Tetrahedron 64 (2008) 9843–9849

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ligands in the cone conformation: synthesis and metal ion extraction

Dongmei Zhang, Jennifer D. Crawford, Richard A. Bartsch *

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

ARTICLE INFO

Article history:
Received 12 June 2008
Received in revised form 31 July 2008
Accepted 31 July 2008
Available online 7 August 2008

Keywords:
Calixarenes
Crown ethers
Molecular recognition
Solvent extraction

ABSTRACT

A series of di-ionizable calix[4]arene-1,2-crown-3 compounds with a sulfur-containing unit bridging the proximate phenolic oxygens have been synthesized. The ionizable groups are oxyacetic acid and *N*-(X)sulfonyl oxyacetamide groups with X=methyl, phenyl, 4-nitrophenyl, and trifluoromethyl, which 'tunes' the acidity of the latter. The efficiency and selectivity of these novel ligands are assessed for competitive solvent extractions of alkali metal cations and of alkaline earth metal cations from aqueous solutions into chloroform. Also the efficiencies for single species extractions of Pb^{2+} and of Hg^{2+} are determined. The results are compared with those reported previously for related ligands in which only oxygen heteroatoms are present in the crown ether unit.

1. Introduction

In calixarene-crown ethers,[1,2] also known as calixcrowns, a calixarene scaffold is combined with a crown ether unit connecting two phenolic oxygens in the former with a polyether chain. Most common are calix[4]crowns, which combine a calix[4]arene platform and a polyether fragment. The first example of this ligand family, *p-tert*-butylcalix[4]arene-1,3-crown-6 ether, was reported in 1983.[3] Metal ion complexation studies have mainly focused on dialkylated-1,3-bridged calix[4]arene-crown ethers, which have been found to exhibit high binding affinity and selectivity in alkali and alkaline earth metal cation extractions.[4–6] In contrast, much less is known about the properties of regioisomeric 1,2-bridged calix[4]crowns,[7] presumably because they are more difficult to synthesize. Also, initial studies suggested that they exhibit poor binding ability for metal cations with little selectivity.[8–13] Compared with un-functionalized calix[4]arenes with phenolic groups on the lower rim, analogues with pendant proton-ionizable groups are found to be much more efficient interfacial carriers for metal cations.[14–16]

Recently, we undertook the synthesis and evaluation of di-ionizable calix[4]arene-1,2-crown ether ligands (Fig. 1) as a new class of metal ion extractants.[17–20] For this series of ligands, the polyether ring was varied from crown-3 (n=1) to crown-4 (n=2) to crown-5 (n=3) to crown-6 (n=4). The ionizable groups for each polyether ring size included both carboxylic acid and *N*-(X)sulfonyl carbamoyl groups in which the acidity was tuned by variation of the electron-withdrawing ability of X.[21,22]

Surprisingly, di-ionized calix[4]arene-1,2-crown-4 ethers in the cone conformation were found to be efficient extractants for alkaline earth metal cations with extraordinarily high selectivity for Ba^{2+}.[17,20] Since the crown ether ring is too small to accommodate Ba^{2+}, we proposed extraction complexes in which the large divalent metal ion was sandwiched between the four polyether oxygens on one side and two ionized groups on the other. The Ba^{2+} extraction selectivity was lower for analogues with larger crown-5 and crown-6 polyether units[18] and essentially disappeared with smaller crown-3 rings.[19]

In addition to variations of the crown ether ring size and identity of the pendant acidic groups in di-ionizable calix[4]arene-1,2-crown compounds, one or more of the oxygen atoms in the crown ether ring could be replaced with sulfur. This substitution should

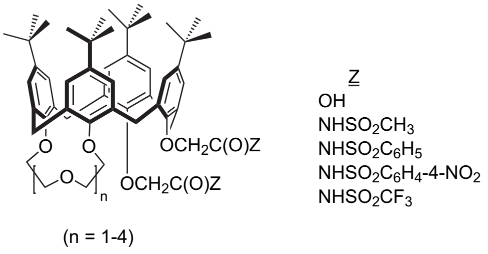
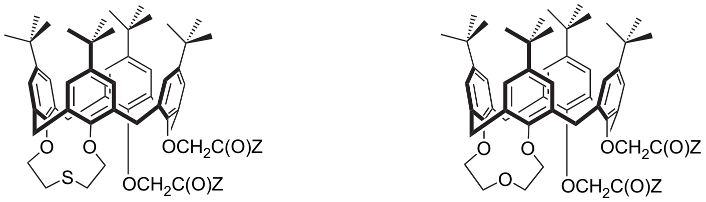


Figure 1. Di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown ether ligands.

---

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

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.115



	Z	
1	OH	6
2	$NHSO_2CH_3$	7
3	$NHSO_2C_6H_5$	8
4	$NHSO_2C_6H_4$-4-NO_2	9
5	$NHSO_2CF_3$	10

Figure 2. Di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ligands **1**–**5** and their -crown-3 analogues **6**–**10**.

favor complexation of softer metal ions. We now report on the synthesis of di-ionizable calix[4]arene-1,2-monothiacrown-3 compounds **1**–**5** (Fig. 2) in which a sulfur atom is part of the linkage that joins the two proximal phenolic oxygens. Metal ion complexing behavior of new ligands **1**–**5** is assessed by solvent extractions of alkali and alkaline earth metal cations, as well as Hg^{2+} and Pb^{2+}. The results are compared with those reported previously for the all-oxygen analogues **6**–**10**.

