


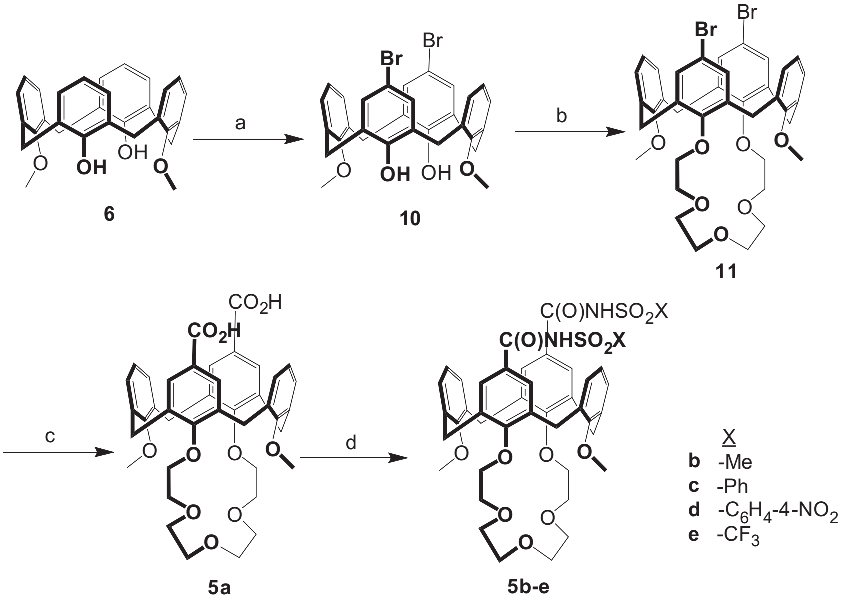
Fig. 3. Isomeric cone calix[4]arene-crown-5 ligands with two pendant acidic groups attached to the lower rim in **4** and to the upper rim in **5**.

Synthesis of upper-rim functionalized di-ionizable ligands **5a**–**e** is presented in Scheme 2. Following a literature procedure,[16] reaction of dimethoxycalix[4]arene **6** with 2 equiv of Br_2 in $CHCl_3$ gave dibrominated dimethoxycalix[4]arene **10** in 84% yield. Reaction of **10** with tetraethylene glycol ditosylate and Cs_2CO_3 in refluxing MeCN provided the dibrominated dimethoxycalix[4]arene-crown-5 **11** in 58% yield. To a solution of calixcrown **11** in THF at −78 °C was added BuLi in hexane followed by bubbling CO_2 into the THF solution of the organolithium intermediate. Following the reaction, addition of aqueous HCl gave the upper rim-substituted di(carboxylic acid) **5a** as a white precipitate in 78% yield. Di(carboxylic acid) **5a** was transformed into the corresponding di(acid chloride) by reaction with oxalyl chloride in refluxing benzene. Commercially available sulfonamides were treated with NaH in THF to convert them into the corresponding sodium salts. Then a THF solution of the di(acid chloride) in THF was added with reaction at room temperature for 24 h. Desired products **5b**–**e** were isolated in 71–80% yields.

The conformation of ligands **5a**–**e** was readily elucidated from their ^1H and ^{13}C NMR spectra. Generally speaking, lower rim alkylation by methyl groups results in more flexible calixcrown ligands due to elimination of intramolecular hydrogen bonding between the hydroxyl groups. However, upper-rim substituents



Scheme 1. Synthesis of di-ionizable calix[4]arene-crown-5 ligands **4a**–**e**. Reagents and conditions (a) MeI, K_2CO_3, MeCN, reflux; (b) $TsO(CH_2CH_2O)_4Ts$, Cs_2CO_3, MeCN, reflux; (c) Me_3SiI, $CHCl_3$, reflux; (d) $BrCH_2CO_2Et$, NaH, THF, rt; (e) TMAOH, aq THF, reflux; (f) (i) $(COCl)_2$, C_6H_6, reflux; (ii) XSO_2NH_2, NaH, THF, rt.



Scheme 2. Synthesis of cone, upper-rim functionalized di-ionizable calix[4]arene-crown-5 ligands **5a**–**e**. Reagents and conditions: (a) Br_2, $CHCl_3$, rt; (b) $TsO(CH_2CH_2O)_4Ts$, Cs_2CO_3, MeCN, reflux; (c) (i) BuLi, THF, −78 °C; (ii) CO_2; (d) (i) $(COCl)_2$, C_6H_6, reflux; (ii) XSO_2NH_2, NaH, THF, rt.

restrict rotation of the phenolic units through the calixarene cavity, especially when acidic groups are present on the upper rim. Cone conformations were observed for ligands **5a**–**e**. A pair of widely separated AB patterns for the bridge protons was observed and both of these protons correlated with a carbon signal at δ 31 ppm, confirming that the ligands are in the cone conformation.[18]

2.3. Effects of position of the two ionizable groups on divalent metal ion extractions

The effects of changing the positions of the two pendant acidic groups from the lower rim in **4a**–**e** to the upper rim in **5a**–**e** were probed using divalent metal ion extractions from aqueous solutions into chloroform. As in our previous studies of di-ionizable calix[4]arene-1,3-crown ether ligands, both competitive solvent extractions of four alkaline earth metal cations and single species extractions of Hg^{2+} and Pb^{2+} were investigated. The solvent extractions include hard[19] alkaline earth metal cations, intermediate Pb^{2+}, and soft Hg^{2+}.

2.3.1. Competitive solvent extraction of alkaline earth metal cations by cone di-ionizable calix[4]arene-crown-5 ligands 4a–e and 5a–e.

*2.3.1. Competitive solvent extraction of alkaline earth metal cations by cone di-ionizable calix[4]arene-crown-5 ligands **4a**–**e** and **5a**–**e**.* For competitive solvent extraction of aqueous solutions of alkaline earth metal cations (2.0 mM in each) with 1.0 mM solutions of the di-ionizable calix[4]arene-crown-5 ligands **4a**–**e** and **5a**–**e** in chloroform, plots of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Figs. 4 and 5, respectively.

