



Comparison of upper and lower rim-functionalized, di-ionizable calix[4]arene-crown-6 structural isomers in divalent metal ion extraction

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ABSTRACT

Upper rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands are synthesized and compared with structural isomers having the two acidic side arms attached to the lower rim. Solvent extractions of selected divalent metal cations (alkaline earth metal cations, Pb^{2+} , and Hg^{2+}) from aqueous solutions into chloroform by the upper and lower rim-functionalized, di-ionizable calix[4]arene-crown-6 isomers are utilized to assess the effects of this structural modification on metal ion complexation abilities of the ligands. The observed effects are compared with those reported for analogous di-ionizable calix[4]arene-crown-5 structural isomers.

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1. Introduction

Calixarenes are a major category of building blocks for supramolecular chemistry research.^{1–4} Structures of these versatile molecules are readily modified. A common structural variation is connecting two of the phenolic oxygens on the lower rim with a polyether chain to give a calixarene-crown ether (also called calixcrown), such as **1** (Fig. 1).⁴

A frequently encountered application of calixarene and calix-

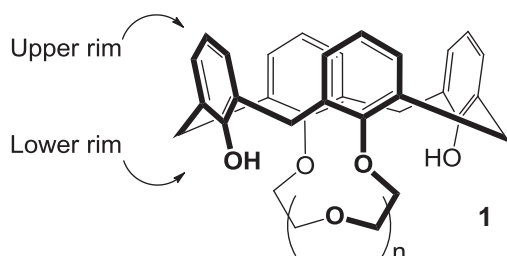


Fig. 1. Upper and lower rims of calix[4]arene-crown- n ($n=2-4$) compounds in the cone conformation.

arene-crown ether compounds is metal ion separation by solvent extraction from an aqueous phase into an organic phase. In earlier studies, we have examined the effects of systematic structural

variations upon metal ion extraction efficiency and selectivity for substituted calix[4]arene-crown ether ligands in which the two remaining phenolic oxygens are substituted with acidic side arms. These structural features include the calixarene conformation (cone, partial cone, 1,3-alternate, 1,2-alternate), crown ether ring size, type of acidic group in the side arm, identification of donor atoms in the crown ether ring, and attachment of lipophilic alkyl groups on the upper rim.^{5–8} These ligands are designed for complexation of divalent metal ions. Ionization of the ligand in the extraction process provides the requisite anions for formation of an electroneutral di-ionized ligand-divalent metal ion complex. This markedly enhances the metal ion extraction efficiency when the aqueous phase anion is hydrophilic chloride, nitrate, or sulfate. In addition to carboxylic acid groups, N -(X)sulfonyl carboxamide functionalities, $-\text{C}(\text{O})\text{NHSO}_2\text{X}$, have been employed. This type of acidic moiety was first utilized in proton-ionizable lariat ethers for alkali metal cation separations.⁹ It represents an important structural modification in that the N -H acidity can be 'tuned' by varying the electron-withdrawing ability of X . Also the N -(X)sulfonyl carboxamidate anions formed by their ionization are softer¹⁰ than carboxylate anions.

In the most recent study, we investigated the effect of moving the two acidic side arms from the lower rim of di-ionizable calix[4]arene-crown-5 ligands to the upper rim (Fig. 2).¹¹ Ligands **2** and **3** are structural isomers with two acidic side arms attached to the lower rim in the former and to the upper rim in the latter. Metal ion binding sites in ionized ligands **2** are the lower rim polyether ring flanked by two ionized side arms and the aromatic nucleus of the calixarene scaffold in cation- π interactions with soft metal

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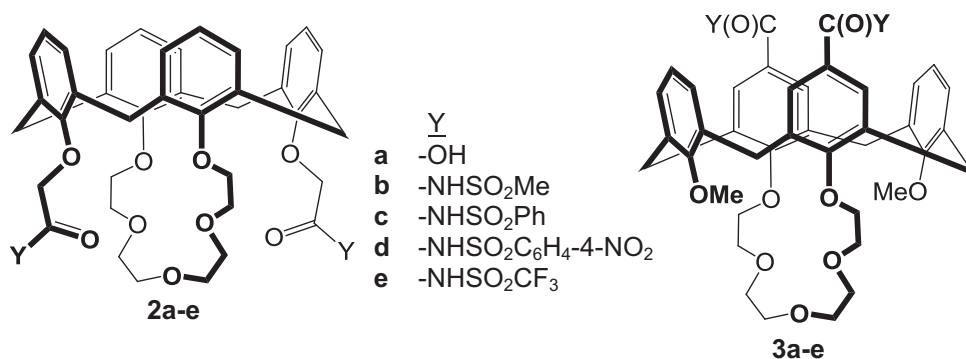


Fig. 2. Di-ionizable calix[4]arene-crown-5 structural isomers in the cone conformation with two acidic side arms on the lower rim in **2a–e** and the upper rim in **3a–e**.

cations.^{12,13} Potential metal ion binding sites in ionized ligands **3** are the lower rim polyether ring, the ionized acidic groups on the upper rim, and a ‘deep pocket’ in which the metal ion interacts with the pendent ionized groups and also has cation– π interactions with the aryl groups of the calixarene. Relocating the acidic side arms was found to exert substantial effects on their divalent metal ion extraction behavior.¹¹ For the lower rim-functionalized ligand series **2a–e** and upper rim-functionalized ligand series **3a–e**, changes in selectivities and efficiencies were observed for different divalent metal cation types, hard¹⁰ alkaline earth metal cations (AEMC), intermediate Pb^{2+} , and soft Hg^{2+} .

