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ORIGINAL ARTICLE

Binding and extraction of alkali and alkaline earth metals by nano-baskets of calix[4]arene-1,2-crown-3

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Abstract The proton di-ionizable *p-tert*-butylcalix[4]-arene-1,2-crown-3 in cone and 1,2-alternate conformations and the *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 in cone conformation were synthesized and the competitive solvent extractions of alkali and alkaline earth metal cations were studied using such nano-baskets. The novelty of this study is investigation of three binding units of calixarene's bowl, crown ether's ring and electron-donor ionizable moieties in a unique scaffold. The calixarene's bowl, crown ether's ring and electron-donor ionizable moieties were selected base upon their complexation ability to show equal binding tendency towards the cations. The objective of this study is to assess the extraction efficiency, selectivity and $pH_{1/2}$ of such complexes. The result of solvent extraction experiments indicated that these compounds were effective extractants towards alkali and alkaline earth metals. Their selectivity was influenced by the acidity of solution and the conformation of calixcrowns. *p-tert*-butylcalix[4]arene-1,2-crown-3 diacid in cone conformation was highly selective to Na^{+} and *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 diacid in cone conformation was highly selective to Ba^{2+} in acidic and basic solutions, respectively.

Keywords Nano-basket · Solvent extraction · Calixcrown · Alkali metal · Alkaline earth metal

Introduction

Nano-baskets of calixarenes and calixcrowns are a versatile class of macrocycles, which have been subject to extensive research in development of many extractants, transporters and stationary phases (using gas chromatograph, Teif Gostar Faraz Co.) over the past four decades [1–5]. Functionalization of calix[4]arenes at both the upper rim and the lower rim has been extensively studied. Attaching donor atoms to the lower rim of a calix[4]arene can improve the binding strength of the parent calixarene dramatically. Two main groups of lower-rim functionalized calix[4]arenes are calix[4]arene podands and calixarene-crown ethers [6, 7]. Distal hydroxyl groups can be connected to give 1,3-bridged calix[4]crowns, while connection between proximal hydroxyl groups leads to 1,2-bridged calix[4]crowns.

Tu et al. [8] synthesized di-ionizable *p-tert*-butylcalix[4]arene-1,3-thiacrown-5 and di-ionizable calix[4]arene-1,2-crown-5 and -crown-6 [9] as the efficient extractants with Ba^{2+}, Pb^{2+} and Hg^{2+} selectivity. They compared the extraction efficiency of the synthesized calixcrowns bearing dicarboxylic acid and *N*-(X)sulfonyl oxyacetamide ($X =$ methyl, phenyl, 4-nitrophenyl, and trifluoromethyl) moieties and revealed that the dicarboxylic acid analogues exhibited little selectivity in extraction of alkaline earth metals [9]. Yang et al. [10] synthesized two series of di-ionizable calix[4]arene-crown-5 isomers in the cone conformation, in which the ionizable groups were attached to the lower and upper rims, respectively. They reported the extraction behaviors of synthesized ligands towards alkaline earth metal, Hg^{2+} and Pb^{2+}. van Leeuwen et al. [11] determined the Ra^{2+} selectivity of four ionizable thiacalix[4]crowns determined in the solutions containing a large excess of alkali and alkaline earth metals. They calculated the selectivity coefficients of Ra^{2+} over alkaline earth metals to be 3.5 for Mg^{2+}, Ca^{2+}, and Sr^{2+}. Owing to very similar chemical properties of Ra^{2+} and Ba^{2+}, those calixcrowns (except only one scaffold) showed no selectivity towards Ra^{2+} over Ba^{2+}.