The extraction selectivity order for ligands **4a**–**e** is $Ba^{2+}>Sr^{2+}>Ca^{2+}\approx Mg^{2+}$. The total metal cation loading approaches 100%, which is consistent with formation of 1:1 divalent metal ion: di-ionized ligand extraction complexes. The Ba^{2+}/Sr^{2+} selectivities for extractants **4b**–**e** increase in the order: $-C(O)NHSO_2Me<-C(O)NHSO_2Ph<-C(O)NHSO_2C_6H_4-4-NO_2<-C(O)NHSO_2CF_3$. This is the

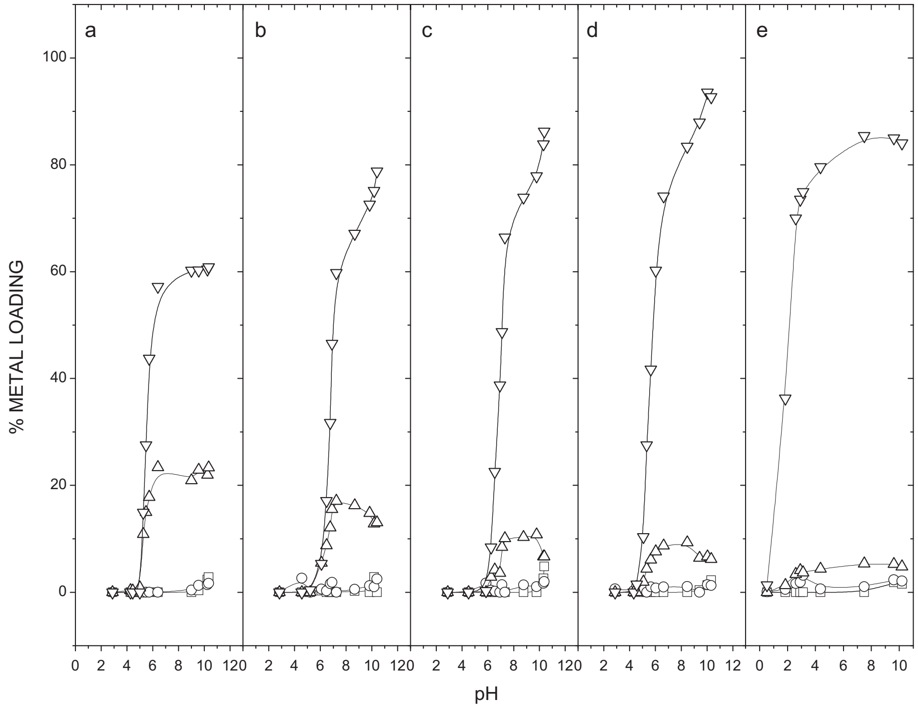


Fig. 4. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations from aqueous solutions into chloroform by lower-rim di-ionizable calix[4]arene-crown-5 ligands **4a**–**e**: (a) **4a**, (b) **4b**, (c) **4c**, (d) **4d**, and (e) **4e**. (□=Mg^{2+}, ○=Ca^{2+}, △=Sr^{2+}, ▽=Ba^{2+}).

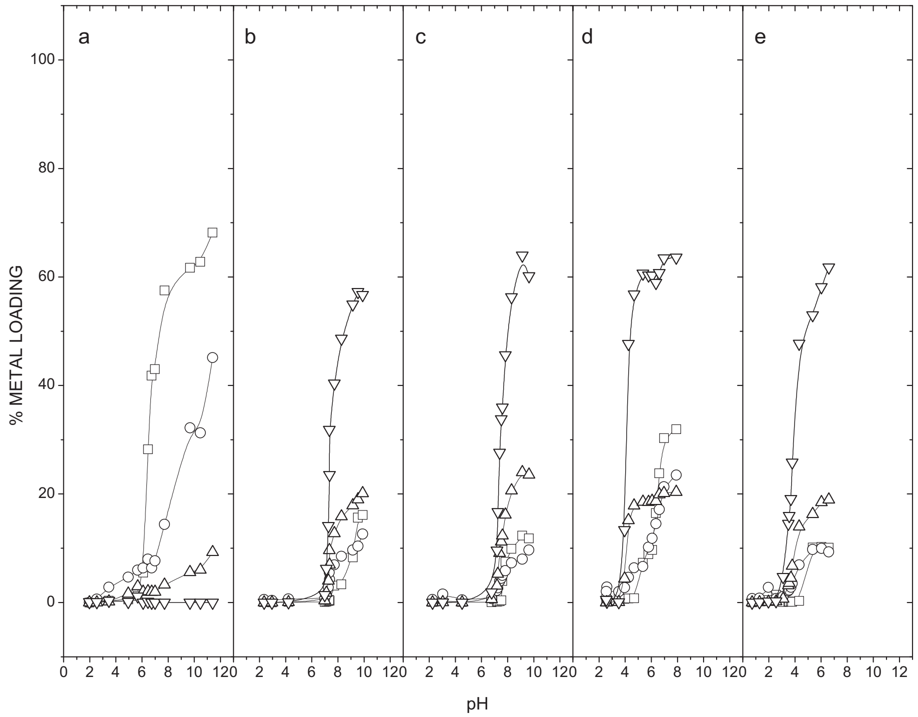


Fig. 5. Percent metal loading versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by upper-rim di-ionizable calix[4]arene-crown-5 ligands **5a**–**e**: (a) **5a**, (b) **5b**, (c) **5c**, (d) **5d**, and (e) **5e**. (□=Mg^{2+}, ○=Ca^{2+}, △=Sr^{2+}, ▽=Ba^{2+}).

same order in which the electron-withdrawing ability of X and the acidity of the ionizable group increase. The lowest Ba^{2+}/Sr^{2+} selectivity is observed with the di(carboxylic acid) **4a**.

Ligands **5b**–**e** also exhibit total metal cation loading approaching 100%. So moving the two ionizable groups to the upper rim does not appreciably alter the alkaline earth metal ion extraction efficiency. Presumably the somewhat higher metal cation loading for ligand **5a** results from contamination of the organic phase by finely divided $Mg(OH)_2$ at the highest pHs. Comparison of the results obtained with **4b**–**e** and **5b**–**e** reveals that the Ba^{2+} extraction selectivity is diminished when the two acid functions are shifted to the upper rim.

The selectivity exhibited in alkaline earth metal cation extraction by upper-rim di(carboxylic acid) **5a** is strikingly different from the Ba^{2+} selectivity shown by ligands **4a**–**e** and **5b**–**e**. With **5a**, the extraction selectivity order is $Mg^{2+}>Ca^{2+}>Sr^{2+}>Ba^{2+}$. Thus, Ba^{2+} changed from the best-extracted alkaline earth metal cation with **4a**–**e** to **5b**–**e** to the worst-extracted species with **5a**.