To gain further insight into how the location of the acidic side arms affects the metal ion extraction behavior of such ligands, we have now extended the comparison of comparison to di-ionizable calix[4]arene-crown-6 structural isomers (Fig. 3). Earlier, we reported results for AEMC extractions by lower rim-functionalized crown-6 analogues **4a–e** (Fig. 3).¹⁴ We now describe the preparation of upper rim-functionalized structural isomers **5a–e** and their solvent extractions of AEMC, Pb^{2+} , and Hg^{2+} . Also, we have expanded the species examined in solvent extractions by the lower rim-functionalized ligands **4a–e** to include Pb^{2+} and Hg^{2+} .

form the organolithium intermediate, and then bubbling in CO_2 . After protonation by aqueous HCl, the crude product was recrystallized to give **5a** in 38% yield. Di(carboxylic acid) **5a** was refluxed with oxalyl chloride in benzene to produce the corresponding di(acid chloride). A commercially available sulfonamide was stirred with NaH in THF. A solution of the di(acid chloride) in THF was added to the sodium sulfonamide mixture. Ligands **5b–e** were obtained in modest 32–55% yields.

Conformational mobility is often observed in calix[4]arenes containing lower rim methoxy groups.¹⁵ However, the NMR spectra of calix[4]arene-crown-5 ligands **3a–e** revealed that they were locked in the cone conformation.¹¹ Examination of the ^1H NMR, ^{13}C NMR, and ^1H – ^{13}C heteronuclear correlation (HETCOR) spectra for ligands **5a–e** reveals conformational mobility based on the de Mendoza rule.¹⁶ For all five ligands, a ^{13}C NMR signal at δ 30–31 ppm correlated to diastereotopic $\text{syn-ArCH}_2\text{Ar}$ bridge protons exhibiting a widely separated AX pattern in the ^1H NMR spectra. A second signal at δ 35–36 ppm correlated with a singlet for the homotopic *anti-ArCH}_2\text{Ar}* bridge protons at 3.62 ppm. Substantial broadening consistent with less conformational mobility was observed for di(carboxylic acid) **5a** than for **5b–e**.

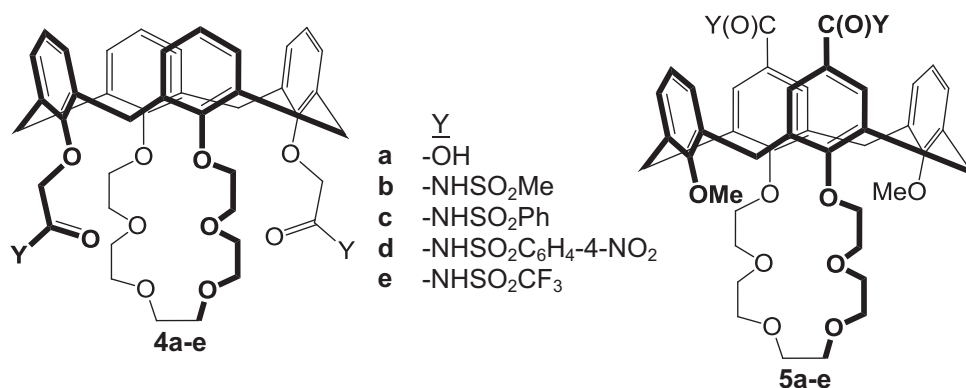


Fig. 3. Calix[4]arene-crown-6 structural isomers **4a–e** with two acidic side arms on the lower rim and **5a–e** with two acidic side arms on the upper rim.

2. Results and discussion

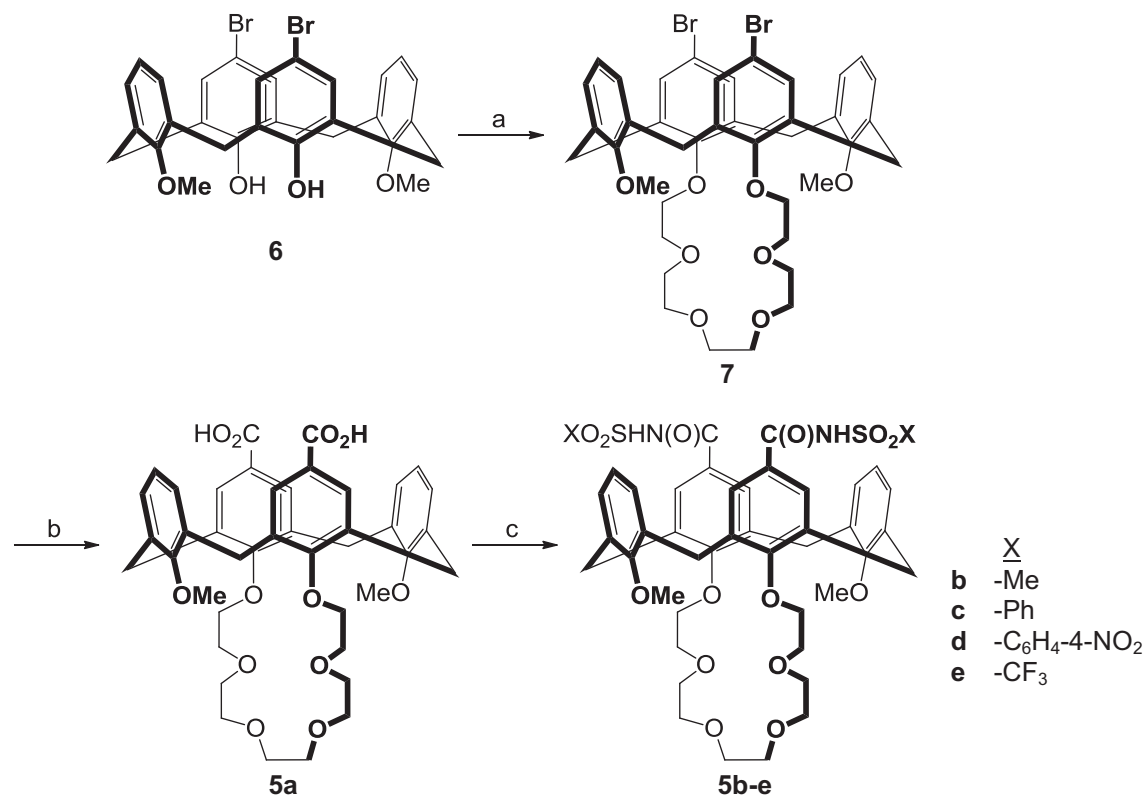
2.1. Synthesis of upper rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands