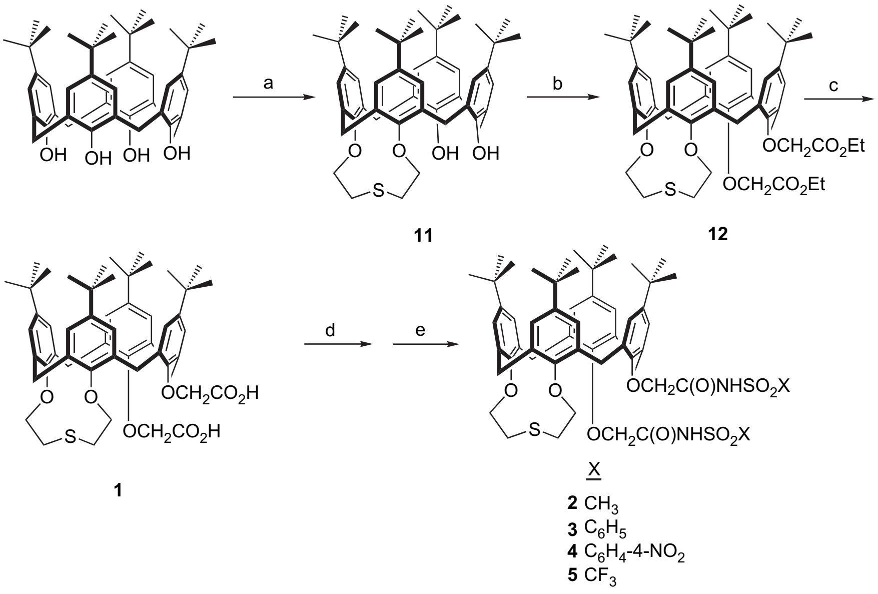
2. Results and discussion

2.1. Synthetic routes

The synthesis of di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 compounds **1**–**5** was performed as depicted in Scheme 1. The first step involved assembling the thiacrown ether unit onto the calix[4]arene scaffold by a Mitsunobu reaction.[23] Thus, *p-tert*-butylcalix[4]arene was treated with triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD) and then reacted with 2,2′-thiodiethanol to form thiacrown **11** in 29% yield. Reaction of **11** with NaH in THF and then ethyl bromoacetate overnight at room temperature produced a 61% yield of diester **12**. Basic hydrolysis of **12** with aqueous Me_4NOH in THF at reflux gave diacid **1** in 91% yield.

Diacid **1** was converted into the corresponding di(acid chloride) by reaction with oxalyl chloride. Conversion to the di(acid chloride) was verified by IR spectroscopy with the disappearance of the carbonyl group absorption at 1740 cm^{-1} and the appearance of a new carbonyl group absorption for the di(acid chloride) at 1810 cm^{-1}. The resultant crude di(acid chloride) was mixed with the appropriate sulfonamide anion in THF to afford ligands **2**–**5** in yields of 30, 81, 40, and 76%, respectively. A fair amount of monosubstituted by-product was obtained from the preparation of **2**. Increasing the reaction time from 12 h to 2 days increased its yield by 7%.

The conformations for compounds **1**–**5**, **11**, and **12** were established by their ^1H and ^{13}C NMR spectra. There were no peaks between 35 and 40 ppm in the ^{13}C NMR spectra for the seven compounds, showing that all four benzene rings have *syn* arrangements. In their ^1H NMR spectra, the bridging methylene group protons were split into three pairs of doublets, with the integration ratio of 1:2:1. In addition, the two methylene protons in the side arms ($-OCH_2C(O)-$) of **1**–**5** and **12** are diastereotopic and exhibited the expected AX patterns. These observations verify that the thiacrown ether rings are attached to the calix[4]arene



Scheme 1. Synthesis of di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ligands **1**–**5** in the cone conformation. (a) $HOCH_2CH_2SCH_2CH_2OH$, TPP, DEAD, toluene, rt, 3 h; (b) NaH, $BrCH_2CO_2Et$, THF, rt, overnight; (c) 10% aq Me_4NOH, THF, reflux, 12 h; (d) oxalyl chloride, C_6H_6, reflux, 10 h, 12 h; (e) NaH, NH_2SO_2X, THF, rt, overnight.

framework via proximate phenolic positions and the compounds are in the cone conformation.

2.2. Competitive solvent extraction of alkali metal cations

Aqueous solutions containing Li^+, Na^+, K^+, Rb^+, and Cs^+ (10.0 mM in each) chlorides were extracted with 1.0 mM solutions of ligands **1**–**5** in chloroform. Plots of metal ion loadings of the organic phase versus the equilibrium pH of the aqueous phase are presented in Figure 3. Note that the metal loadings were negligible when the aqueous phases are highly acidic. This verifies that the ligands are ineffective extractants in their non-ionized forms. The maximal combined alkali metal cation loadings observed for ligands **1**–**5** were all close to 200%, which is consistent with the formation of 2:1 metal ion-di-ionized ligand extraction complexes.

Under the conditions of high metal loading (i.e., alkaline aqueous phase pH), Na^+ extraction selectivity is observed for all five of the di-ionizable calixthiacrown ligands. However, the plots for ligands **1** (Z=OH), **2** ($Z=NHSO_2Me$), and **5** ($Z=NHSO_2CF_3$) differ from those for ligands **3** ($Z=NHSO_2Ph$) and **4** ($Z=NHSO_2C_6H_4$-4-NO_2) in that the latter are Li^+-selective for extractions from acidic aqueous solutions, whereas the former are Na^+ selective. This suggests some type of special favorable interaction of the mono-ionized ligand with Li^+ when the acidic function contains an aryl group.

Comparison of the extraction profiles shown in Figure 3 for ligands **1**–**5** with those reported for analogues **6**–**10**[19] in which sulfur in the bridging unit is replaced with oxygen reveals considerable similarity. However, careful scrutiny reveals that for the same acidic function, the di-ionizable calixthiacrown ligand extracts Li^+ with greater propensity. This is most apparent for the comparison of dicarboxylic acid ligands **1** and **6**. Since Li^+ is a hard metal ion, this is opposite to the effect expected when a soft sulfur ligation site is replaced with harder oxygen.

2.3. Competitive solvent extraction of alkaline earth metal cations

Aqueous solutions containing Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} (2.0 mM in each) chlorides were extracted with 1.0 mM solutions of ligands **1**–**5** in chloroform. Plots of metal loading of the organic phase versus the equilibrium pH of the aqueous phase are shown in Figure 4.

With ligands **1**–**5**, all four of the alkaline earth metal cation species are extracted into the chloroform phases from weakly acidic, neutral, and alkaline aqueous phases. From alkaline solutions, the combined metal loading of the organic phase approaches 100% as would be expected for extraction complexes comprised of a divalent metal cation and the di-ionized calix[4]arene-1,2-monothiacrown-3 ligand. Under the conditions of high loading, the dicarboxylic acid ligand **1** exhibits an extraction selectivity of $Ca^{2+}>Ba^{2+}>Mg^{2+}>Sr^{2+}$. With the change to *N*-(X)sulfonyl oxyacetamide acidic functions in ligands **2**–**5**, the best extracted cation is Ba^{2+} with diverse patterns for the other three alkaline earth metal cations.