For ligand series **5a**–**e** with the two acidic groups on the upper rim, the alkaline earth metal cation selectivity changes as the type of ionizable group is varied from carboxylic acid in **5a** to *N*-(X)sulfonyl carbamoyl in **5b**–**e**. As ionized species, the former should be a harder divalent metal ion coordination site than the latter. The extraction selectivity observed with **5a** correlates with the hardness of the alkaline earth metal cations. This suggests that the primary coordination site for association of the alkaline earth metal cations with di-ionized ligand **5a** is with the two carboxylate ion centers on the upper rim. With the *N*-(X)sulfonyl carbamoyl groups, interactions of the softer ionized group sites on the upper rim with the divalent cations are weaker allowing for participation of the crown ether ring or the π-electron rich cavity of the calix[4]arene unit favoring extraction of the softer alkaline earth metal cation.

*2.3.2. Single species solvent extraction of Hg^{2+} by cone di-ionizable calix[4]arene-crown-5 ligands **4a**–**e** and **5a**–**e**.* Aqueous solutions containing 0.25 mM Hg^{2+} were extracted by 0.25 mM solutions of ligands **4a**–**e** and **5a**–**e** in chloroform. Data for Hg^{2+} loading of the organic phase versus the equilibrium pH of the aqueous phase in extractions with **4a**–**e** and **5a**–**e** are presented as open and filled circles, respectively, in Fig. 6. Each panel in this figure gives the extraction profiles for a Series **4** and a Series **5** ligand with the same ionizable group.

Ligands **5a**–**e** are all moderately good extractants for Hg^{2+} with **5c** and **5e** giving significantly higher metal loading levels than those for the other three members of the series. In the comparison of Hg^{2+} extraction by Series **4** and Series **5** ligands with the same acidic groups, three different categories are noted for the five different ionizable functions. For the two di(carboxylic acid) ligands **4a** and **5a**, a significantly higher extraction level is observed when the two ionizable groups are attached to the lower rim. For the acidic functions of $-C(O)NHSO_2X$ with X=Me, Ph, and $C_6H_4-4-NO_2$, much higher levels of extraction are found when the two ionizable groups are attached to the upper rims. Finally, when the two acidic groups are $-C(O)NHSO_2CF_3$, the Hg^{2+} loadings are the same for ligands **4e** and **5e**. Thus the effect of moving the acidic groups from the lower rim to the upper rim for extraction of soft Hg^{2+} is found to depend upon the identity of the particular ionizable function.

*2.3.3. Single species solvent extraction of Pb^{2+} by cone di-ionizable calix[4]arene-crown-5 ligands **4a**–**e** and **5a**–**e**.* For single species extraction of Pb^{2+}, aqueous solutions containing 1.00 mM Pb^{2+} were extracted with 0.50 mM solutions of ligands **4a**–**e** and **5a**–**e** in chloroform. Plots of Pb^{2+} loading of the organic phase versus the equilibrium pH of the aqueous phase for **4a**–**e** (open circles) and for **5a**–**e** (filled circles) are presented in Fig. 7. Each panel contains the data for a Series **4** ligand and a Series **5** ligand with the same ionizable group.

All members of Series **4** produce near quantitative Pb^{2+} loadings based on formation of 1:1 Pb^{2+}-di-ionized ligand extraction complexes.

Ligands **5a**–**e** show two strikingly different extraction behaviors toward Pb^{2+}. High metal loading levels are observed for **5a** and **5e**. In sharp contrast, ligands **5b**–**d** are very poor Pb^{2+} extractants.

When the data for ligands **4** and **5** are considered together, two patterns are evident. If the acidic groups are $-CO_2H$ or $-C(O)NHSO_2CF_3$, both the Series **4** and **5** ligands show strong extraction propensities toward Pb^{2+}. On the other hand, when the ionizable groups are $-C(O)NHSO_2X$ with X=Me, Ph or $-C_6H_4-4-NO_2$, extraction of Pb^{2+} is strongly facilitated by location of the two acidic functions on the lower rims in **4b**–**d**.

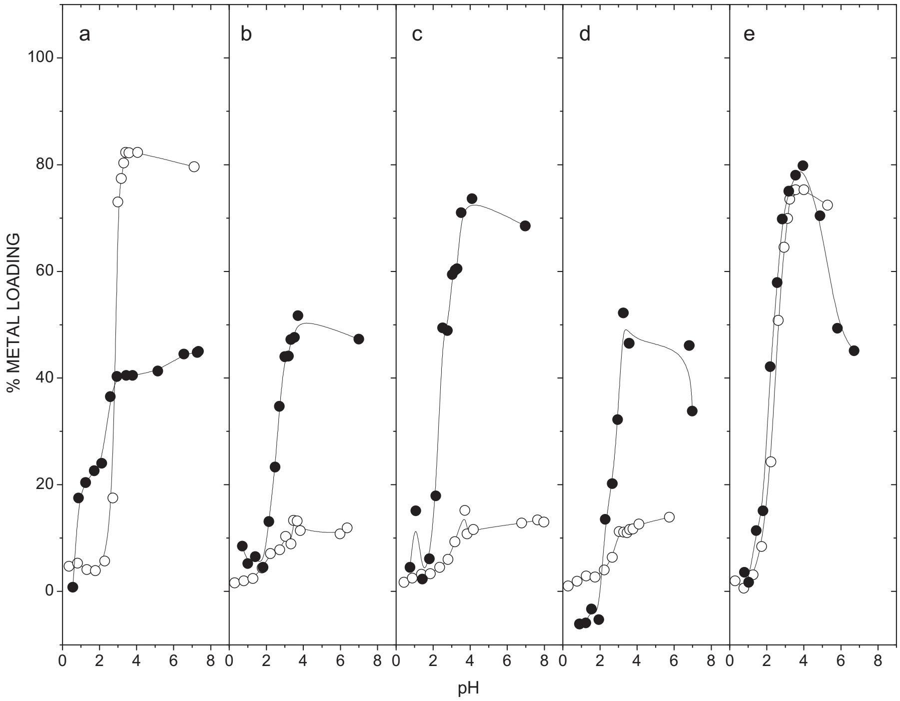


Fig. 6. Percent metal loading versus the equilibrium pH of the aqueous phase for single species solvent extraction of Hg^{2+} into chloroform by lower-rim di-ionizable calix[4]arene-crown-5 compounds **4a**–**e** and upper-rim di-ionizable calix[4]arene-crown-5 ligands **5a**–**e**: (a) **4a** and **5a**, (b) **4b** and **5b**, (c) **4c** and **5c**, (d) **4d** and **5d**, and (e) **4e** and **5e**. (○=**4a**–**e**, ●=**5a**–**e**).