Preparation of ligands **5a–e** with two acidic side arms on the upper rim is summarized in Scheme 1. Refluxing a mixture of dibrominated dimethoxycalix[4]arene **6**,¹¹ Cs_2CO_3 , and pentaethylene glycol ditosylate¹⁴ in MeCN gave a 73% yield of dibrominated dimethoxycalix[4]arene-crown-6 **7**. Di(carboxylic acid) **5a** was synthesized by dissolving **7** in THF at -78°C , adding BuLi to

In addition to the NMR spectral results, new ligands **5a–e** were characterized by IR spectroscopy and by combustion analysis.

2.2. Metal ion extractions by di-ionizable calix[4]arene-crown-6 isomers **4a–e** and **5a–e**

Divalent metal ion extractions from aqueous solutions into chloroform were utilized to probe the effect of moving the acidic side arms from the lower rim in the previously reported¹² crown-6 ligands **4a–e** to the upper rim in crown-6 ligands **5a–e**. Results from competitive solvent extractions of AEMC (Mg^{2+} , Ca^{2+} , Sr^{2+} ,



Scheme 1. Synthesis of calix[4]arene-crown-6 ligands **5a–e** with two acidic side arms on the upper rim. Reagents and conditions: (a) TsO(CH₂CH₂O)₅Ts, Cs₂CO₃, MeCN, reflux; (b) (i) BuLi, THF, –78 °C; (ii) CO₂; (c) (i) (COCl)₂, C₆H₆, reflux; (ii) XSO₂NH₂, NaH, THF, rt.

and Ba²⁺) by ligands **4a–e** were presented previously.¹⁷ We report here the results for competitive solvent extractions of AEMC by ligands **5a–e** and single species extractions of Hg²⁺ and Pb²⁺ by ligands **4a–e** and **5a–e**. These solvent extractions included hard AEMC, intermediate Pb²⁺, and soft Hg²⁺.¹⁰

2.2.1. Competitive solvent extraction of AEMC by di-ionizable calix[4]arene-crown-6 ligands 4a–e and 5a–e. Competitive solvent extractions of aqueous AEMC solutions (2.00 mM in each) were conducted with 1.00 mM solutions of ligands **4a–e** and **5a–e** in chloroform. Plots of metal loadings of the organic phase versus the equilibrium pH of the aqueous phase are shown in Figs. 4 and 5 (redrawn from the published data¹⁷), respectively.

All ligands **4a–e** reached 100% total metals loadings for formation of 1:1 complexes and showed very good-to-excellent Ba²⁺ selectivity. The high Ba²⁺ selectivity was attributed to the size fit of this hard AEMC within the hard polyether cavity. Also, electrostatic stabilization is provided by the ionized side arms on the lower rim, one on each side of the polyether-complexed divalent metal ion.

Upper rim-functionalized ligands **5a–d** performed moderately well in AEMC extractions. Ligand **5d** gave the highest total metals loading, reaching 86%. The ionizable group identity in the upper rim-functionalized ligands **5a–d** is seen to affect the selectivity in AEMC extractions. The Ca²⁺ selectivity observed with di(carboxylic acid) **5a** changed to modest extraction selectivity for Ba²⁺ when the acidic function was *N*-(X)sulfonyl carboxamide in ligands **5b–d**. The Ca²⁺ selectivity for **5a** suggests greater participation of the hard ionized groups in **5a**. With **5b–d**, the softer ionized group sites on the upper rim allow greater participation of the crown ether unit or the π -electron rich cavity of the calix[4]arene unit.

Overall comparisons of AEMC extraction efficiency and selectivities for lower rim-functionalized ligands **4a–d** with those upper rim-functionalized ligands **5a–d** show the former to be more effective. Surprisingly, ligand **5e** was found to be a very poor AEMC

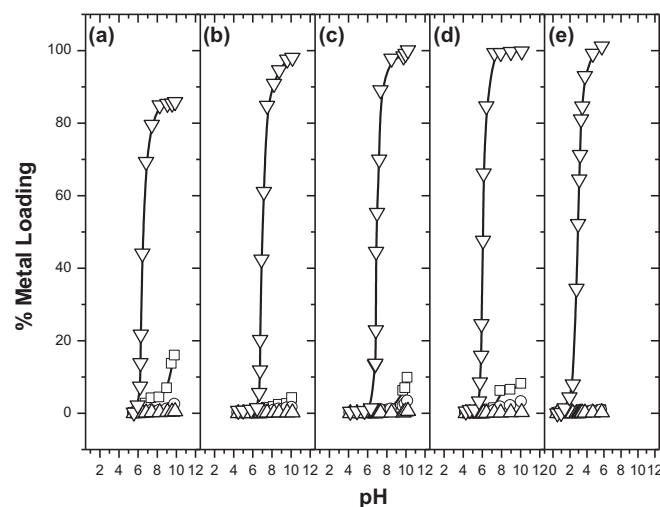


Fig. 4. Percent metal loading versus the equilibrium pH of the aqueous phase for competitive solvent extraction of AEMC into chloroform by lower rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **4a–e**: (a) **4a**, (b) **4b**, (c) **4c**, (d) **4d**, (e) **4e**. (\square = Mg²⁺, \circ = Ca²⁺, \triangle = Sr²⁺, ∇ = Ba²⁺.)