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It is found that the 1,3-bridged calix[4]crowns exhibit high binding affinity and selectivity toward alkali and alkaline earth metal cations [12], while the researches on 1,2-bridged calix[4]crowns lag far behind. Combining crown ethers with calix[4]arenes increases the cation binding ability of the parent calixarenes, and control of the selectivity is obtained through modulation of the crown ether size [13–16]. Attachment of proton-ionizable groups to calixcrowns can further improve their extraction properties because the ionized group not only participates in metal ion coordination, but also eliminates the need to transfer aqueous phase anions into the organic phase. Ungaro et al. [17] reported the first di-proton-ionizable calix[4]crown-5 in 1984 and it showed quite high efficiency in extraction of divalent cations from water into dichloromethane. Combining crown ethers with calix[4]arenes increases the cation binding ability of the parent calixarenes [18–20]. The selectivity can be affected by the crown ether size, the identity of donor atoms on the crown ether moiety and the conformation of the calixarene platform. To further explore the influence of these factors on the extraction characteristics of *p*-*tert*-butylcalix[4]arene-1,2-crown ethers toward metal ions, series of di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-3 compounds in the cone conformation and the 1,2-alternate conformation, as well as *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-3 in the cone conformation have now been synthesized.

There are two kinds of side chain in the calixcrown skeleton that were studied including two ionizable carboxylic acid moieties and the crown-ether moieties. The ionizable moieties not only participate in cooperative metal ion coordination, but also eliminate the need to transfer the anions from the aqueous phase into the organic phase by operating in a cation-exchange mode with the metal cation. In this study, two proton-ionizable function groups were incorporated into calix[4]arene scaffold. A special feature of such modification is that the acidity of the ionizable moiety can be tunable by changing the functional group from hydroxyl to other groups due to different electron-withdrawing abilities of functional group. A wide range of pH environments can be examined when these ionizable groups are incorporated into the calixcrown skeleton. These extractants exhibit excellent extraction selectivity for alkali and alkaline earth metals.

In this study, three proton-ionizable calixcrowns with different proton-ionizable moieties were synthesized including cone *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diacid, 1,2-alternate *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diacid, and cone *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-3 diacid. Competitive solvent extractions of alkali metal cations and alkaline earth metal cations were performed using them, in which 1.0 mM solutions of di-ionizable calix[4]arene ligands in chloroform as well as the plots of cation loading of the organic phase *vs* the equilibrium pH of the aqueous phase were presented. In the following, the synthesis and the extraction procedures of three conformers were presented, respectively.

Synthesis of calix[4]crown-3 conformers

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. 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 500 MHz and ^{13}C 126 MHz) spectrometer in $CDCl_3$ with Me_4Si as internal standard unless mentioned otherwise. Chemical shifts (δ) are given in ppm downfield from TMS and coupling constants (J) values are in Hz.

The commonly employed method which involves the reaction of *p*-*tert*-butylcalix[4]arene (**1**) and diethylene glycol ditosylate in the presence of strong base failed to give *p*-*tert*-butylcalix[4]arene-1,2-crown-3 (**2**). Variations of the base, as well as elevating reaction temperature, were performed, but no detectable compound **2** was found. Another entirely different method was utilized for the synthesis of *p*-*tert*-butylcalix[4]arene-1,2-crown-3 (**2**) (Fig. 1). Under Mitsunobu reaction conditions, *p*-*tert*-butylcalix[4]arene (**1**) was treated with triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD) and reacted with diethylene glycol to form compound **2**. The reaction was quenched after 0.5 h and gave a 54% yield. Compared with the commonly used methods, the Mitsunobu reaction had a much shorter reaction time with a reasonable yield. Also, conversion of the diethylene glycol into diethylene glycol ditosylate was not necessary. *p*-*tert*-butylcalix[4]arene-1,2-crown-3 (**2**) was treated with sodium hydride in THF and reacted with ethyl bromoacetate at room temperature for 2 days to form *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diester (**3**) in the cone conformation in 61% yield. The synthesis procedure is shown in Fig. 1, schematically. The resulting diester **3** was hydrolyzed with aqueous tetramethylammonium hydroxide in THF under reflux to give diacid **4** in 88% yield. *p*-*tert*-butylcalix[4]arene-1,2-crown-3 (**2**) was treated with potassium hydride in THF and reacted with ethyl bromoacetate at room temperature for 3 days to form *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diester **5** in the 1,2-alternate conformation in 48% yield. The synthesis is depicted in

Fig. 1. The resulting diester **5** was hydrolyzed with aqueous tetramethylammonium hydroxide in THF under reflux to give diacid **6** in 96% yield.