Comparison of the extraction profiles shown in Figure 4 for ligands **1**–**5** with those reported for analogues **6**–**10** in which the sulfur heteroatom in the bridging unit is replaced with oxygen reveals better selectivity among the alkaline earth metal cations for the former.

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

Aqueous solutions of Pb^{2+} (1.0 mM) nitrate were extracted with 0.50 mM solutions of di-ionizable calix[4]arene-1,2-monothiacrown-3 compounds **1**–**5** in chloroform. Plots of metal loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Figure 5a. For comparison, published data for single species Pb^{2+} extractions by all-oxygen crown ether analogues **6**–**10** are shown in Figure 5b.

All five of the ligands **1**–**5** exhibit essentially quantitative metal loading for the formation of 1:1 extraction complexes of Pb^{2+} with the di-ionized extractants. The pH for half loading, $pH_{0.5}$, is a qualitative measure of ligand acidity. For the *N*-(X)sulfonyl carboxamides **2**–**5**, the $pH_{0.5}$ values are 4.9, 4.9, 4.0, and 3.3, respectively, in accord with the electron-withdrawing power of the X group. For the dicarboxylic acid ligand **1**, the $pH_{0.5}$ value is 3.7.

Comparison of the Pb^{2+} extraction profiles for the di-ionizable calix[4]arene-1,2-monothiacrown-3 ligands **1**–**5** (Fig. 5a) and their di-ionizable calix[4]arene-1,2-crown-3 analogues **6**–**10**[19] (Fig. 5b), respectively, reveals that with the same acidic function the former

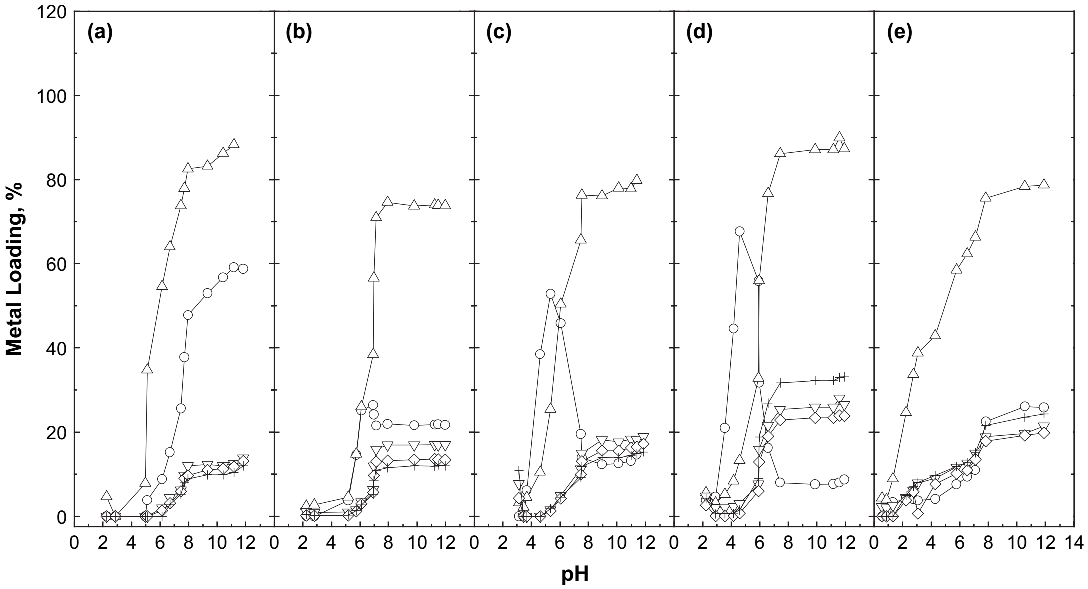


Figure 3. Percent metals loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkali metal cations into chloroform by di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ethers (a) **1**; (b) **2**; (c) **3**; (d) **4**; (e) **5**. (○=Li^+, △=Na^+, ▽=K^+, ◇=Rb^+, +=Cs^+).

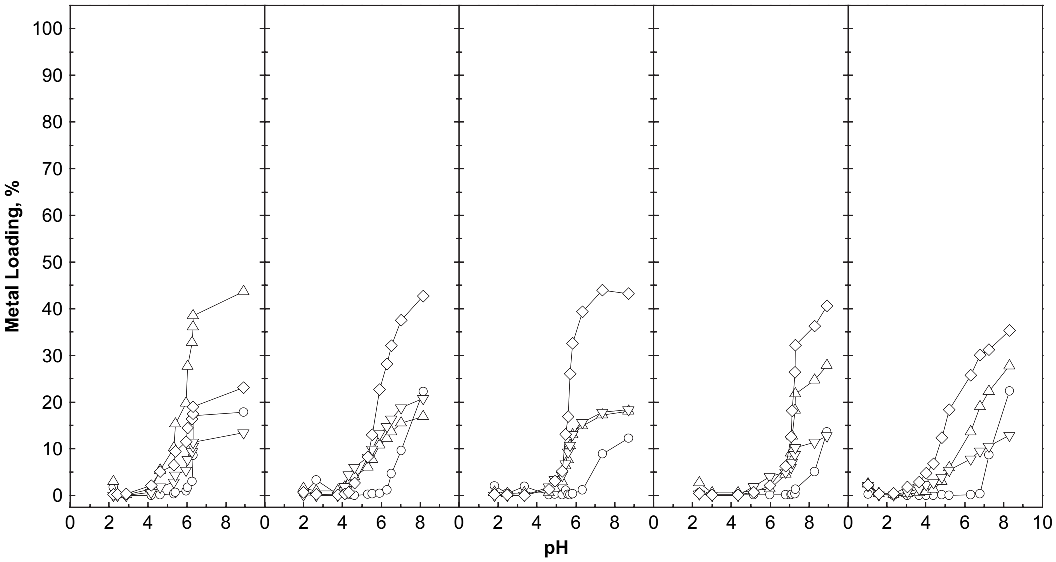


Figure 4. Percent metals loading versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ethers **1**–**5** (○=Mg^{2+}, △=Ca^{2+}, ▽=Sr^{2+}, ◇=Ba^{2+}).

are generally better extractants. The differences are striking for the *N*-(X)sulfonyl carboxamides with X=CH_3 and X=C_6H_5. Thus, calix[4]arene-1,2-monothiacrown-3 ligands **2** and **3** effectively transport Pb^{2+} into the organic phase; whereas their calix[4]arene-1,2-crown-3 analogues **7** and **8** are very weak Pb^{2+} extractants. Thus, replacement of a soft sulfur ligation site in the crown ring with a hard oxygen atom leads to less efficient complexation of Pb^{2+}, a borderline metal ion. This effect appears to be more pronounced for the less acidic ionizable groups.

