

Calix[4]arene-thiacrown-5 di(carboxylic acid) regioisomers as metal ion extractants

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Abstract A regioisomer of a previously reported *p*-tert-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) is prepared in which the thiocrown ring attachment sites are moved from distal phenolic oxygens of a cone *p*-tert-butylcalix[4]arene scaffold to proximal phenolic oxygens. The influence of this structural variation in the di-ionizable calixcrown ligand on competitive solvent extractions of alkali metal cations and of alkaline earth metal cations and single species solvent extractions of Hg²⁺ and Pb²⁺ from aqueous solutions into chloroform is evaluated.

Keywords Calixarenes · Crown compounds · Ionic recognition · Metal ion extraction

For calix-crowns ether compounds, also called calixcrowns, a calixarene scaffold is combined with a crown ether unit joining two phenolic oxygens of the former 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 unit that bridges two distal phenolic oxygens (Fig. 1). Ungaro and coworkers reported the first example of this ligand family, *p*-tert-butylcalix[4]arene-1,3-crown-6, in 1983 [7]. Much less frequently encountered are calix[4]arene-1,2-crown compounds with a polyether bridge between two proximal phenolic oxygens.

Incorporation of pendant proton-ionizable groups (PIG)s into calix[4]arene-crown ligands markedly enhances their metal ion extraction ability compared with non-ionizable

analogues. The ionized groups not only participate in cooperative metal ion coordination, but also eliminate the need to transfer aqueous phase anions into the organic diluents by operating in a cation-exchange mode with the metal cation [8–10].

In 2007, we reported [11] the synthesis of *p*-tert-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1** (Fig. 2) and determined its metal ion extraction behavior. To probe the influence of the sulfur atom in the crown ring of **1**, the extraction results were compared with those for *p*-tert-butylcalix[4]arene-1,3-crown-5 di(carboxylic acid) **2**. For Hg²⁺ extraction from aqueous solution into chloroform, ligand **1** gave 80% metal loading of the organic phase (for formation of a 1:1 metal ion-di-ionized ligand complex). Under the same conditions, only 10% metal loading was achieved with ligand **2**.

In this paper, we describe the synthesis of *p*-tert-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3** and determine its metal ion extraction properties towards alkali metal cations (AMC) and alkaline earth metal cations (AEMC), as well as Hg²⁺ and Pb²⁺. Ligands **1** and **3** are regioisomers differing only the connection site of the thiocrown unit to the *p*-tert-butylcalix[4]arene scaffold in the cone conformation. In the present study, we probe how this structural variation influences their metal ion complexation behavior.

Experimental

General

Reagents were purchased from commercial suppliers and used directly, unless noted otherwise. *p*-tert-Butylcalix[4]arene (**4**) was obtained from Eburon Organics

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Fig. 1 Structures of two calix[4]arene-crown ether regioisomers

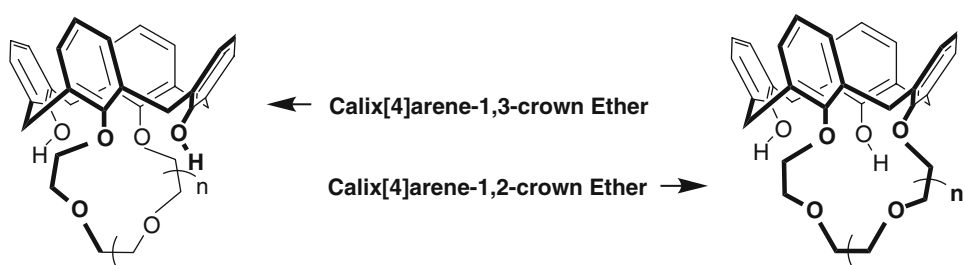
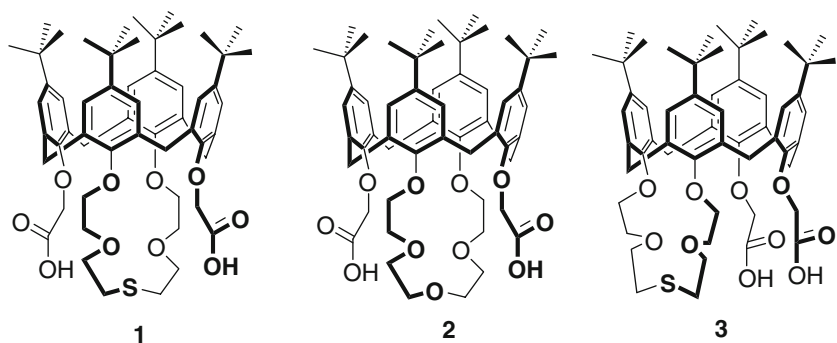