Preparation of *p-tert*-butylcalix[4]arene-1,2-crown-3 (**2**)

To a mixture of *p-tert*-butylcalix[4]arene (6.50 g, 10 mmol), diethylene glycol (1.59 g, 15 mmol) and TPP (8.00 g, 30 mmol) in 200 mL of toluene, a 40% solution of DEAD (5.22 g, 30 mmol) in toluene was added dropwise. The mixture was stirred at room temperature for 0.5 h. Then the solution was evaporated to dryness and the residue was extracted with hexane (3 × 30 mL) followed by evaporation and subsequent stirring in hexane and ethyl acetate. The precipitate was filtered and the filtrate was purified by chromatography on silica gel with hexane–EtOAc (9:1) as eluent to give a white solid (3.90 g, 54%) with mp 198–199 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 3342 (O–H), 1249 and 1124 (C–O); ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 18 H, CH_3), 1.21 (s, 18 H, CH_3), 3.26–3.45 (m, 4 H, $ArCH_2Ar$), 4.01 (t, $J = 10.5$ Hz, 2 H, OCH_2CH_2O), 4.12 (t, $J = 11.0$ Hz, 2 H, OCH_2CH_2O), 4.28-4.46 (m, 7 H, OCH_2CH_2O, $ArCH_2Ar$), 4.82 (d, $J = 12.0$ Hz, 1 H, $ArCH_2Ar$), 6.94–7.06 (m, 6 H, ArH), 7.15 (d, $J = 2.0$ Hz, 2 H, ArH), 8.87 (s, 2 H, OH); ^{13}C NMR ($CDCl_3$): δ 31.30, 31.50, 32.66, 33.01, 33.90, 34.18, 75.32, 125.31, 125.58, 125.60, 126.45, 128.32, 128.84, 129.15, 133.88, 134.62, 142.81, 147.42, 149.14, 150.34. Anal. Calcd for $C_{48}H_{62}O_5$: C, 80.18; H, 8.69. Found: C, 80.08; H, 8.37%.

Preparation of cone *p-tert*-butylcalix[4]arene-1,2-crown-3 diester (**3**)

p-tert-butylcalix[4]arene-1,2-crown-3 (**2**) (5.00 g, 6.95 mmol) in 50 mL of THF was added dropwise into a mixture of NaH (0.85 g, 35.4 mmol) in 50 mL of THF. After stirring for 2 h at room temperature, ethyl bromoacetate (6.95 g, 41.7 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC. After 48 h, the reaction was quenched by careful addition of 0.01 N HCl and evaporated in vacuo. At room temperature, the residue was dissolved in CH_2Cl_2, the solution was washed with 0.01 N HCl and water, dried over $MgSO_4$, and the solvent was evaporated in vacuo. Chromatographic purification on silica gel with hexane–EtOAc (2:8) as eluent gave an oil (3.81 g, 61%). IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1760 (C=O), 1253 and 1128 (C–O); ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 18 H, CH_3), 1.12 (s, 18 H, CH_3), 1.34 (t, $J = 7.0$ Hz, 6 H, OCH_2CH_3), 3.09 (d, $J = 12.0$ Hz, 1 H, $ArCH_2Ar$), 3.18 (d, $J = 12.0$ Hz, 2 H, $ArCH_2Ar$), 3.24 (d, $J = 13.0$ Hz, 1 H, $ArCH_2Ar$), 3.83–3.92 (m, 2 H, OCH_2CH_2O), 4.07 (d, $J = 12.0$, 2 H, OCH_2CH_2O), 4.20 (m, 2 H, OCH_2CH_2O), 4.27 (q, $J = 7.0$, 4 H, OCH_2CH_3), 4.42 (d, $J = 10.5$ Hz, 2 H, OCH_2CH_2O), 4.54-4.65 (m, 3 H, $ArCH_2Ar$, OCH_2Ar), 4.88 (d, $J = 15.5$ Hz, 2 H, OCH_2CO), 4.96 (d, $J = 12.0$ Hz, 1 H, $ArCH_2Ar$), 6.76–6.84 (m, 4 H, ArH), 6.86 (d, $J = 2.5$ Hz, 2 H, ArH), 6.92 (d, $J = 2.0$ Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.33, 31.02, 31.32, 31.42, 33.82, 33.88, 53.42, 60.62, 72.03, 73.04, 75.24, 124.35, 125.39, 125.55, 132.72, 134.03, 134.35, 134.81, 144.84, 145.34, 152.88, 152.93, 170.28. Anal. Calcd for $C_{56}H_{74}O_9$: C, 75.47; H, 8.37. Found: C, 75.22; H, 8.23%.