2.5. Single species solvent extraction of Hg^{2+}

Aqueous solutions of Hg^{2+} (0.25 mM) nitrate were extracted with 0.25 mM solutions of di-ionizable calix[4]arene-1,2-monothiacrown-3 compounds **1**–**5** in chloroform. Plots of metal loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Figure 6a. For comparison, previously reported data for single species Hg^{2+} extractions by all-oxygen crown ether analogues **6**–**10**[19] are shown in Figure 6b.

All four of the *N*-(X)sulfonyl carbamoyl calix[4]arene-1,2-thiacrown ligands **2**–**5** exhibit essentially quantitative metal loading for the formation of 1:1 extraction complexes of Hg^{2+} with the di-ionized extractants. For the dicarboxylic acid compound **1**, the maximal metal loading diminishes slightly to 90%. For the *N*(X)sulfonyl carboxamide ligands **2**–**5**, the $pH_{0.5}$ values are 2.3, 1.9, 1.1, and 0.8, respectively, in agreement with the electron-withdrawing power of X. For the dicarboxylic acid ligand **1**, the $pH_{0.5}$ value is 1.5.

Comparison of the Hg^{2+} extraction profiles for the di-ionizable calix[4]arene-1,2-monothiacrown-3 ligands **1**–**5** (Fig. 6a) and their di-ionizable calix[4]arene-1,2-crown-3 analogues **6**–**10**[19] (Fig. 6b), respectively, reveals that with the same acidic function the former are generally more efficient extractants. This is particularly evident for the dicarboxylic acid ligands **1** and **6**. For the thiacrown-3 extractant **1**, approximately 90% maximal metal loading is achieved. On the other hand, the reported data for crown-3 compound **6** only approached a maximum of 20% metal loading.

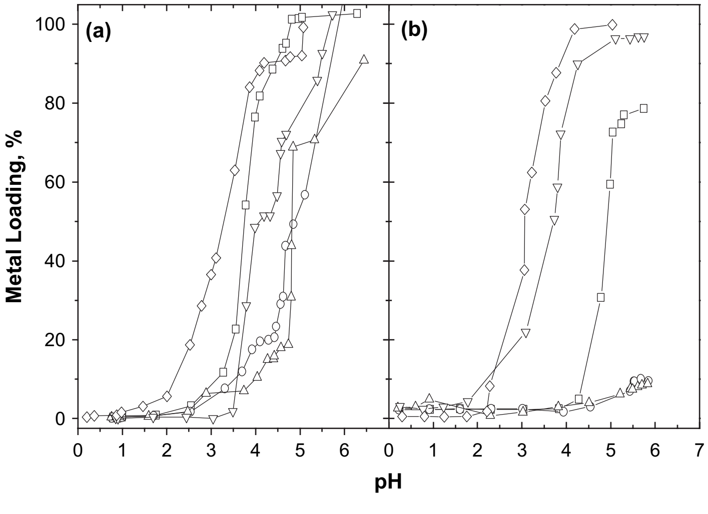


Figure 5. Percent metal loading versus the equilibrium pH of the aqueous phase for Pb^{2+} extraction from aqueous phases into chloroform by (a) di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ethers **1**–**5** (□=**1**, ○=**2**, △=**3**, ▽=**4**, ◇=**5**) and (b) di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-3 ethers **6**–**10** (□=**6**, ○=**7**, △=**8**, ▽=**9**, ◇=**10**).

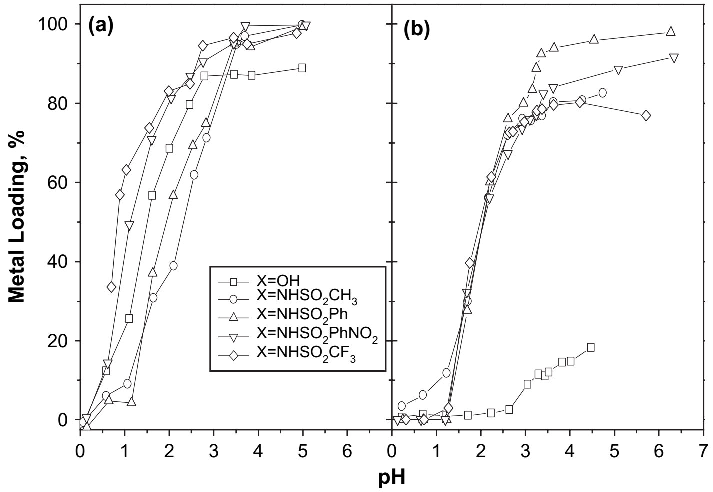


Figure 6. Percent metal loading versus the equilibrium pH of the aqueous phase for Hg^{2+} extraction from aqueous phase into chloroform by (a) di-ionizable *p-tert*-butylcalix[4]arene-1,2-monothiacrown-3 ethers **1**–**5** (□=**1**, ○=**2**, △=**3**, ▽=**4**, ◇=**5**) and (b) di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-3 ethers **6**–**10** (□=**6**, ○=**7**, △=**8**, ▽=**9**, ◇=**10**).

2.6. Conclusions from the metal ion extraction studies

To probe the influence of replacing a hard oxygen ligation site in the crown ring of di-ionizable calix[4]arene-1,2-crown-3 ligands **6**–**10** with soft sulfur, the series of di-ionizable calix[4]arene-1,2-monothiacrown-3 compounds **1**–**5** was prepared. Since the crown rings in both ligand series are too small to accommodate metal ions within their central cavities, extraction complexes are envisioned in which a divalent metal cation is sandwiched between the crown ring on one side and the two ionized groups on the other. Metal ion complexation by ligands **1**–**5** was probed by competitive extractions from aqueous solutions into chloroform for alkali metal cations and for alkaline earth metal cations and by single species extractions of Pb^{2+} and Hg^{2+}. For alkaline earth metal ion extractions, the thiacrown ligands **2**–**5** are more selective for Ba^{2+} than their crown analogues **7**–**10**. For borderline Pb^{2+} and soft Hg^{2+}, the thiacrown ligands **1**–**5** are more efficient extractants than crown analogues **6**–**10**.