Fig. 2 Structures of three cone calix[4]ene-crown-5 di(carboxylic acids)



International of Lubbock, Texas. Acetonitrile (MeCN) was dried over CaH_2 and distilled just before use. Tetrahydrofuran (THF) was dried over sodium wire with benzophenone ketyl as indicator and distilled just before use. Infrared spectra were taken with a Perkin-Elmer 1600 FT-IR spectrophotometer as deposits from CH_2Cl_2 solution onto NaCl plates. The absorptions are given in wavenumbers (cm^{-1}). NMR spectra were recorded with a Varian Unity Inova FT-500 spectrometer (500 MHz for ^1H , 126 MHz for ^{13}C) in CDCl_3 with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm downfield from TMS and coupling constant (J) values are given in Hz. Melting points were determined with a Mel-Temp apparatus. Combustion analysis was performed by Desert Analytics Laboratory/Columbia Analytical Services of Tucson, Arizona.

Synthesis of cone 5,11,17,23-tetrakis-(1,1-dimethylethyl)-25,26-dihydroxycalix[4]arene-thiacrown-5 (**5**)

A slurry of *p*-tert-butylcalix[4]arene (**4**) (2.50 g, 3.86 mmol) and Cs_2CO_3 (12.58 g, 38.60 mmol) in MeCN (400 mL) was refluxed for 2 h under nitrogen. The ditosylate derived from 1,4,10,13-tetraoxa-7-thiatridecane [12, 13] (2.10 g, 4.05 mmol) was dissolved in MeCN (100 mL) and the solution was added dropwise during a 3 h period. The mixture was refluxed for 5 days. After evaporation of the MeCN in vacuo, CH_2Cl_2 (150 mL) and 10% HCl solution (150 mL) were added to the residue. The organic phase was separated, washed with water (2×250 mL), dried over MgSO_4 and evaporated

in vacuo. The residue was chromatographed on silica gel with hexanes-EtOAc (20:1 to 4:1 gradient) as eluent to give **5** (0.34 g, 11%) as a white solid with mp 124–126 °C. IR $\nu_{\text{max}}/\text{cm}^{-1}$: br 3,332 (OH). δ_{H} (CDCl_3 , 500 MHz) 1.10 (s, 18H, $\text{C}(\text{CH}_3)_3$), 1.20 (s, 18H, $\text{C}(\text{CH}_3)_3$), 2.93–2.98 (m, 2H, $\text{SCH}_2\text{CH}_2\text{O}$), 3.12–3.18 (m, 2H, $\text{SCH}_2\text{CH}_2\text{O}$), 3.31–3.36 (m, 4H, ArCH_2Ar), 3.93–4.25 (m, 12H, $\text{SCH}_2\text{CH}_2\text{O}$, $\text{OCH}_2\text{CH}_2\text{O}$), 4.28 (d, 1H, $J = 13.0$ Hz, ArCH_2Ar), 4.35 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.50 (d, 1H, $J = 13.0$ Hz, ArCH_2Ar), 6.91–7.00 (m, 8H, ArH), 8.56 (s, 2H, OH). δ_{C} (CDCl_3 , 126 MHz) 30.6, 30.7, 31.2, 31.5, 32.3, 32.6, 69.2, 73.4, 75.1, 125.0, 125.3, 126.0, 126.0, 128.2, 128.8, 133.0, 133.7, 142.4, 146.6, 149.0, 151.6. Calc. for $\text{C}_{52}\text{H}_{70}\text{O}_6\text{S}$: C, 75.87; H, 8.57; S, 3.89%. Found: C, 76.08; H, 8.43; S, 4.06%.