extractant compared with **5a–d**, reaching only 12% of total metals loading. In contrast, the previously examined¹⁴ lower rim-functionalized analogue **4e** gave better Ba²⁺ selectivity than those observed with **4a–d**. The reason of the ineffectiveness of ligand **5e** as an AEMC extractant is not apparent at this time.

2.2.2. Single species solvent extraction of Pb²⁺ by di-ionizable calix[4]arene-crown-6 ligands 4a–e and 5a–e. For solvent extraction of aqueous Pb²⁺ (1.00 mM) solutions by 0.50 mM solutions of ligands **4a–e** and **5a–e** in chloroform, plots of Pb²⁺ loading of the organic phase versus the equilibrium pH of the aqueous phase are shown in

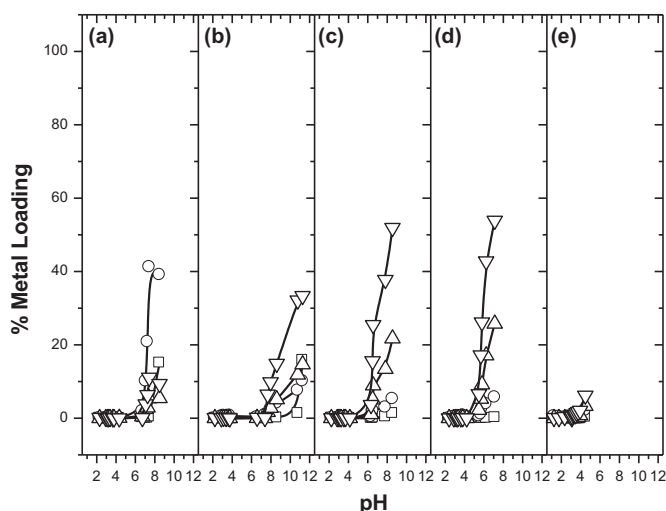


Fig. 5. Percent metal loading versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by upper rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **5a–e**: (a) **5a**, (b) **5b**, (c) **5c**, (d) **5d**, (e) **5e**. (\square = Mg^{2+} , \circ = Ca^{2+} , \triangle = Sr^{2+} , ∇ = Ba^{2+} .)

Fig. 6. In this figure, each panel compares the extraction efficiency toward intermediate Pb^{2+} for a given acidic side arm attached to the lower (open symbols) and upper (filled symbols) rims.

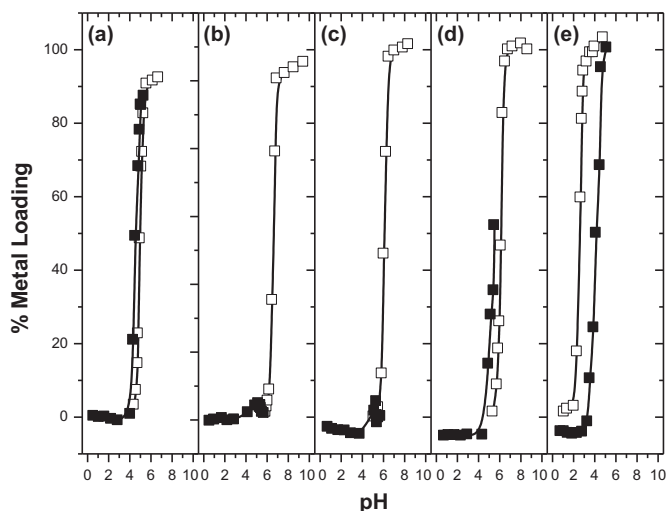


Fig. 6. Percent metal loading versus equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} into chloroform by lower rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **4a–e** and upper rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **5a–e**: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

All lower rim-functionalized ligands **4a–e** showed very high extraction efficiencies for Pb^{2+} with di(carboxylic acid) **4a** being the only ligand in this series to have a metal loading percentage below 100%.

Upper rim-functionalized ligands **5a** and **5e** were found to be very good Pb^{2+} extractants with the latter reaching 100% metal loading for formation of a 1:1 complex. On the other hand, ligands **5b** and **5c** were very poor Pb^{2+} extractants. Ligand **5d** is a moderately efficient extractant for Pb^{2+} , reaching 52% metal loading. For ligands **5b–e**, electron withdrawal by X in the *N*-(X)sulfonyl carboxamide moiety affected Pb^{2+} extraction efficiency. The metal loading for intermediate Pb^{2+} increased in the order $\text{X} = -\text{Me}$, $-\text{Ph}$, $-\text{C}_6\text{H}_4-4-\text{NO}_2$, $-\text{CF}_3$ as the acidity of the upper rim side arms was enhanced. This is also the order of increasing softness of the ionized group.