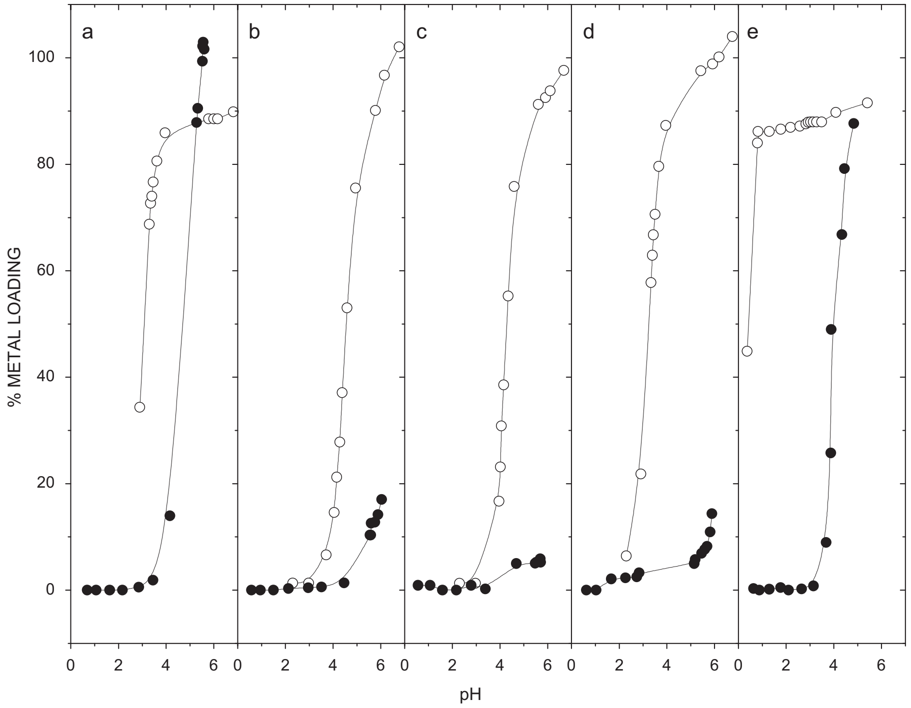


Fig. 7. Percent metal loading versus the equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} into chloroform by lower-rim di-ionizable calix[4]arene-crown-5 compounds **4a**–**e** and upper-rim di-ionizable calix[4]arene-crown-5 ligands **5a**–**e**: (a) **4a** and **5a**, (b) **4b** and **5b**, (c) **4c** and **5c**, (d) **4d** and **5d**, and (e) **4e** and **5e**. (○=**4a**–**e**, ●=**5a**–**e**).

3. Conclusions

Synthetic routes are established for two series of di-ionizable calix[4]arene-crown-5 isomers in cone conformations. In Series **4** ligands, the two acidic side arms are attached to the lower rim of the calix[4]arene unit. In Series **5** compounds, the two ionizable groups are connected to the upper rim of the calix[4]arene scaffold. In both series, ligands with five different acidic functions are employed including $-CO_2H$ and $-C(O)NHSO_2X$ with variation in the inductive effects of X.

To probe the effect of locating the two ionizable groups on the lower-rim versus the upper rim, solvent extraction of divalent cations from aqueous solutions into chloroform are employed. This includes extractions of hard alkaline earth metal cations, intermediate Pb^{2+}, and soft Hg^{2+}.

From comparison of the extraction results for the Series **4** and **5** isomers, insight into the effect of locating the two acidic groups on the lower-rim versus the upper rim is gained. The effect is found to differ depending upon the metal ion species being extracted and the identity of the ionizable groups.

Ligands in Series **4** and **5** are efficient alkaline earth metal cation extractants and nearly all exhibit selectivity for Ba^{2+}, which would fit within the crown ether cavity. The exception is ligand **5e** with extraction selectivity for Mg^{2+} suggesting coordination with the oxygens of the two carboxylate groups on the upper rim of the di-ionized ligand.

When the results are taken together, the Series **5** ligands are better Hg^{2+} extractants (45–80% loading) than the compounds in Series **4**. This suggests coordination of soft Hg^{2+} in the π-electron rich cavity of the calix[4]arene unit near the ionized groups on the upper rim. Ligands of Series **4** exhibit large differences in their abilities to extract Hg^{2+}. Compounds **4b**–**d** are found to be very poor Hg^{2+} extractants. On the other hand, ligands **4a** and **4e** give high metal loadings (near 80%). Reasons for the high variability in Hg^{2+} extractions within the Series **4** ligands are not evident at this time.

For intermediate Pb^{2+}, all five of the Series **4** extractants exhibit high metal loadings indicating that positioning of the ionizable groups near the crown ether unit in the extraction complex is preferred. Compounds **5b**–**d** are found to be very poor extractants for Pb^{2+}. In contrast, ligands **5a** and **5e** give high metal loadings. Determining the reasons for the extreme variability in Pb^{2+} extractions within the Series **5** ligands will require further investigation.

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 solutions on NaCl plates. The ^1H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR (^1H 500 MHz and ^{13}C 126 MHz) spectrometer in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts (δ) are given in parts per million downfield from TMS and coupling constants values (J) are in hertz. Elemental analysis was performed by Desert Analytics Laboratory (now Columbia Analytical Services) of Tucson, Arizona. For compounds **5a**, **5c**, and **11**, the combustion analysis results indicated the presence of small amounts of CH_2Cl_2 in the samples. This was verified by singlets at δ 5.32 in their ^1H NMR spectra.

Reagents were purchased from commercial suppliers and used directly unless stated otherwise. 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. DMF was dried over activated 4 Å molecular sieves for 24 h before use. Synthesis of the ditosylate of tetraethylene glycol was performed by a conventional aqueous THF method.[20]

For use in the metal ion extractions, reagent-grade chloroform was washed with an equal volume of deionized water to remove the stabilizing ethanol and stored in the dark. Vortexing and centrifugation of two-phase extraction mixtures were performed with a Glas-Col Multi-Pulse vortexer and a Becton-Dickinson Clay Adams Brand® centrifuge, respectively. The pH of the aqueous phase for an extraction experiment was measured with a Fisher Accumet AR25 pH meter with a Corning 476,157 combination pH electrode.