3. Experimental

3.1. General

Melting points were determined with a Mel-Temp melting point apparatus. Infrared (IR) spectra were recorded with a Perkin–Elmer Model 1600 FT-IR spectrometer as deposits from CH_2Cl_2 solution on NaCl plates. The ^1H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR (^1H at 500 MHz and ^{13}C at 126 MHz) spectrometer in $CDCl_3$ with Me_4Si as internal standard unless mentioned otherwise. Chemical shifts (δ) are given in parts per million downfield from TMS and coupling constants (J) values are in hertz. Elemental analysis was performed by Desert Analytics Laboratory of Tucson, Arizona.

Reagents were obtained from commercial suppliers and used directly, unless otherwise noted. Acetonitrile (MeCN) was dried over CaH_2 and distilled immediately before use. Tetrahydrofuran (THF) was dried over sodium with benzophenone as an indicator and distilled just before use. Cs_2CO_3 was activated by heating at 150 °C overnight under high vacuum and stored in a desiccator.

For use in the metal ion extractions, reagent-grade chloroform was washed with an equal volume of DI 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 from an extraction experiment was determined with a Fisher Accumet AR25 pH meter with a Corning 476157 combination pH electrode.

*3.1.1. 5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26-calix[4]arene-25,26-monothiacrown-3 (**11**) in the cone conformation*

To a mixture of *p-tert*-butylcalix[4]arene (23.00 g, 35.5 mmol), 2,2′-thiodiethanol (6.49 g, 53.2 mmol), and TPP (27.92 g, 106.5 mmol) in 600 mL of toluene, a 40% solution of DEAD (46.35 g, 106.5 mmol) in toluene (135 mL) was added dropwise. The mixture was stirred at room temperature for 3 h and evaporated to dryness in vacuo. The residue was extracted with hexane (3×300 mL). The combined extracts were filtered and evaporated in vacuo. Chromatography on silica gel with hexanes–EtOAc (49:1) as eluent gave a white solid (7.55 g, 29%) with mp 110–115 °C. IR: 3338 (O–H), 1247 (C–O) cm^{-1}. ^1H NMR: δ 1.19 (s, 18H, CH_3), 1.21 (s, 18H, CH_3), 3.17–3.26 (m, 2H, OCH_2CH_2S), 3.29–3.41 (m, 6H, $ArCH_2Ar$, OCH_2CH_2S), 3.93 (t, J=10.0 Hz, 2H, OCH_2CH_2S), 4.33 (d, J=13.0 Hz, 2H, $ArCH_2Ar$), 4.35 (d, J=13.5 Hz, 1H, $ArCH_2Ar$), 3.62–4.68 (m, 2H, OCH_2CH_2S), 5.05 (d, J=12.0 Hz, 1H, $ArCH_2Ar$), 6.99 (d, J=2.5 Hz, 2H, ArH), 7.01 (d, J=2.5 Hz, 2H, ArH), 7.02 (d, J=2.5 Hz, 2H, ArH), 7.14 (d, J=2.5 Hz, 2H, ArH). ^{13}C NMR: δ 31.2, 31.3, 31.5, 32.7, 33.0, 33.9, 34.2, 36.9, 53.4, 125.3, 125.5, 125.9, 126.4, 128.8, 128.9, 133.6, 134.8, 142.9, 147.5, 149.0, 150.2. Anal. Calcd for $C_{48}H_{62}O_4S$: C, 78.43; H, 8.50. Found: C, 78.75; H, 8.41%.

*3.1.2. 5,11,17,12-Tetrakis(1,1-dimethylethyl)-27,28-bis[(ethoxycarbonyl)methoxy]calix[4]arene-25,26-monothiacrown-3 (**12**) in the cone conformation*

p-tert-Butylcalix[4]arene-1,2-thiacrown-3 (**11**) (2.00 g, 2.72 mmol) in THF (40 mL) was added dropwise to a mixture of NaH (0.96 g, 8.16 mmol) in THF (40 mL). After stirring for 2 h, ethyl bromoacetate (2.72 g, 16.32 mmol) was added. The mixture was stirred overnight and the excess NaH was destroyed by careful addition of dilute HCl. The solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2. The mixture was washed with dilute HCl and water, dried over $MgSO_4$, and evaporated in vacuo. Chromatography on silica gel with EtOAc–hexanes (3:97) gave a white solid (1.13 g, 46%) with mp 61–63 °C. IR: 1759 (C=O), 1248 and 1128 (C–O) cm^{-1}. ^1H NMR: δ 1.04 (s, 18H, CH_3), 1.12 (s, 18H, CH_3), 1.34 (t, J=7.0 Hz, 6H, CH_2CH_3), 3.02–3.09 (m, 2H, OCH_2CH_2S), 3.12 (d, J=12.5 Hz, 1H, $ArCH_2Ar$), 3.17 (d, J=12.5 Hz, 2H, $ArCH_2Ar$), 3.25 (d, J=12.5 Hz, 1H, $ArCH_2Ar$), 3.46–3.54 (m, 2H, OCH_2CH_2S), 3.72–3.79 (m, 2H, OCH_2CH_2S), 4.24–4.32 (m, 4H, OCH_2CH_3), 4.50 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 4.52 (d, J=16.0 Hz, 2H, OCH$_2$CO), 4.71–4.77 (m, 2H, OCH$_2$CH$_2$S), 4.78 (d, J=12.5 Hz, 2H, ArCH$_2$Ar), 4.90 (d, J=16.0 Hz, 2H, OCH$_2$CO), 5.29 (d, J=12.0 Hz, 1H, ArCH$_2$Ar), 6.78 (d, J=2.5 Hz, 2H, ArH), 6.80 (d, J=2.5 Hz, 2H, ArH), 6.86 (d, J=2.5 Hz, 2H, ArH), 6.90 (d, J=2.5 Hz, 2H, ArH). ^{13}C NMR: δ 14.3, 30.9, 31.3, 31.4, 31.5, 31.7, 31.79, 33.82, 33.9, 35.0, 60.7, 72.1, 75.9, 124.8, 125.2, 125.4, 125.6, 132.4, 134.0, 134.2, 135.0, 145.0, 145.4, 152.7, 153.0, 170.2. Anal. Calcd for $C_{56}H_{74}O_8S\cdot 1.5H_2O$: C, 71.99; H, 8.31. Found: C, 71.85; H, 8.38%.