Synthesis of cone 5,11,17,23-tetrakis-(1,1-dimethylethyl)-25,26-bis[(ethoxycarbonyl)methoxy]calix[4]arene-thiacrown-5 (**6**)

A mixture of **5** (1.20 g, 1.46 mmol) in THF (50 mL) and NaH (0.35 g, 14.60 mmol) was stirred under nitrogen at room temperature for 30 min and ethyl bromoacetate (0.54 g, 3.21 mmol) was added. The mixture was stirred at room temperature for another 24 h. After evaporation of the THF in vacuo, CH_2Cl_2 (25 mL) and 10% HCl solution (25 mL) were added to the residue. The organic layer was separated and washed with water (2×50 mL), dried over MgSO_4 and evaporated in vacuo. The residue was chromatographed on silica gel with hexanes-EtOAc (50:1 to 4:1 gradient) to give 1.03 g (71%) of diester **6** as a white solid with mp 92–94 °C. IR $\nu_{\text{max}}/\text{cm}^{-1}$: 1,760 ($\text{C}=\text{O}$). δ_{H}

(CDCl₃, 500 MHz) 1.08 (s, 36H, C(CH₃)₃), 1.29 (t, $J = 6.0$ Hz, 6H, OCH₂CH₃), 2.88–3.01 (m, 4H, SCH₂CH₂O), 3.13–3.22 (m, 4H, ArCH₂Ar), 3.89 (t, 4H, $J = 6.0$ Hz, SCH₂CH₂O), 3.97–4.17 (m, 12H, OCH₂CH₂O), 4.24 (q, 4H, $J = 7.0$ Hz, OCH₂CH₃), 4.50 (d, 1H, $J = 13.0$ Hz, ArH), 4.50 (d, 2H, $J = 13.0$ Hz, ArCH₂Ar), 4.72–4.85 (m, 5H, ArCH₂Ar, OCH₂C(O)), 6.79–6.82 (m, 8H, ArH). δ_{H} (CDCl₃, 126 MHz) 14.3, 31.2, 31.4, 31.4, 33.8, 33.9, 60.5, 69.7, 71.6, 73.0, 73.7, 125.0, 125.1, 125.4, 133.2, 133.4, 133.5, 134.0. Calc. for C₆₀H₈₂O₁₀S: C, 72.40; H, 8.30; S, 3.22%. Found: C, 72.15; H, 8.12; S, 3.00%.

Synthesis of cone 5,11,17,23-tetrakis (1,1-dimethylethyl)-25,26-bis(carboxymethoxy)-calix[4]arene-thiacrown-5 (**3**)

A solution of **6** (0.73 g, 0.73 mmol), 25 mL of 10% aq tetramethylammonium hydroxide (TMAOH) and 25 mL of THF was refluxed for 24 h. After evaporation of the THF in vacuo, 20 mL of 6 N HCl solution was added to the residue. The mixture was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with water (2 × 50 mL) and dried over MgSO₄. After evaporation of the CH₂Cl₂ in vacuo, 0.66 g (95%) of **3** was obtained as a pale yellow solid with mp 132–134 °C. IR $\nu_{\text{max}}/\text{cm}^{-1}$: 3391 (CO₂H), 1753 (C=O). δ_{H} (CDCl₃, 500 MHz) 1.08 (s, 18H, C(CH₃)₃), 1.09 (s, 18H, C(CH₃)₃), 2.92–3.08 (m, 4H, SCH₂CH₂O), 3.18 (d, $J = 13.0$ Hz, 1H, ArCH₂Ar), 3.23–3.27 (m, 3H, ArCH₂Ar), 3.79–3.97 (m, 8H, SCH₂CH₂O, OCH₂CH₂O), 4.09–4.23 (m, 6H, ArCH₂Ar, OCH₂C(O)), 4.43 (d, 1H, $J = 13.0$ Hz, ArCH₂Ar), 4.50–4.65 (m, 5H, ArCH₂Ar, OCH₂C(O)), 4.87–5.12 (br s, 2H, CO₂H), 6.83–6.90 (m, 8H, ArH). δ_{C} (CDCl₃, 126 MHz) δ 30.6, 30.8, 31.3, 31.4, 33.9, 34.0, 68.9, 71.5, 73.0, 74.4, 125.2, 125.4, 125.7, 125.7, 133.0, 133.2, 133.5, 134.4, 145.6, 146.7, 151.0, 152.1, 171.2. Calc. for C₅₆H₇₄O₁₀S·0.3CH₂Cl₂: C, 70.09; H, 7.79; S, 3.32%. Found: C, 69.88; H, 7.76; S, 3.35%.