4.2. Synthesis of cone, lower rim, di-carboxyl calix[4]arene-crown-5 ligand 4a

*4.2.1. 25,27-Dimethoxycalix[4]arene (**6**).* To a suspension of calix[4]arene (**3**) (8.30 g, 19.56 mmol) and anhydrous K_2CO_3 (3.57 g, 25.87 mmol) in MeCN (160 mL) under nitrogen was added CH_3I (2.43 mL, 41.10 mmol) and the mixture was refluxed for 24 h. After evaporation of the solvent in vacuo, the residue was taken up in CH_2Cl_2 (200 mL) and the solution was washed with 1 N HCl (2×80 mL) and brine (2×50 mL). The organic layer was dried over $MgSO_4$. After recrystallization from EtOH–CH_2Cl_2, 4.50 g (51%) of **6** was obtained as a white solid with mp 305–307 °C (lit.[16] mp >300 °C). IR (deposit on a NaCl plate from CH_2Cl_2 solution): 3100 (OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.40 and 4.30 (AB q, J=13.3 Hz, 8H), 3.98 (s, 6H), 6.65–6.73 (m, 4H), 6.86 (d, J=7.6 Hz, 4H), 7.07 (d, J=7.4, 4H), 7.75 (s, 2H).

*4.2.2. 25,27-Dimethoxycalix[4]arene-crown-5 (**7**).* To a solution of **6** (4.52 g, 10.00 mmol) in MeCN (1500 mL) under nitrogen, Cs_2CO_3 (13.03 g, 40.00 mmol) and the ditosylate of tetraethylene glycol (5.52 g, 11.00 mmol) were added and the mixture was refluxed for 24 h. The MeCN was removed in vacuo. To the residue, CH_2Cl_2 (350 mL) and 10% aqueous HCl (350 mL) were added. The organic layer was separated, washed with water (2×100 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was recrystallized from CH_2Cl_2 (20 mL) and MeOH (120 mL) to give 4.46 g (73%) of **7** as a white solid with mp 216–218 °C (lit.[17] mp 220–221 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 3.19 and 4.41 (AB q, J=13.0 Hz, 8H), 3.56 (t, J=3.0 Hz, 4H), 3.74 (t, J=3.0 Hz, 4H), 3.92 (d, J=4.5 Hz, 4H), 3.98 (d, J=4.5 Hz, 4H), 4.12 (s, 6H), 6.41 (t, J=7.5 Hz, 2H), 6.52 (d, J=7.5 Hz, 4H), 6.90 (t, J=7.5 Hz, 2H), 7.12 (d, J=7.5 Hz, 4H).

*4.2.3. 25,27-Dihydroxycalix[4]arene-crown-5 (**8**).* To a solution of **7** (1.96 g, 2.99 mmol) in $CHCl_3$ (120 mL) under nitrogen was added Me_3SiI (0.84 mL, 6.27 mmol) and the solution was refluxed for 4 h. The color of the solution changed from yellow to pink after 10–15 min of refluxing. After cooling to room temperature, the reaction was quenched with 10% aqueous HCl. The organic layer was separated, washed with satd aq $Na_2S_2O_3$ and water (2×50 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallized from CH_2Cl_2 (15 mL) and MeOH (75 mL) to give 1.46 g (78%) of **8** as a white solid with mp 271–274 °C (lit.[21] mp 275–276 °C). IR (deposit on a NaCl plate from CH_2Cl_2 solution): 3374 (OH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.36 and 4.42 (AB q, J=13.0 Hz, 8H), 3.86 (t, J=5.5 Hz, 4H), 3.96 (t, J=5.5 Hz, 4H), 4.06–4.14 (m, 8H), 6.67 (t, J=7.5 Hz, 2H), 6.71 (t, 2H, J=7.5 Hz), 6.86 (d, J=7.5 Hz, 4H), 7.07 (d, J=7.5 Hz, 4H), 7.74 (s, 2H).

*4.2.4. Cone 25,27-di[(ethoxycarbonyl)methoxy]calix[4]arene-crown-5 (**9**).* To a solution of **8** (2.61 g, 4.48 mmol) in THF (54 mL) and DMF (6 mL) under nitrogen was added NaH (1.08 g, 44.80 mmol). The mixture was stirred at room temperature for 30 min before addition of $BrCH_2CO_2Et$ (4.00 mL, 35.50 mmol). The mixture was stirred for 24 h at room temperature and then the reaction was quenched by addition of 1 N HCl (10 mL). After the solvent was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (80 mL). The solution was washed with water (2×40 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was recrystallized from a mixed solvent of CH_2Cl_2 (5 mL) and MeOH (50 mL). For compound **9**, 1.66 g (50%) was realized as a pale yellow solid with mp 201–204 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 1758 (C═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, J=7.0 Hz, 6H), 3.23 and 4.60 (AB q, J=13.0 Hz, 8H), 3.71–3.79 (m, 8H), 4.04 (t, J=6.5 Hz, 4H), 4.18 (q, J=7.0 Hz, 4H), 4.30 (t, J=6.5 Hz, 4H), 4.87 (s, 4H), 6.51 (s, 6H), 6.73 (t, J=7.5 Hz, 2H), 6.89 (d, J=7.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 31.4, 60.5, 69.6, 70.3, 70.9, 71.1, 72.8, 122.4, 127.9, 128.7, 134.4, 135.3, 154.6, 152.0, 170.0. Anal. Calcd for $C_{44}H_{50}O_{11}$: C, 70.01; H, 6.68. Found: C, 69.86; H, 6.93.

*4.2.5. Cone 25,27-di(carboxymethoxy)calix[4]arene-crown-5 (**4a**).* To a solution of diester **9** (2.40 g, 3.18 mmol) in THF (40 mL) was added 10% aqueous tetramethylammonium hydroxide (40 mL) and the solution was refluxed for 24 h. The THF was evaporated in vacuo and the residue was acidified with 6 N HCl (25 mL). CH_2Cl_2 (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo to give 1.87 g (84%) of **4a** as a white solid with mp 270–274 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 2800–3300 (–CO_2H), 1746 (C═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.33 and 4.42 (AB q, J=13.0 Hz, 8H), 3.87 (s, 8H), 3.93–3.99 (m, 4H), 4.04–4.12 (m, 4H), 5.33 (s, 4H), 6.51 (t, J=8.0 Hz, 2H), 6.63 (d, J=7.5 Hz, 4H), 6.93 (t, J=7.5 Hz, 2H), 7.13 (d, J=7.5 Hz, 4H), 10.80 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.3, 70.2, 70.8, 74.0, 124.2, 129.3, 129.4, 133.6, 136.0, 154.2, 155.8, 172.3. Anal. Calcd for $C_{40}H_{42}O_{11}$: C, 68.76; H, 6.06. Found C, 68.40; H, 6.33.