3.1.3. *5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-bis(carboxymethoxy)calix[4]arene-25,26-monothiacrown-3 (**1**) in the cone conformation*

A solution of diester **12** (1.13 g, 1.25 mmol) in THF (30 mL) and 10% aq Me$_4$NOH (30 mL) was refluxed overnight. The solvent was evaporated in vacuo and the residue was dissolved in CH$_2$Cl$_2$ (100 mL). The organic layer was washed with 1 N HCl until pH 1 and then with brine (100 mL) and water (100 mL), dried over MgSO$_4$, and evaporated in vacuo to give a white solid (0.90 g, 85%) with mp 202–205 °C. IR: 3217 (O–H), 1760 (C=O), 1246 and 1127 (C–O) cm^{-1}. ^{1}H NMR: δ 1.07 (s, 18H, CH$_3$), 1.12 (s, 18H, CH$_3$), 3.07–3.14 (m, 2H, OCH$_2$CH$_2$S), 3.15 (d, J=12.5 Hz, 1H, ArCH$_2$Ar), 3.27 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 3.31 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 3.67–3.75 (m, 2H, OCH$_2$CH$_2$S), 4.33 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 4.49 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 4.58 (d, J=16.5 Hz, 2H, OCH$_2$CO), 4.59–4.66 (m, 2H, OCH$_2$CH$_2$S), 4.78 (d, J=16.0 Hz, 2H, OCH$_2$CO), 5.59 (d, J=12.5 Hz, 1H, ArCH$_2$Ar), 5.29 (d, J=12.0 Hz, 1H, ArCH$_2$Ar), 6.86 (d, J=2.0 Hz, 2H, ArH), 6.88 (d, J=2.5 Hz, 2H, ArH), 6.91 (d, J=2.5 Hz, 2H, ArH), 6.97 (d, J=2.5 Hz, 2H, ArH). ^{13}C NMR: δ 25.6, 30.6, 31.2, 31.4, 31.5, 31.6, 33.9, 34.0, 36.0, 68.0, 71.7, 77.6, 109.9, 124.8, 125.5, 125.9, 126.1, 133.1, 133.2, 133.3, 135.2, 145.6, 146.8, 151.4, 152.5, 171.6. Anal. Calcd for $C_{52}H_{66}O_8S$: C, 73.38; H, 7.82. Found: C, 73.12; H, 7.54%.

3.2. General procedure for 5,11,17,23-tetrakis(1,1-dimethylethyl)-27,28-bis[*N*-(X)sulfonyl carbamoyl-methoxy]calix[4]arene-25,26-monothiacrown-3 compounds 2–5 in the cone conformation

Oxalyl chloride (1.06 mL, 12.35 mmol) was added to diacid **1** (0.70 g, 0.82 mmol) in benzene (50 mL) and the mixture was refluxed for 10 h. After verifying conversion to the di(acid chloride) by IR spectrophotometry, the solvent was evaporated in vacuo. The appropriate sulfonamide (2.05 mmol) in THF (5 mL) was added to NaH (0.295 g, 12.3 mmol) in THF (20 mL) and the mixture was stirred at room temperature for 2 h. The di(acid chloride) solution was added and the mixture was stirred overnight (the reaction mixture was stirred for 2 days in the preparation for **2**). The excess NaH was destroyed by careful addition of water. The THF was evaporated in vacuo. To the residue was added CH$_2$Cl$_2$ and the mixture was washed with 6 N HCl, dried over MgSO$_4$ and evaporated in vacuo.

3.2.1. *5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-bis[N-(methane)sulfonyl carbamoyl-methoxy]calix[4]arene-25,26-monothiacrown-3 (**2**) in the cone conformation*

The crude product was purified by chromatography on silica gel with MeOH–CH$_2$Cl$_2$ (1:500 to 8:500) as eluent to give a white solid (0.22 g, 37%) with mp 170–172 °C. IR: 3231 (N–H), 1722 (C=O), 1345 and 1153 (S=O), 1245 and 1125 (C–O) cm^{-1}. ^{1}H NMR: δ 1.03 (s, 18H, CH$_3$), 1.15 (s, 18H, CH$_3$), 3.12–3.25 (m, 5H, ArCH$_2$Ar, OCH$_2$CH$_2$S), 3.32 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 3.39 (d, J=13.5 Hz, 1H, ArCH$_2$Ar), 3.41 (s, 6H, SO$_2$CH$_3$), 3.72–3.80 (m, 2H, OCH$_2$CH$_2$S), 4.25 (d, J=12.5 Hz, 2H, ArCH$_2$Ar), 4.40 (d, J=16.0 Hz, 2H, OCH$_2$CO), 4.59 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 4.61–4.67 (m, 2H, OCH$_2$CH$_2$S), 5.16 (d, J=16.0 Hz, 2H, OCH$_2$CO), 5.40 (d, J=12.5 Hz, 1H, ArCH$_2$Ar), 6.79 (d, J=2.5 Hz, 2H, ArH), 6.80 (d, J=2.5 Hz, 2H, ArH), 6.88 (d, J=2.5 Hz, 2H, ArH), 6.96 (d, J=2.0 Hz, 2H, ArH), 9.55 (s, 1H, NH). ^{13}C NMR: δ 29.7, 31.2, 31.40, 31.42, 31.60, 31.63, 31.7, 33.9, 34.0, 36.1, 41.7, 53.4, 74.7, 76.6, 124.9, 125.6, 125.9, 126.7, 132.3, 132.3, 133.0, 134.8, 145.7, 146.4, 152.4, 152.7, 169.3. Anal. Calcd for $C_{54}H_{72}O_{10}S_3N_2$: C, 64.51; H, 7.22; N, 2.79. Found: C, 64.60; H, 7.06; N, 2.60%.