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 capped, polypropylene, 15-mL centrifuge tube was vortexed for 10 min with a Glas-Col Multi-Pulse Vortex Mixer. The tube was centrifuged with a Clay Adams Compact II Centrifuge for 10 min to promote 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

to 10.0 mL with deionized water and the alkali 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 with a Fisher Accumet AR25 pH meter with a Corning 476157 combination pH electrode.

Procedure for competitive extraction of alkaline earth metal cations

The procedure for competitive extraction of alkaline earth metal cations was the same as that reported previously [11].

Procedure for single species extraction of Pb²⁺

The procedure for single species extraction of Pb²⁺ was the same as that reported previously [11], except that a Shimadzu AA-6300 atomic absorption spectrophotometer was utilized.

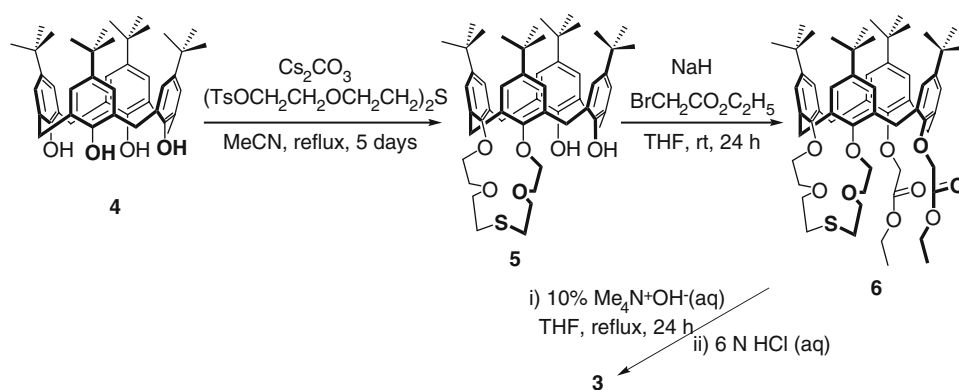
Procedure for single species extraction of Hg²⁺

An aqueous solution (3.0 mL) of 0.25 mM Hg(NO₃)₂ with TMAOH or HNO₃ for pH adjustment and 3.0 mL of 0.25 mM solution of **3** in chloroform in a capped, polypropylene, 15-mL centrifuge tube were vortexed for 10 min at room temperature and then centrifuged for 10 min at room temperature. A 0.50-mL portion of the aqueous phase was removed and diluted to 5.0 with deionized water. The pH of the aqueous phase from the initial extraction was measured. A 1.0-mL portion of the diluted aqueous phase was added to 100 mL of 1.0 N H₂SO₄ in a glass reaction bottle, which was then connected to a Shimadzu MVU-1A mercury vaporizer unit. The Hg²⁺ in the sample was reduced using 5.0 mL of SnCl₂ solution prepared by dissolving 20 g of SnCl₂·H₂O in 40 mL of conc HCl and diluting the solution to 200 mL with deionized 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-6300 spectrophotometer. The vapor was then pumped to a waste receptacle, where it was re-oxidized with a 0.5% solution of KMnO₄ in 5% H₂SO₄.