2.2.3. Single species solvent extraction of Hg^{2+} by di-ionizable calix[4]arene-crown-6 ligands **4a–e and **5a–e**.** For single species solvent extraction of aqueous Hg^{2+} solutions (0.25 mM) by 0.25 mM solutions of di-ionizable ligands **4a–e** and **5a–e** in chloroform, plots of metal loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 7. Each panel compares the extraction efficiencies for soft Hg^{2+} for a given acidic side arm attached to the lower (open symbols) and upper (filled symbols) rims.

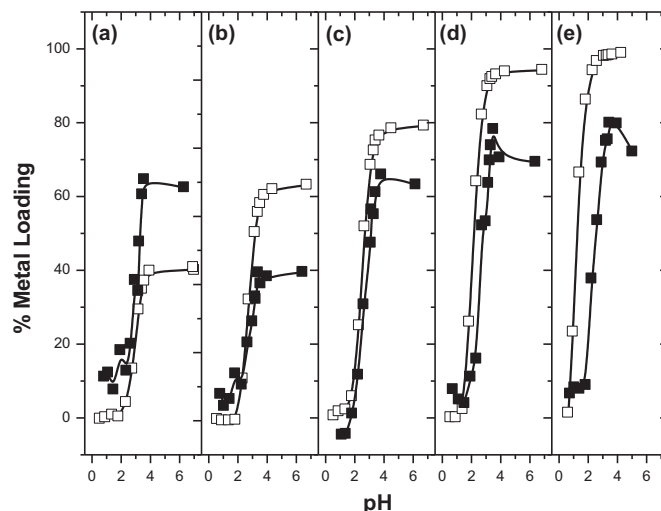


Fig. 7. Percent metal loading versus equilibrium pH of the aqueous phase for single species solvent extraction of Hg^{2+} into chloroform by lower rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **4a–e** and upper rim-functionalized, di-ionizable calix[4]arene-crown-6 ligands **5a–e**: (a) **4a** and **5a**, (b) **4b** and **5b**, (c) **4c** and **5c**, (d) **4d** and **5d**, (e) **4e** and **5e**. (\square = **4a–e**, \blacksquare = **5a–e**.)

For the di-ionizable calix[4]arene-crown-6 ligands **4a–e** and **5a–e**, the extraction efficiencies for soft Hg^{2+} were in the range of 40–100%. Whether it is better to have the acidic side arms attached to the lower or upper rim depended upon the acid group. For di(carboxylic acid)s **4a** and **5a**, Hg^{2+} loading for the latter was 60%; whereas the metal loading for the former was only 40%. Thus when the side arm contained a hard carboxylate anion, extraction of soft Hg^{2+} was favored by having the acidic side arms on the upper rim. With the *N*-(X)sulfonyl carboxamide ionizable groups, the lower rim-functionalized ligands **4b–e** provided a 16–27% higher metal loading than the **5b–e** analogues. For both series **4b–e** and **5b–e**, there was a stepwise increase in Hg^{2+} extraction as X was varied in the order $-\text{Me} < -\text{Ph} < -\text{C}_6\text{H}_4-4-\text{NO}_2 < -\text{CF}_3$. This is the order of increasing ligand acidity within each series. Ligands **4e** and **5e** with the softest ionizable groups in the side arms were the most efficient extractants for soft Hg^{2+} .

3. Conclusions

In earlier investigations of systematic structural variations in di-ionizable calix[4]arene-crown-5 ligand series **2a–e** and **3a–e**, two acidic side arms were attached to the lower rim in **2a–e** and to the upper rim in **3a–e**. In the present study, a new series of di-ionizable calix[4]arene-crown-6 ligands **5a–e** with two acidic side arms on the upper rim was prepared for comparison with the previously reported, structurally isomeric crown-6 ligand series **4a–e** having two acidic side arms on the lower rim. The objective was to compare the divalent metal ion complexing properties of the crown-6 ligand series **4a–e** and **5a–e** to ascertain if it is better to have the two acidic side arms attached to the lower or upper rim, respectively. Another objective was to determine if the difference in divalent metal ion complexing behavior for lower versus upper rim attachment of the acidic side arms varies as the crown ether ring

size in the di-ionizable calix[4]arene-crown ether is changed from crown-5 to crown-6.

For these comparisons, the ionizable groups in the acidic side arms were $-\text{CO}_2\text{H}$ and $-\text{C}(\text{O})\text{NHSO}_2\text{X}$, in which the acidity may be 'tuned' by varying the inductive effects of X.

NMR spectra revealed that in contrast to the lower rim-functionalized ligands **4a–e**, which were locked in the cone conformation, analogous upper rim-functionalized ligands **5a–e** were conformationally mobile.

In competitive extraction of AEMC by di(carboxylic acid) **5a**, there was selectivity for hard Ca^{2+} suggesting dominant interaction with the ionized groups on the upper rim. Ba^{2+} selectivity for softer *N*-(X) sulfonyl carboxamide ligands **4b–e** and **5b–e** was consistent with enhanced metal ion- π -aryl or metal ion-polyether interaction. The lower rim-functionalized ligands were more effective and selective extractants for Ba^{2+} than their upper rim-functionalized analogues.

Comparison of these results for AEMC extractions by crown-6 ligands with those published for crown-5 analogues revealed for the crown-6 ligands a greater benefit in having the acidic side arms on the lower rim versus the upper rim.

For single species extractions of intermediate Pb^{2+} , high efficiency was observed for all members of the lower rim-functionalized series **4a–e**, but only for ligands **5a** and **5e** from the upper rim-functionalized series. For upper rim-functionalized ligands **5b** and **5c**, Pb^{2+} extraction was negligible. A modest level of Pb^{2+} extraction was observed for ligand **5d**. Thus, for the series **5b–e** with soft *N*-(X)sulfonyl carboxamide side arms attached to the upper rim, Pb^{2+} extraction increased as X was varied in the order $-\text{Me}$, $-\text{Ph}$ < $-\text{C}_6\text{H}_4-4-\text{NO}_2$ < $-\text{CF}_3$.