3.2.2. *5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-bis-[N-(benzene)sulfonyl carbamoyl-methoxy]calix[4]arene-25,26-monothiacrown-3 (**3**) in the cone conformation*

The product was obtained as a pale yellow solid (0.75 g, 81%) with mp 138–140 °C. IR: 3260 (N–H), 1721 (C=O), 1361 and 1163 (S=O), 1236 and 1125 (C–O) cm^{-1}. ^{1}H NMR: δ 1.00 (s, 18H, CH$_3$), 1.13 (s, 18H, CH$_3$), 3.05–3.18 (m, 6H, ArCH$_2$Ar, OCH$_2$CH$_2$S), 3.23 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 3.66–3.74 (m, 2H, OCH$_2$CH$_2$S), 4.21 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 4.29 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 4.30 (d, J=15.5 Hz, 2H, OCH$_2$CO), 4.55–4.61 (m, 2H, OCH$_2$CH$_2$S), 5.03 (d, J=15.5 Hz, 2H, OCH$_2$CO), 5.42 (d, J=12.0 Hz, 1H, ArCH$_2$Ar), 6.68 (d, J=2.5 Hz, 2H, ArH), 6.73 (d, J=2.5 Hz, 2H, ArH), 6.82 (d, J=2.5 Hz, 2H, ArH), 6.93 (d, J=2.0 Hz, 2H, ArH), 7.49–7.56 (m, 6H, ArH), 8.07–8.13 (m, 4H, ArH), 9.62 (s, 1H, NH). ^{13}C NMR: δ 31.2, 31.3, 31.4, 31.5, 31.7, 33.8, 33.9, 35.9, 74.6, 76.4, 124.9, 125.5, 125.8, 126.4, 126.7, 128.6, 129.0, 129.2, 132.1, 132.3, 132.8, 133.0, 134.1, 134.8, 138.3, 145.6, 146.3, 152.4, 152.5, 167.9. Anal. Calcd for $C_{64}H_{76}O_{10}S_3N_2\cdot 0.2H_2O$: C, 67.84; H, 6.80; N, 2.47. Found: C, 67.40; H, 6.52; N, 2.87%.

3.2.3. *5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-bis-[N-(4-nitrobenzene)sulfonyl carbamoyl-methoxy]calix[4]-arene-25,26-monothiacrown-3 (**4**) in the cone conformation*

The crude product was purified by chromatography on silica gel with MeOH–CH$_2$Cl$_2$ (1:250 to 1:100) as eluent. The product was washed with 6 N HCl, dried over MgSO$_4$ and evaporated in vacuo to give a yellow solid (0.40 g, 40%) with mp 165–167 °C. IR: 3219 (N–H), 1722 (C=O), 1350 and 1161 (S=O), 1246 and 1125 (C–O) cm^{-1}. ^{1}H NMR: δ 1.00 (s, 18H, CH$_3$), 1.13 (s, 18H, CH$_3$), 3.05–3.23 (m, 6H, ArCH$_2$Ar, OCH$_2$CH$_2$S), 3.26 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 3.70–3.79 (m, 2H, OCH$_2$CH$_2$S), 4.18 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 4.28 (d, J=15.5 Hz, 2H, OCH$_2$CO), 4.46 (d, J=13.0 Hz, 1H, ArCH$_2$Ar), 4.55–4.63 (m, 2H, OCH$_2$CH$_2$S), 5.20 (d, J=16.0 Hz, 2H, OCH$_2$CO), 5.38 (d, J=12.0 Hz, 1H, ArCH$_2$Ar), 6.69 (d, J=2.5 Hz, 2H, ArH), 6.76 (d, J=2.5 Hz, 2H, ArH), 6.83 (d, J=2.5 Hz, 2H, ArH), 6.94 (d, J=2.5 Hz, 2H, ArH), 8.27–8.32 (m, 4H, ArH), 8.34–8.39 (m, 4H, ArH), 9.66 (s, 1H, NH). ^{13}C NMR: δ 29.7, 31.2, 31.3, 31.66, 33.9, 34.0, 35.9, 74.4, 76.5, 124.2, 124.9, 125.5, 126.0, 126.9, 130.2, 132.1, 132.2, 132.8, 134.8, 143.6, 145.8, 146.6, 150.8, 152.4, 152.5, 168.3. Anal. Calcd for $C_{64}H_{74}O_{14}S_3N_4\cdot 0.6C_6H_6$: C, 64.12; H, 6.18; N, 4.42. Found: C, 64.39; H, 5.96; N, 4.07%.

3.2.4. *5,11,17,23-Tetrakis(1,1-dimethylethyl)-27,28-bis-[N-(trifluoromethane)sulfonyl carbamoyl-methoxy]calix-[4]arene-25,26-monothiacrown-3 (**5**) in the cone conformation*

The crude product was purified by chromatography on silica gel with MeOH–CH$_2$Cl$_2$ (1:99) as eluent. The product was washed with 6 N HCl, dried over MgSO$_4$ and evaporated in vacuo to give a white solid (0.70 g, 76%) with mp 156–158 °C. IR: 2963 (N–H), 1751 (C=O), 1364 and 1131 (S=O), 1260 and 1131 (C–O) cm^{-1}. ^{1}H NMR: δ 1.02 (s, 18H, CH$_3$), 1.15 (s, 18H, CH$_3$), 3.08–3.24 (m, 5H, ArCH$_2$Ar, OCH$_2$CH$_2$S), 3.33 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 3.41 (d, J=13.5 Hz, 1H, ArCH$_2$Ar), 3.70–3.79 (m, 2H, OCH$_2$CH$_2$S), 4.21 (d, J=13.0 Hz, 2H, ArCH$_2$Ar), 4.48–4.62 (m, 5H, OCH$_2$CO, OCH$_2$CH$_2$S, ArCH$_2$Ar), 5.25 (d, J=17.5 Hz, 2H, OCH$_2$CO), 5.43 (d, J=12.5 Hz, 1H, ArCH$_2$Ar), 6.74–6.83 (m, 4H, ArH), 6.87 (d, J=2.0 Hz, 2H, ArH), 6.96 (d, J=2.0 Hz, 2H, ArH). ^{13}C NMR: δ 30.8, 31.0, 31.2, 31.4, 31.5, 31.6, 31.7, 33.9, 34.0, 35.9, 53.4, 74.3, 117.8, 120.4, 125.0, 125.7, 126.0, 126.9, 132.1, 132.3, 132.8, 134.8, 145.8, 146.8, 152.3, 152.5, 167.5. Anal. Calcd for $C_{54}H_{66}O_{10}S_3F_6N_2\cdot 0.4C_6H_6$: C, 59.19; H, 6.02; N, 2.45. Found: C, 59.13; H, 6.36; N, 2.44%.