Results and discussion

In the multi-step synthesis of previously reported for *p*-tert-butylcalix[4]arene-1,3-thiacrown-5 dicarboxylic acid **1** [11], the initial step was reaction of *p*-tert-butylcalix[4]arene (**4**)

Scheme 1 Synthesis of *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3** in the cone conformation



with K_2CO_3 and the ditosylate of 1,4,10,13-tetraoxa-7-thiatridecane in MeCN. The yield of *p*-*tert*-butylcalix[4]arene-1,3-thiacrown-5 was very low (13%). Later when the base was changed from K_2CO_3 to Cs_2CO_3 in an attempt to enhance the yield, it was discovered that the regioselectivity of this reaction had changed. The ring-closure product was now found to be *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-5 (**5**) (Scheme 1), albeit still in a very low yield of 11%. This was very surprising, since a strong base (such as NaH) is normally required for cyclization to form a calix[4]arene-1,2-crown ether [14].

The *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-5 (**5**) was reacted with ethyl bromoacetate and NaH in THF to give diester **6** in 71% yield. Subsequent hydrolysis of diester **6** with TMAOH in H_2O –THF (1:1) gave diacid **3** in 95% yield.

The conformation of the calix[4]arene unit and regioselectivity of the crown linkage attachment were verified by the NMR spectra of compounds **3**, **5** and **6**. Due to fewer symmetry elements in calix[4]arene-1,2-thiacrown-5 compounds **3**, **5** and **6** than in their previously reported calix[4]arene-1,3-thiacrown-5 analogues [11], the 1H and ^{13}C NMR spectra of the former exhibit extra complexity. There are no peaks between 36 and 40 ppm in their ^{13}C NMR spectra. This demonstrates that all four benzene rings in the calix[4]arene unit have *syn*-arrangements, which verifies the cone conformation. Due to the 1,2-connected crown units, each of the methylene group protons in the crown loop has a different local magnetic environment and they are diastereotopic to each other. The difference is caused by the crown linkage restricting free rotation about single bonds causing one H of the methylene group to face the crown and the other to point away. For *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3**, a portion of the 1H – ^{13}C heterocosity spectrum is shown in Fig. 3. Three carbon signals were observed for the bridge carbons and are correlated to 3 AB pairs of protons. These data confirm the proximal crown linkage.

The metal ion complexing abilities of ligand **3** were probed by solvent extraction of metal ions from aqueous

solutions into chloroform, a convenient solvent for screening the metal ion extraction behavior of ligands. For five alkali metal cations (AMC) and for four alkaline earth metal cations (AEMC), competitive solvent extractions were utilized. With Hg^{2+} and Pb^{2+} , single species solvent extractions were employed.

Since our earlier paper about *p*-*tert*-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1** [11] included extraction data for divalent metal cations only, competitive solvent extractions of AMC from aqueous solutions into chloroform were performed for both of the regioisomeric calix-thiacrowns **1** and **3**. 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** and **3** in chloroform. Plots of metal ion loadings of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 4. Note that the metal loadings were negligible when the aqueous phases were highly acidic. This confirms that the ligands are ineffective extractants in their non-ionized forms. Since the ligands are di(carboxylic acid)s, the maximal metal loadings by monovalent AMC is 200%. The maximal combined metals loading of about 160% for ligand **3** surpasses that of approximately 70% for ligand **1**. Thus, the proximal attachment site for the crown ring in **3** more than doubles the AMC extraction efficiency compared to regioisomer **1**.

The AMC extraction selectivities for calix[4]arene-thiacrown-5 regioisomers **1** and **3** also show appreciable differences. For the 1,2-thiacrown-5 ligand **3**, the extraction selectivity order under conditions of maximal loading (i.e. highly alkaline pH) is $Na^+ \gg Li^+ \gg K^+, Rb^+, Cs^+$ (Fig. 4b). The ligand exhibits very high extraction selectivity for Na^+ until half loading of **3** takes place at about pH \sim 8. This indicates that the mono-ionized form of ligand **3** is a very selective extractant for Na^+ . A possible explanation is an extraction complex with Na^+ complexed in the crown cavity and one carboxylate group coordinating also. Above pH 8, some extraction of Li^+ also takes place.