4.3. General procedure for synthesis of cone 25,27-di[*N*-(X) sulfonyl carboxamidomethoxy]calix[4]arene-crown-5 compounds 4b–e

Di(carboxylic acid) **4a** (1.20 g, 1.72 mmol) was dried using a benzene azeotrope. To the resulting solution under nitrogen, oxalyl chloride (1.20 mL, 13.70 mmol) was added and the solution was refluxed for 20 h. Progress of the conversion was monitored by IR spectroscopy. The C═O peak absorbs at 1740 cm^{-1} for **4a** and at 1810 cm^{-1} for the corresponding di(acid chloride). The solvent and excess oxalyl chloride were evaporated in vacuo and the residue was subjected to oil pump vacuum for 20 min. The di(acid chloride) was used directly in the following reaction without further purification. The commercial sulfonamide (3.50 mmol) was reacted with NaH (0.84 g, 35.00 mmol) in freshly distilled THF (50 mL) under nitrogen. The crude di(acid chloride) was dissolved in freshly distilled THF (25 mL) and the solution was added into the flask with the sulfonamide sodium salt and the mixture was stirred at room temperature for 24 h. The THF was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with 1 N HCl (2×100 mL) and then water (2×100 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was recrystallized from a mixed solvent of CH_2Cl_2 (10 mL) and MeOH (50 mL).

*4.3.1. Cone 25,27-di[N-(methanesulfonyl) carbamoylmethoxy]calix[4]arene-crown-5 (**4b**).* The compound was obtained in 48% yield as a white solid with mp 288–290 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 1716 (C═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.24 (s, 6H), 3.31 and 4.40 (AB q, J=13.0 Hz, 8H), 3.87–3.88 (m, 4H), 3.95–3.97 (m, 4H), 4.00–4.02 (m, 4H), 4.10–4.12 (m, 4H), 5.31 (s, 4H), 6.46 (t, J=7.5 Hz, 2H), 6.54 (d, J=7.5 Hz, 4H), 6.97 (t, J=7.5 Hz, 2H), 7.15 (d, J=7.5 Hz, 4H), 10.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.4, 42.1, 70.9, 71.4, 72.6, 123.9, 124.3, 128.8, 129.3, 133.3, 136.4, 154.5, 154.6, 170.0. Anal. Calcd for $C_{42}H_{48}N_2O_{13}S_2$: C, 59.14; H, 5.67; N, 3.28. Found: C, 59.34; H, 5.77; N, 3.30.

*4.3.2. Cone 25,27-di[N-(benzenesulfonyl) carbamoylmethoxy]calix[4]arene-crown-5 (**4c**).* The compound was produced in 51% yield as a white solid with mp 277–279 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 1720 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.98 and 4.11 (AB q, J=13.0 Hz, 8H), 3.85–3.92 (m, 12H), 3.98–4.00 (m, 4H), 5.13 (s, 4H), 6.36 (dd, J=6.5 Hz, 2H), 6.42 (d, J=7.0 Hz, 4H), 6.85 (dd, J=7.5 Hz, 2H), 6.95 (d, J=7.5 Hz, 4H), 7.51 (t, J=8.0 Hz, 4H), 7.63–7.66 (m, 2H), 8.06 (d, J=8.0 Hz, 4H), 10.82 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.2, 70.7, 71.0, 71.0, 71.4, 72.5, 123.7, 124.0, 128.7, 128.8, 129.0, 129.3, 133.3, 134.3, 136.4, 139.5, 154.2, 154.6, 168.1. Anal. Calcd for $C_{52}H_{52}N_2O_{13}S_2$: C, 63.92; H, 5.36; N, 2.87. Found: C, 63.76; H, 5.55; N, 2.75.

*4.3.3. Cone 25,27-di[N-(4-nitrobenzenesulfonyl) carbamoylmethoxy] calix[4]arene-crown-5 (**4d**).* The compound was realized in 65% yield as a pale yellow solid with mp 291–293 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 1718 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.02 and 4.12 (AB q, J=13.0 Hz, 8H), 3.88–3.90 (m, 4H), 3.95–4.10 (m, 12H), 5.19 (s, 4H), 6.35–6.42 (m, 6H), 6.84 (dd, J=7.0 Hz, 2H), 6.93 (d, J=7.5 Hz, 4H), 8.22 (d, J=9.0 Hz, 4H), 8.32 (d, J=9.0 Hz, 4H), 10.95 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.3, 70.7, 71.0, 71.4, 72.5, 124.0, 124.3, 124.4, 128.8, 129.2, 130.3, 133.0, 136.2, 144.6, 151.2, 154.1, 154.4, 168.3. Anal. Calcd for $C_{52}H_{50}N_4O_{17}S_2$: C, 58.53; H, 4.72; N, 5.25. Found: C, 58.68; H, 4.97; N, 5.10.

*4.3.4. Cone 25,27-di[N-(trifluoromethanesulfonyl) carbamoylmethoxy]calix[4]arene-crown-5 (**4e**).* The compound was obtained in 53% yield as a white solid with mp 227–229 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 1751 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.32 and 4.30 (AB q, J=13.0 Hz, 8H), 3.86–3.89 (m, 4H), 3.91–3.94 (m, 4H), 4.00–4.03 (m, 4H), 4.10–4.12 (m, 4H), 5.34 (s, 4H), 6.46 (t, J=7.5 Hz, 2H), 6.53 (d, J=7.5 Hz, 4H), 6.97 (t, J=7.5 Hz, 2H), 7.14 (d, J=7.5 Hz, 4H), 11.14 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 32.4, 70.7, 70.8, 70.8, 71.8, 72.3, 124.1, 124.7, 128.9, 129.4, 133.1, 136.2, 153.8, 154.5, 167.3. Anal. Calcd for $C_{42}H_{42}F_6N_2O_{13}S_2$: C, 52.50; H, 4.41; N, 2.92. Found: C, 52.28; H, 4.62; N, 2.67.