These contrasting results between lower rim- and upper rim-functionalization are very similar to the extraction behaviors exhibited by lower rim-functionalized, di-ionized calix[4]arene-crown-5 analogues **2a–e** and upper rim-functionalized crown-5 analogues **3a–e**.¹³ Ligands in series **2a–e** all exhibited high levels of Pb^{2+} extraction. Ligands **3a** and **3e** were very good extractants for Pb^{2+} , and very low loadings were observed for **3b–d**.

For soft Hg^{2+} , all lower rim-functionalized ligands **4b–e** containing the *N*-(X)-sulfonyl carboxamide moiety were more efficient in single species extractions than their upper rim analogues **5b–e**. However, the upper rim-functionalized di(carboxylic acid) **5a** was a more effective extractant than **4a**. Ligands **4e** and **5e** with the softest ionized group were the most efficient Hg^{2+} extractants, suggesting maximal soft metal ion- π aryl interactions.

Although crown-6 ligands **4a–e** and **5a–e** were found to exhibit considerable similarity to those reported for crown-5 ligands **2a–e** and **3a–e** in AEMC and Pb^{2+} extractions, the Hg^{2+} extractions showed a marked ring size effect. For the crown-6 ligands, Hg^{2+} extraction efficiency was higher for di(carboxylic) acids **4a** and **5a** when the acidic side arms were attached to the upper rim. In contrast for the crown-5 di(carboxylic) acids **2a** and **3a**, the Hg^{2+} extraction level was higher when the acidic side arms were on the lower rim. For the crown-6 *N*-(X)sulfonyl carboxamides, Hg^{2+} extraction by crown-6 ligands **4b–e** and **5b–e** is favored when the acidic side arms are attached to the lower rim. On the other hand for crown-5 *N*-(X)sulfonyl carboxamides **2b–e** and **3b–e**, the Hg^{2+} extraction level is greater when the acidic side arms are on the upper rim.

Thus, expansion of the polyether ring in the calixcrown ligands by a single ethyleneoxy unit is found to reverse the preferred acidic side arm attachment sites in Hg^{2+} extraction.

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 absorptions are expressed in wavenumbers (cm^{-1}). 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 at 296 K in CDCl_3 with TMS as internal standard. Chemical shifts (δ) are given in parts per million (ppm) downfield from TMS and coupling constant values (*J*) are given in hertz. Combustion analysis was performed by Desert Analytics Laboratory (now Columbia Analytical Services) of Tucson, Arizona. For compounds **5e** and **6**, the combustion analysis results indicated the presence of small amounts of C_6H_6 and CH_2Cl_2 , respectively. This was verified by singlets at δ 7.36 and 5.32, respectively, in their ^1H NMR spectra.

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 immediately before use. Dibrominated dimethoxycalix[4]arene **6**¹¹ and pentaethylene glycol ditosylate¹⁴ were prepared according to literature procedures.

4.2. Synthesis of di(carboxylic acid) ligand **5a**

4.2.1. 5,17-Dibromo-25,27-dimethoxycalix[4]arene-crown-6 (7). A mixture of **6** (5.00 g, 8.20 mmol) and Cs_2CO_3 (6.65 g, 20.15 mmol) in MeCN (600 mL) was stirred under nitrogen for 30 min. A solution of pentaethylene glycol ditosylate (4.95 g, 9.00 mmol) in MeCN (50 mL) was added dropwise over a 1-h period. The mixture was refluxed for 24 h, the solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (250 mL). The solution was washed with 5% aqueous HCl (100 mL) and then H_2O (2×250 mL). The organic layer was dried over MgSO_4 . The solvent was evaporated in vacuo to give a solid, which was chromatographed on silica gel with hexanes–EtOAc (3:2) as eluent to obtain off-white solid **7** (4.83 g, 73%) with mp 220–222 °C. ^1H NMR (500 MHz, CDCl_3): δ 3.06, 4.23 (AX, *J*=12.5 Hz, 2H), 3.10 (s, 2H), 3.14, 4.40 (AX, *J*=12.5 Hz, 4H), 3.39–3.52 (m, 2H), 3.57 (s, 3H), 3.61 (s, 1H), 3.59–3.99 (m, 18H), 4.00 (s, 3H), 6.45 (s, 2H), 6.57 (s, 1H), 6.97 (t, *J*=7.5 Hz, 2H), 7.06 (d, *J*=7.5 Hz, 1H), 7.10 (s, 1H), 7.14 (d, *J*=7.5 Hz, 2H), 7.30 (d, *J*=7.5 Hz, 1H), 7.27–7.33, 6.40–7.19 (m, 10H). ^{13}C NMR (126 MHz, CDCl_3): δ 30.6, 35.9, 58.9, 60.8, 61.5, 70.5, 70.7, 70.8, 70.8, 71.0, 71.2, 71.3, 73.1, 74.2, 114.9, 115.3, 121.7, 122.6, 123.0, 128.9, 129.0, 131.2, 131.6, 133.1, 133.9, 135.8, 136.3, 154.7, 155.1, 159.1. Anal. Calcd for $\text{C}_{40}\text{H}_{44}\text{O}_8\text{Br}_2 \cdot 0.2\text{CH}_2\text{Cl}_2$: C, 58.22; H, 5.59. Found: C, 58.22; H, 5.59.