For the 1,3-thiacrown-5 analogue **1**, the AMC extraction selectivity order was $K^+ > Na^+ > Li^+ > Rb^+, Cs^+$

Fig. 3 Portion of the ^1H - ^{13}C heterocosity NMR spectrum for ligand **3** in CDCl_3

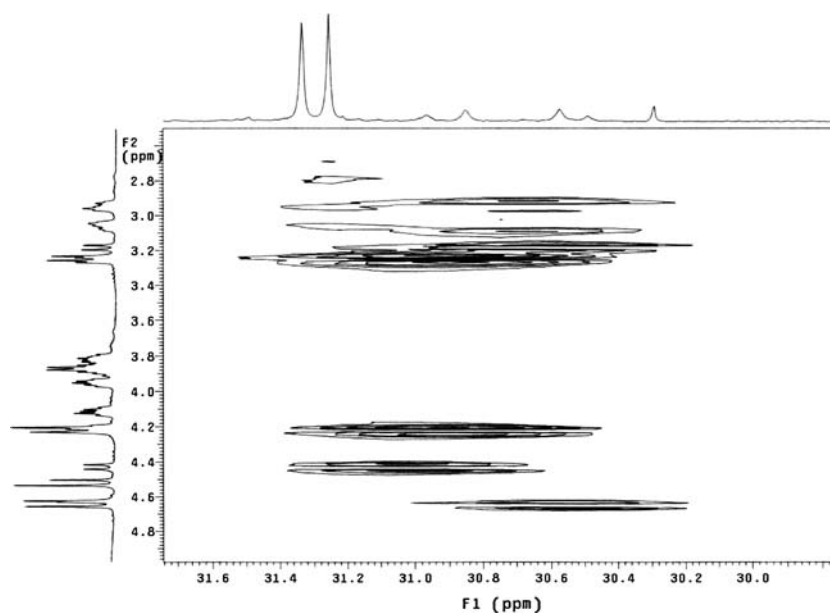
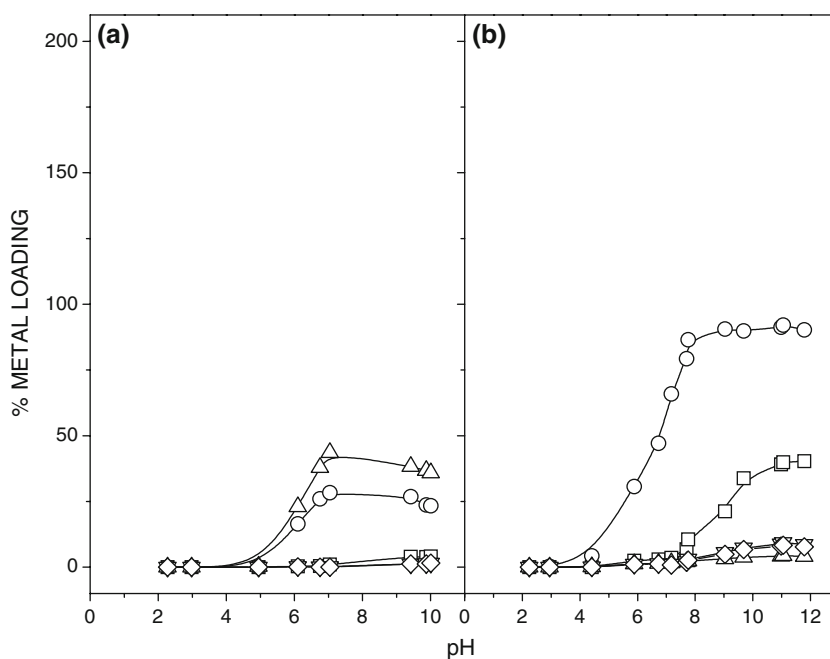


Fig. 4 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkali metal cations into chloroform by: **a** *p*-*tert*-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1** and **b** *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3** (open squares Li^+ , open circles Na^+ , open triangles K^+ , open inverted triangles Rb^+ , open diamonds Cs)



(Fig. 4a). An increase in the crown ring size is anticipated when the crown unit is joined through the 1,3-phenolic oxygens in **1** rather than the 1,2-phenolic oxygens in **3**. This may explain the preferred extraction of larger K^+ by **1**.