4.4. Synthesis of cone, upper rim, di-carboxy calix[4]arene-crown-5 ligand 5a

*4.4.1. 11,23-Dibromo-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (**10**).*[16] To a stirred solution of **6** (5.00 g, 11.05 mmol) in $CHCl_3$ (225 mL) at 0 °C was added dropwise a solution of Br_2 (3.55 g, 22.10 mmol) in $CHCl_3$ (225 mL) during a 2-h period. Afterward the reaction mixture was kept at room temperature for 2 h. The precipitate was filtered and the solid was washed with cold $CHCl_3$ (20 mL). The filter cake was stirred in CH_2Cl_2 (50 mL) at room temperature for 2 h and filtered. The solid was dried in vacuo to give **10** as a white solid with mp 362 °C (lit.[16] mp >300 °C) in 84% yield.

*4.4.2. 11,23-Dibromo-25,27-dimethoxycalix[4]arene-crown-5 (**11**).* A mixture of **10** (5.00 g, 8.22 mmol) and Cs_2CO_3 (6.69 g, 20.55 mmol) in MeCN (600 mL) under nitrogen was stirred at reflux for 30 min and then a solution of the ditosylate of tetraethylene glycol (4.56 g, 9.04 mmol) in MeCN (50 mL) was added during a 1-h period. The mixture was refluxed for 66 h and allowed to cool to room temperature. After evaporation of the solvent in vacuo, the residue was taken up in CH_2Cl_2 (250 mL) and the resulting solution was washed with 2 N HCl (100 mL) and water (2×250 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. Recrystallization of the residue from CH_2Cl_2–MeOH gave **11** in 58% yield as a white solid with mp 260–264 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 3.14 (d, J=12.5 Hz, 4H), 3.52 (m, 4H), 3.72 (m, 4H), 3.90 (m, 8H), 4.09 (s, 6H), 4.45 (d, J=12.5 Hz, 4H), 6.65 (s, 4H), 6.95 (t, J=7.5 Hz, 2H), 7.12 (d, J=7.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.0, 70.8, 70.8, 71.5, 73.2, 76.5, 77.0, 77.2, 123.1, 128.7, 130.6, 135.8, 154.6, 159.1. Anal. Calcd for $C_{38}H_{40}O_7Br_2\bullet 0.2CH_2Cl_2$: C, 58.41; H, 5.18. Found: C, 58.60; H, 5.14.

*4.4.3. 25,27-Dimethoxy-11,23-di(carboxy)calix[4]arene-crown-5 (**5a**).* A solution of **11** (1.00 g, 1.32 mmol) in freshly distilled THF (50 mL) under nitrogen was cooled in a dry ice–acetone bath for 30 min before the addition of 1.6 M *n*-BuLi–hexanes solution (4.62 mmol). The mixture was stirred for 15 min at that temperature before CO_2 was bubbled through the solution for 30 min. After another 30 min at −78 °C, the mixture was allowed to warm to room temperature. After evaporating the THF in vacuo, 1 N HCl was added to the residue. The precipitate was filtered and the filter cake was washed with water (25 mL) and then CH_2Cl_2 (25 mL) to give **5a** (0.72 g, 78%) as a white solid with mp 372–374 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 3305 (OH), 1751 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.25 (d, J=20.5 Hz, 4H), 3.58 (m, 4H), 3.69 (m, 4H), 3.88 (m, 8H), 4.15 (s, 6H), 4.35 (d, J=20.5 Hz, 4H), 6.40–6.95 (m, 3H), 7.20–7.62 (m, 7H), 12.15 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.5, 39.0, 39.7, 40.0, 67.0, 70.6, 73.8, 123.0, 128.8, 129.5, 133.7, 135.6, 158.7, 159.7, 166.8. Anal. Calcd for $C_{40}H_{42}O_{11}\bullet 0.2CH_2Cl_2$: C, 67.46; H, 5.97. Found: C, 67.72; H, 5.49.

4.5. General procedure for preparation of the 25,27-dimethoxy-11,23-di[*N*-(X-sulfonyl) carbamoyl]calix[4]arene-crown-5 compounds 5b–e

Diacid **5a** (1.00 g, 1.49 mmol) was dried with a benzene azeotrope before addition of oxalyl chloride (1.89 g, 14.90 mmol) in benzene (50 mL). The solution was refluxed overnight. Diacid **5a** has poor solubility in benzene, while a clear solution was obtained upon formation of di(acid chloride). After conversion to the di(acid chloride) was confirmed by an IR shift of the C=O functional group absorption from 1695 cm^{-1} in **5a** to 1752 cm^{-1} for the di(acid chloride), the benzene was evaporated in vacuo and the residue was subjected to oil pump vacuum for 30 min. The residue was dissolved in freshly distilled THF (20 mL) and the solution was added to a mixture of the appropriate sulfonamide (3.28 mmol) and NaH (0.35 g, 14.90 mmol) in THF (25 mL) under nitrogen at room temperature. The reaction mixture was refluxed for 2 days. The THF was removed in vacuo and CH_2Cl_2 (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 $MgSO_4$. Evaporation of the CH_2Cl_2 in vacuo gave the crude product, which was purified by column chromatography on silica gel.

*4.5.1. Cone 25,27-dimethoxy-11,23-di[N-(methanesulfonyl) carbamoyl]calix[4]arene-crown-5 (**5b**).* After chromatography with CH_2Cl_2–MeOH (250:1 to 10:1) as eluent, **5b** was isolated in 75% yield as a white solid with mp 212–218 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 3249 (NH), 1680 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.95 (s, 6H), 3.29 (d, J=12.0 Hz, 4H), 3.63 (m, 4H), 3.77 (m, 4H), 3.95 (m, 8H), 4.15 (s, 6H), 4.55 (d, J=12.0 Hz, 4H), 6.63–7.50 (m, 10H), 9.01 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.1, 61.1, 70.6, 71.3, 73.8, 76.7, 77.0, 77.2, 123.8, 128.5, 129.1, 134.6, 135.3, 160.4, 166.6. Anal. Calcd for $C_{42}H_{48}O_{13}N_2S_2$: C, 59.14; H, 5.67; N, 3.28. Found: C, 59.35; H, 5.64; N, 3.01.