4.2.2. 5,17-Bis(carboxy)-25,27-dimethoxycalix[4]arene-crown-6 (5a). To a solution of **7** (1.00 g, 1.23 mmol) in THF (50 mL) at -78°C under nitrogen was added BuLi in hexanes (3.84 mL, 6.15 mmol, *M*=1.6). The solution was stirred for 1 h. Carbon dioxide was bubbled into the solution for 3 h and then the solution was stirred for another 30 min. The mixture was allowed to warm to room temperature and 5% aqueous HCl (10 mL) was added. The solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 . The organic layer was washed with 6 N HCl and then with water. The organic layer was dried over MgSO_4 . The solvent was evaporated in vacuo. The solid residue was recrystallized from MeCN to obtain white solid **5a** (0.35 g, 38%), which decomposed at 278–280 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3260 (O–H), 1690 (C=O) cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.07 (s, 1H), 3.10, 4.25 (AX, *J*=12.5 Hz, 2H), 3.18, 4.44 (AX, *J*=12.5 Hz, 4H), 3.38–3.52 (m, 2H), 3.54–3.62 (m, 3H), 3.62–3.98 (m, 19H), 4.00 (s, 3H), 6.88–7.05 (m, 5H), 7.05–7.15 (m, 2H), 7.19 (d, *J*=7.5 Hz, 1H), 7.32 (d, *J*=7.5 Hz, 1H), 7.68 (s, 1H), 12.35–13.71 (br s, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 30.5, 35.6, 58.8, 60.6, 61.4, 70.4, 70.5, 70.7, 70.8, 70.9, 71.2, 71.3, 73.0, 74.0, 121.7, 122.9, 123.2, 128.9, 129.0, 129.6, 130.5, 130.9, 131.2,

131.7, 133.3, 134.0, 134.7, 136.4, 136.4, 158.2, 160.0, 160.5, 172.1, 172.6. Anal. Calcd for $C_{42}H_{46}O_{12}$: C, 67.71; H 6.12. Found: C, 67.91; H, 6.24.

4.3. General procedure for synthesis of 5,17-bis[*N*-(X)sulfonyl carbamoylmethoxy]-25,27-dimethoxycalix[4]arene-crown-6 ligands **5b–e**

Di(carboxylic acid) **5a** (0.50 g, 0.68 mmol) was dried with a benzene azeotrope before addition of oxalyl chloride (0.58 mL, 6.75 mmol) in benzene (25 mL). The solution was refluxed for 6 h. Formation of the di(acid chloride) was confirmed by an IR shift of the C=O absorption from 1690 cm^{-1} in **5a** to 1747 cm^{-1} . The benzene was evaporated in vacuo and the residue was dried under oil-pump vacuum for 30 min. The sodium sulfonamide salt was prepared under nitrogen by dropwise addition of the appropriate sulfonamide (1.69 mmol) dissolved in THF (20 mL) to a mixture of NaH (0.16 g, 6.75 mmol) in THF (20 mL). This mixture was stirred for 2 h followed by dropwise addition of the di(acid chloride) in THF (10 mL). The mixture was stirred overnight (4 h for *p*-nitrobenzenesulfonamide) at room temperature after which the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 , and H_2O (10 mL) was carefully added. The organic layer was washed with 6 N HCl until pH=1 and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by column chromatography.

4.3.1. 5,17-Bis(*N*-methanesulfonyl carbamoylmethoxy)-25,27-dimethoxycalix[4]arene-crown-6 (5b**).** The crude product was recrystallized from MeCN to give 0.18 g of recovered **5a** and a residue, which was chromatographed on silica gel with CH_2Cl_2 –MeOH (50:1) as eluent and then a second column with EtOAc–hexanes (4:1) as eluent to give off-white solid **5b** (0.12 g, 50%, accounting for recovered starting material) with mp 295–297 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3181 (NH), 1688 (C=O), 1345, 1146 (SO_2) cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 3.13, 4.36 (AX, $J=12.5$ Hz, 2H), 3.15 (s, 6H), 3.19 (s, 1H), 3.22, 4.47 (AX, $J=12.5$ Hz, 4H), 3.39–3.85 (m, 17H), 3.91 (s, 5H), 3.96–4.06 (m, 2H), 4.09 (s, 3H), 6.71–7.44 (m, 10H), 8.93–9.20 (br s, 1H), 9.20–9.37 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.6, 30.8, 36.1, 41.2, 41.4, 59.9, 61.2, 61.5, 70.5, 70.7, 70.8, 70.8, 70.9, 71.2, 73.3, 74.7, 122.1, 1231, 123.6, 126.0, 126.5, 127.8, 128.6, 129.2, 129.4, 131.8, 132.6, 133.5, 134.6, 135.3, 136.1, 136.2, 158.2, 158.9, 160.1, 160.8, 166.5, 166.9. Anal. Calcd for $C_{44}H_{52}O_{14}N_2S_2$: C, 58.91; H, 5.84; N, 3.12. Found: C, 58.79; H, 5.97; N, 2.85.