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 calix[4]arene-1,2-thiacrown-5 **3** in chloroform. For the competitive alkaline earth metal cation (AEMC) extraction, a plot of metal loading of the organic phase versus the equilibrium pH of the aqueous phase is presented in Fig. 5b. From alkaline solutions, the combined

metal loading approaches 100%, as would be expected for extraction complexes comprised of a divalent metal cation and the di-ionized ligand **3**. The competitive extraction selectivity order is Ba^{2+} , $\text{Ca}^{2+} > \text{Sr}^{2+} > \text{Mg}^{2+}$. Thus, ligand **3** does not exhibit the pronounced preference for Ba^{2+} extraction reported earlier for regioisomer **1** (Fig. 5a). For ligand **1**, the AEMC extraction selectivity order was $\text{Ba}^{2+} \gg \text{Mg}^{2+}$, $\text{Sr}^{2+} > \text{Ca}^{2+}$. The difference in Ca^{2+} extraction behavior for regioisomers **3** and **1** is striking. In competitive AEMC extractions, Ca^{2+} is one of the best extracted ions with **3**, but is the worst extracted species with **1**.

Fig. 5 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by: **a** *p-tert*-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1** and **b** *p-tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3** (open squares Mg^{2+} , open circles Ca^{2+} , open triangles Sr^{2+} , open inverted triangles Ba^{2+})

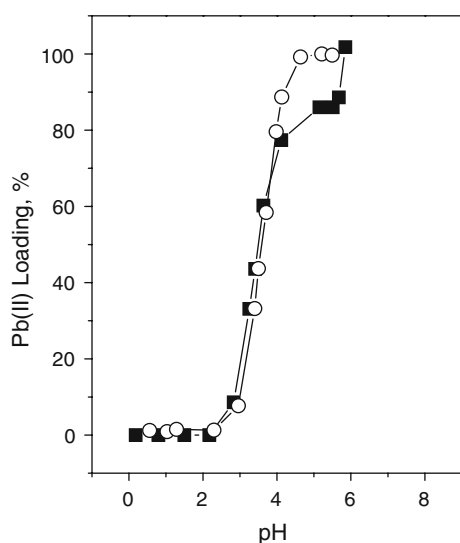
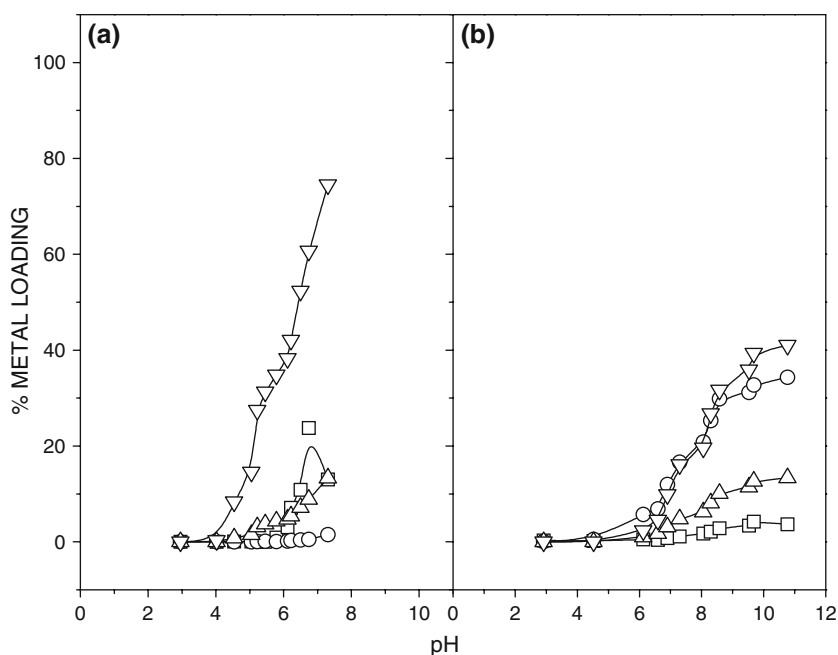