*4.5.2. Cone 25,27-dimethoxy-11,23-di[N-(benzenesulfonyl) carbamoyl] calix[4]arene-crown-5 (**5c**).* Chromatography with CH_2Cl_2–MeOH (250:1 to 10:1) as eluent produced **5c** in 79% yield as a white solid with mp 288–290 °C. IR (deposit on a NaCl plate from CH_2Cl_2 solution): 3175 (NH), 1680 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.20 (d, J=12.4 Hz, 4H), 3.55 (m, 4H), 3.75 (m, 4H), 3.90 (m, 8H), 4.15 (s, 6H), 4.44 (d, J=12.3 Hz, 4H), 6.97 (m, 7H), 7.25 (m, 6H), 7.55 (m, 7H), 8.05 (m, 4H), 9.82 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.5, 31.2, 36.8, 43.6, 60.4, 65.9, 76.7, 77.0, 77.2, 128.3, 128.6, 128.7, 129.6, 129.8, 130.0, 131.4, 133.5, 133.8, 134.0, 134.2, 138.6, 138.8, 156.7, 157.5, 170.6. Anal. Calcd for $C_{52}H_{52}O_{13}N_2S_2\bullet 0.1CH_2Cl_2$: C, 63.49; H, 5.34; N, 2.84. Found: C, 63.30; H, 5.53; N, 3.08.

*4.5.3. Cone 25,27-dimethoxy-11,23-di[N-(4-nitrobenzenesulfonyl) carbamoyl]calix[4]arene-crown-5 (**5d**).* Chromatography with CH_2Cl_2–MeOH (250:1 to 10:1) as eluent gave **5d** in 71% yield as a yellow solid with mp 268–270 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3414 (NH), 1685 (C═O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.29 (d, *J*=13.0 Hz, 4H), 3.51–3.87 (m, 16H), 4.08 (s, 6H), 4.32 (d, *J*=13.0 Hz, 4H), 6.88 (t, *J*=7.5 Hz, 2H), 7.22 (d, *J*=7.5 Hz, 4H), 7.31 (s, 4H), 8.12 (d, *J*=9.0 Hz, 4H), 8.36 (d, *J*=9.0 Hz, 4H), 12.48 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.6, 60.8, 69.9, 70.0, 70.5, 74.2, 123.2, 124.2, 128.9, 129.2, 129.2, 134.1, 134.9, 145.0, 150.0, 158.5, 160.6, 165.0. Anal. Calcd for $C_{52}H_{50}N_4O_{17}S_2$: C, 58.53, H, 4.72; N, 5.25. Found: C, 58.15; H, 4.89; N, 5.12.

*4.5.4. Cone 25,27-dimethoxy-11,23-di[N-(trifluoromethanesulfonyl) carbamoyl]calix[4]arene-crown-5 (**5e**).* Chromatography with CH_2Cl_2–MeOH (250:1 to 10:1) as eluent produced **5e** in 80% yield as a pale yellow solid with mp 192 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3620 (NH), 1729 (C═O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (d, *J*=13.0 Hz, 4H), 3.55 (t, *J*=3.0 Hz, 4H), 3.74 (t, *J*=3.0 Hz, 4H), 3.92–4.01 (m, 8H), 4.44 (d, *J*=13.0 Hz, 4H), 6.95 (s, 4H), 7.00 (t, *J*=7.0 Hz, 2H), 7.23 (d, *J*=7.0 Hz, 4H), 9.77 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 31.1, 70.5, 70.8, 71.6, 73.4, 117.8, 120.4, 123.5, 125.7, 128.6, 129.1, 135.0, 136.0, 159.1, 160.6, 164.2. Anal. Calcd for $C_{42}H_{42}F_6N_2O_{13}S_2$: C, 52.50, H, 4.41; N, 2.92. Found: C, 52.80; H, 4.75; N, 3.16.

4.6. Solvent extraction procedures

4.6.1. Competitive extraction of alkaline earth metal cations into chloroform. An aqueous solution of the alkaline earth metal chlorides with $Ba(OH)_2$ or HCl for pH adjustment (2.00 mL, 2.0 mM in each of the four alkaline earth metal cation species) and 2.00 mL of a 1.0 mM ligand solution in chloroform were placed in a capped, polypropylene, 15-mL centrifuge tube and vortexed for 10 min. The tube was centrifuged for 10 min for phase separation. A 1.50-mL portion of the organic phase was removed and added to 3.00 mL of 0.10 M HCl in a new capped, polypropylene, 15-mL centrifuge tube. The tube was vortexed for 10 min and centrifuged for 10 min. A 1.00 mL portion of the aqueous phase from stripping was removed and diluted to 10.0 mL with deionized water. The alkaline earth metal cation concentrations 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 measured.

4.6.2. Single species extraction of Hg^{2+} into chloroform. An aqueous solution of 0.25 mM $Hg(NO_3)_2$ with HNO_3 or TMAOH for pH adjustment (3.00 mL) and 3.00 mL of a 0.25 mM ligand solution in chloroform were placed in a capped, polypropylene, 15-mL centrifuge tube. The tube was vortexed for 10 min and then centrifuged for 10 min to allow for phase separation. A 0.50-mL sample of the aqueous phase was removed and diluted to 5.00 mL with deionized water. The pH of the aqueous phase was measured. A 1.00-mL portion of the diluted sample was added to 100 mL of 1.0 N H_2SO_4 in a glass reaction bottle, which was then placed on a Shimadzu MVU-1A Mercury Vaporizor Unit. The Hg^{2+} in the sample was reduced using 5 mL of a 0.5 M solution of $SnCl_2$. The reduced mercury vapor was then pumped through a flow cell and the mercury concentration was measured at 253.6 nm with a Shimadzu AA-6300 Spectrophotometer.

4.6.3. Single species extraction of Pb^{2+} into chloroform. A 1.00 mM aqueous solution of $Pb(NO_3)_2$ with tetramethylammonium hydroxide (TMAOH) or HNO_3 for pH adjustment (2.00 mL) and a 0.50 mM ligand solution in chloroform (2.00 mL) in a capped, polypropylene, 15-mL centrifuge tube was vortexed for 10 min. The tube was then centrifuged for 10 min to facilitate phase separation. A 1.50-mL portion of the organic phase was removed and placed in a new, 15-mL polypropylene centrifuge tube with 3.00 mL of 4.0 M HNO_3. The tube was vortexed for 10 min and then centrifuged for 10 min. The Pb^{2+} concentration of the aqueous phase from stripping was determined using a Shimadzu AA-6300 Spectrophotometer. The pH of the aqueous phase in the initial extraction was measured.

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