4.3.2. 5,17-Bis(*N*-benzenesulfonyl carbamoylmethoxy)-25,27-dimethoxycalix[4]arene-crown-6 (5c**).** The crude product was chromatographed on silica gel with CH_2Cl_2 –MeOH (100:1) as eluent and then a second column with EtOAc–hexanes (4:1) as eluent to give white solid **5c** (0.22 g, 32%) with mp 267–270 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3256 (NH), 1696 (C=O), 1350, 1148 (SO_2) cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 3.08, 4.31 (AX, $J=12.5$ Hz, 2H), 3.19, 4.43 (AX, $J=12.5$ Hz, 4H), 3.21 (s, 2H), 3.37–3.56 (m, 2H), 3.57 (s, 3H), 3.60–4.02 (m, 18H), 4.07 (s, 3H), 6.83 (s, 2H), 6.91 (s, 1H), 6.97 (t, $J=7.5$ Hz, 2H), 7.08 (d, $J=7.5$ Hz, 1H), 7.17 (d, $J=7.5$ Hz, 2H), 7.27 (s, 1H), 7.33 (d, $J=7.5$ Hz, 1H), 7.50 (t, $J=7.5$ Hz, 2H), 7.54–7.64 (m, 4H), 8.07 (d, $J=7.5$ Hz, 2H), 8.13 (d, $J=7.5$ Hz, 2H), 9.04–9.49 (br s, 1H), 9.64–9.99 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.8, 36.3, 60.3, 61.2, 61.4, 70.5, 70.6, 70.7, 70.8, 70.8, 70.9, 71.5, 71.2, 73.3, 74.7, 122.1, 123.3, 123.6, 126.7, 126.8, 128.0, 128.4, 128.7, 128.8, 128.9, 129.2, 129.5, 132.0, 132.5, 133.4, 133.9, 134.3, 135.2, 135.6, 135.9, 128.8, 138.9, 157.6, 158.2, 158.8, 159.8, 160.6, 165.4, 166.2. Anal. Calcd for $C_{54}H_{56}O_{14}N_2S_2$: C, 63.51; H, 5.53; N, 2.74. Found: C, 63.49; H, 5.62; N, 2.52.

4.3.3. 5,17-Bis(*N*-*p*-nitrobenzenesulfonyl carbamoylmethoxy)-25,27-dimethoxycalix[4]arene-crown-6 (5d**).** The crude product was chromatographed on silica gel with EtOAc–hexanes (4:1) as eluent

to give white solid **5d** (0.36 g, 53%) with mp 282–283 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3266 (NH), 1699 (C=O), 1348, 1147 (SO_2) cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 3.08, 4.34 (AX, $J=12.5$ Hz, 2H), 3.17 (s, 2H), 3.18, 4.44 (AX, $J=12.5$ Hz, 4H), 3.29–3.81 (m, 17H), 3.81–4.02 (m, 6H), 4.05 (s, 3H), 6.80 (s, 2H), 6.82–7.03 (m, 3H), 7.08 (d, $J=7.5$ Hz, 1H), 7.17 (d, $J=7.5$ Hz, 2H), 7.28–7.34 (m, 2H), 8.17–8.51 (m, 8H), 9.01–9.20 (br s, 1H), 9.55–9.77 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.7, 30.7, 36.1, 60.2, 61.3, 61.6, 70.4, 70.5, 70.7, 70.7, 70.8, 70.9, 71.1, 71.2, 73.4, 74.7, 122.3, 122.9, 123.4, 124.1, 124.2, 125.9, 126.1, 127.8, 128.4, 128.8, 129.2, 129.5, 130.2, 130.3, 123.1, 123.3, 133.6, 134.7, 135.5, 135.8, 136.1, 144.0, 144.2, 150.6, 150.7, 157.5, 158.3, 159.0, 160.2, 161.1, 165.5, 166.4. Anal. Calcd for $C_{54}H_{54}O_{18}N_4S_2$: C, 58.37; H, 4.90; N, 5.04. Found: C, 58.45; H, 4.95; N, 5.07.

4.3.4. 5,17-Bis(*N*-trifluoromethanesulfonyl carbamoylmethoxy)-25,27-dimethoxycalix[4]arene-crown-6 (5e**).** The crude product was chromatographed on silica gel with EtOAc–hexanes (4:1) as eluent to give white solid **5e** (0.30 g, 44%) with mp 224–226 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3210 (NH), 1716 (C=O), 1390, 1135 (SO_2) cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 3.14, 4.38 (AX, $J=12.5$ Hz, 2H), 3.18 (s, 2H), 3.25, 4.49 (AX, $J=12.5$ Hz, 4H), 3.33–3.51 (m, 2H), 3.58 (s, 3H), 3.61–3.83 (m, 12H), 3.92 (s, 4H), 3.95–4.06 (m, 2H), 4.08 (s, 3H), 6.90 (s, 2H), 6.97 (s, 1H), 7.03 (t, $J=7.5$ Hz, 2H), 7.14 (d, $J=7.5$ Hz, 1H), 7.23 (d, $J=7.5$ Hz, 2H), 7.34 (d, $J=7.5$ Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.9, 31.0, 36.4, 59.8, 61.5, 61.9, 70.7, 70.8, 70.9, 71.0, 71.0, 71.2, 71.4, 71.5, 73.7, 75.0, 115.5, 115.6, 118.1, 118.2, 120.6, 120.8, 122.6, 123.2, 123.3, 123.6, 124.0, 125.0, 125.3, 129.2, 129.6, 129.8, 132.1, 132.8, 134.1, 135.4, 136.0, 136.1, 158.0, 158.3, 159.1, 161.3, 162.0. Anal. Calcd for $C_{44}H_{46}F_6O_{14}N_2S_2 \cdot 1.5C_6H_6$: C, 56.73; H, 4.94; N, 2.50. Found: C, 56.94; H, 4.55; N, 2.59.

4.4. Solvent extraction procedures

Competitive solvent extraction AEMC, single species extraction of Hg^{2+} , and single species extraction of Pb^{2+} into chloroform were performed as previously described.¹¹

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