3.3. Procedure for competitive extraction of alkali metal cations

An aqueous solution of the alkali metal chlorides with LiOH or HCl for pH adjustment (2.0 mL, 10.0 mM in each alkali metal cation species) and 2.0 mL of a 1.0 mM solution of the ligand in chloroform in a metal-free, capped, polypropylene, 15-mL centrifuge tube was vortexed for 10 min at room temperature. The tube was centrifuged for 10 min for phase separation. 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 centrifuged for 10 min. The aqueous phase from this stripping was diluted 10-fold with DI water and the alkali metal cation concentrations were determined with a Dionex DX-120 on chromatograph with a CS12A column with conductivity detection and membrane suppression (Dionex Model CMMS-II). The pH of the aqueous phase from the initial extraction step was determined.

3.4. Procedure for competitive extraction of alkaline earth metal cations

An aqueous solution of the alkaline earth metal chlorides with $Ba(OH)_2$ or HCl for pH adjustment (2.0 mL, 2.0 mM in each alkaline earth metal cation species) and 2.0 mL of 1.0 mM solution of the ligand in chloroform in a metal-free, capped, polypropylene, 15-mL centrifuge tube was vortexed for 10 min at room temperature. The tube was centrifuged for 10 min for phase separation. 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 centrifuged for 10 min. The aqueous phase from this stripping was diluted 10-fold with DI water and the alkaline earth metal cation concentrations were determined with a Dionex DX-120 ion chromatograph with a CS12A column with conductivity detection and membrane suppression (Dionex Model CMMS-II). The pH of the aqueous phase from the initial extraction step was determined.

3.5. Procedure for single species extraction of Pb^{2+}

An aqueous solution (2.0 mL) of 1.0 mM $Pb(NO_3)_2$ with TMAOH or HNO_3 for pH adjustment and 2.0 mL of a 0.50 mM solution of the ligand in chloroform in a metal-free, capped, polypropylene, 15-mL centrifuge tube was vortexed for 10 min at room temperature and then centrifuged for 10 min for phase separation. A 1.5-mL portion of the organic phase was removed and added to 3.0 mL of 4.0 M HNO_3 in a new, 15-mL, polypropylene centrifuge tube. The tube was vortexed for 10 min and then centrifuged for 10 min. A 2.0-mL sample of the aqueous phase after this stripping was diluted to 10 mL with DI water in a volumetric flask for determination of the Pb^{2+} by atomic absorption using the absorption at 283.3 nm.

3.6. Procedure for single species extraction of Hg^{2+}

An aqueous solution (3.0 mL) of 0.25 mM $Hg(NO_3)_2$ with TMAOH or HNO_3 for pH adjustment and 3.0 mL of 0.25 mM ligand solution in chloroform in a metal-free, capped, polypropylene, 15-mL centrifuge tube were vortexed for 10 min at room temperature and then centrifuged for 10 min. A 0.50-mL portion of the aqueous phase was removed and diluted to 5.00 mL with DI water. The pH of the aqueous phase was measured. A 1.0-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 connected to a Shimadzu MVU-1A mercury vaporizer unit. The Hg^{2+} in the sample was reduced using 5.0 mL of $SnCl_2$ solution, prepared by dissolving 20 g of $SnCl \cdot H_2O$ in 40 mL of concd HCl and diluting the solution to 200 mL with DI water. 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-630 spectrophotometer. The vapor was then pumped to a waste receptacle, where it was re-oxidized using a 0.5% solution of $KMnO_4$ in 5% H_2SO_4.[24]

Acknowledgements

We thank the Division of Chemical Sciences, Geosciences, and Biosciences of the Office of Basic Energy Sciences of the U.S. Department of Energy (Grant DE-FG02-90ER1446) for support of this research.

References and notes

1. Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Boston, 2001; p 365.
2. Salorinne, K.; Nissinen, M. *J. Inclusion Phenom. Macrocyclic Chem.* **2008**, *61*, 11.
3. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Andreeti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075.
4. Dijkstra, P. J.; Brunink, J. A.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567.
5. Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979.
6. Lamare, V.; Dozol, J.-F.; Ugozzoli, F.; Casnati, A.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 1559.
7. Yamamoto, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1994**, 1559.
8. Arduini, A.; Casnati, A.; Doni, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597.
9. Arduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235.
10. Arduini, A.; Domiano, L.; Pochini, A.; Secchi, A.; Ungaro, R.; Ugozzoli, F.; Struck, O.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1997**, *53*, 3762.
11. Arnaud-Neu, F.; Caccamese, S.; Fuangswadi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041.
12. Arnaud-Neu, F.; Ferguson, G.; Fuangswadi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Petringa, A. *J. Org. Chem.* **1998**, *63*, 7770.
13. Mathieu, A.; Asfari, Z.; Thuery, P.; Nierlich, M.; Faure, S.; Vicens, J. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *40*, 173.
14. Ungaro, R.; Pochini, A.; Andretti, G. D. *J. Inclusion Phenom.* **1984**, *2*, 199.
15. Arduini, A.; Pochini, A.; Reverberi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.
16. Ogata, M.; Fujimoto, K.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4505.
17. Tu, C.; Surowiec, K.; Purkiss, D. W.; Bartsch, R. A. *Tetrahedron Lett.* **2006**, *46*, 3443.
18. Tu, C.; Liu, D.; Surowiec, K.; Purkiss, D. W.; Bartsch, R. A. *Org. Biomol. Chem.* **2006**, *4*, 2933.
19. Zhang, D.; Cao, X.; Purkiss, D. W.; Bartsch, R. A. *Org. Biomol. Chem.* **2007**, *4*, 1251.
20. Tu, C.; Surowiec, K.; Bartsch, R. A. *Tetrahedron* **2007**, *63*, 4184.
21. Talanova, G. G.; Hwang, H.-S.; Talanov, V. S.; Bartsch, R. A. *Chem. Commun.* **1998**, 419.
22. Talanova, G. G.; Hwang, H.-S.; Talanov, V. S.; Bartsch, R. A. *Chem. Commun.* **1998**, 1329.
23. Csokai, V.; Grün, A.; Bitter, I. *Tetrahedron Lett.* **2003**, *44*, 4681.
24. This method replaces the Hg^{2+} photometric analysis as the mercury dithizonate complex used previously.[17–20] Test experiments were run to verify that the same results were obtained with both analytical procedures.