Fig. 6 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for solvent extraction of Pb^{2+} into chloroform by: **a** open circles *p-tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3**; and **b** filled squares *p-tert*-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1**

Aqueous solutions of Pb^{2+} (1.0 mM) nitrate were extracted with 0.50 mM solutions of calix[4]arene-1,2-crown-5 di(carboxylic acid) **3** in chloroform. A plot of metal loading of the organic phase versus the equilibrium pH of the aqueous phase by ligand **3** (open circles) is presented in Fig. 6. Data reported previously for Pb^{2+} extractions by regioisomeric ligand **1** (filled squares) are also shown. As can be seen, both ligands **3** and **1** are effective extractants for removal of Pb^{2+} from acidic aqueous solutions. Although the extraction profiles are

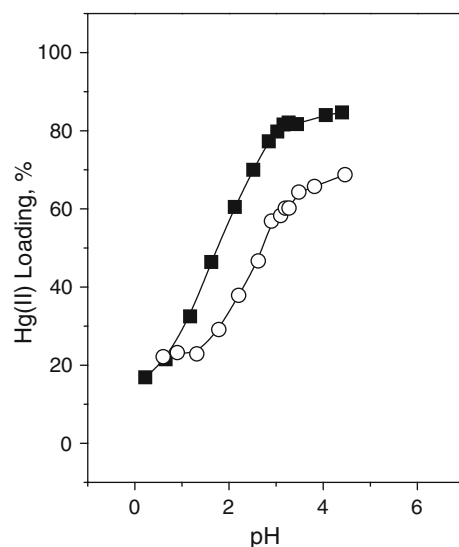


Fig. 7 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for solvent extraction of Hg^{2+} into chloroform by: **a** open circles *p-tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3**; and **b** filled squares *p-tert*-butylcalix[4]arene-1,3-thiacrown-5 di(carboxylic acid) **1**

essentially the same for **3** and **1** until 80% metal loading is reached, the calix[4]arene-1,2-crown-5 di(carboxylic acid) **3** reaches 100% metal loading at a lower pH value than ligand **1**. Based upon this observation, ligand **3** is judged to be a slightly stronger Pb^{2+} extractant than its regioisomer **1**.

Aqueous solutions of Hg^{2+} (0.25 mM) nitrate were extracted with 0.25 mM solutions of *p-tert*-butylcalix[4]arene-1,2-thiacrown-5 di(carboxylic acid) **3** in chloroform. A plot of the metal loading of the organic phase

versus the equilibrium pH of the aqueous phase is presented in Fig. 7 (*open circles*). For comparison, previously reported data for single species Hg^{2+} extractions by regioisomer **1** (*filled squares*) are also shown. This comparison of the extraction data for regioisomeric ligands **3** and **1** reveals a lower propensity of the former for Hg^{2+} extraction from acidic aqueous solution into chloroform.

Summary

The structures of di-ionizable calix[4]arene-thiacrown-5 ligands **3** and **1** differ only in the attachment site of the thiacycrown ring to the cone conformer of the *p-tert*-butylcalix[4]arene scaffold. In the former, the thiacycrown ring is attached through proximal phenolic oxygens; and in the latter, it is joined through distal phenolic oxygens. To probe how this systematic structural variation influences metal ion complexation, competitive solvent extractions of AMC and of AEMC and single species extractions of Hg^{2+} and of Pb^{2+} were conducted. For AMC and for Pb^{2+} , regioisomer **3** is more selective and/or efficient than **1**. For AEMC and for Hg^{2+} , regioisomer **1** is more selective and/or efficient than **3**.

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