Preparation of cone *p-tert*-butylcalix[4]arene-1,2-crown-3 diacid (**4**)

There were no peaks between 35 and 40 ppm in the ^{13}C NMR spectra for compound **4** revealing that all four benzene rings have *syn*-arrangements. In the ^{1}H NMR spectra for this compound, the bridging methylene protons are split into three pairs of doublets with an integration ratio of 1:2:1. *p-tert*-butylcalix[4]arene-1,2-crown-3 diester (**3**) (3.00 g, 3.05 mmol) in 60 mL of THF and 60 mL of 10% Me_4NOH was refluxed overnight. The solvent was evaporated in vacuo and the residue was dissolved in 100 mL of CH_2Cl_2. The organic layer was washed with 1 N HCl solution until pH 1, and then washed with 60 mL of brine

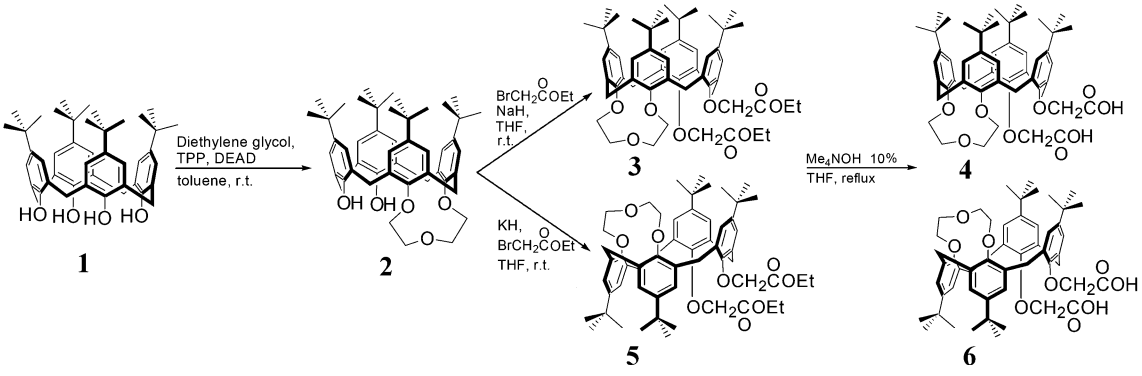


Fig. 1 Synthesis of *p-tert*-butylcalix[4]arene-1,2-crown-3 di-carboxylic acids (**4** and **6**)

and 60 mL of water, dried over MgSO$_4$, and evaporated in vacuo to give a white solid (2.49 g, 88%) with mp 255–256 °C. IR (deposit from CH$_2$Cl$_2$ solution on a NaCl plate) v_{max}/cm^{-1} 3217 (O–H), 1761 (C=O), 1203 and 1121 (C–O); ^{1}H NMR (CDCl$_3$): δ 1.07 (s, 18 H, CH$_3$), 1.11 (s, 18 H, CH$_3$), 3.12 (d, $J = 12.0$ Hz, 1 H, ArCH$_2$Ar), 3.22–3.36 (m, 3 H, ArCH$_2$Ar), 3.81–3.92 (m, 2 H, OCH$_2$CH$_2$O), 4.11 (d, $J = 12.5$ Hz, 2 H, OCH$_2$CH$_2$O), 4.20 (t, $J = 11.0$ Hz, 2 H, OCH$_2$CH$_2$O), 4.25–4.38 (m, 4 H, OCH$_2$CH$_2$O, ArCH$_2$Ar), 4.49 (d, $J = 13.0$ Hz, 1 H, ArCH$_2$Ar), 4.58 (d, $J = 16.5$ Hz, 2 H, OCH$_2$CO), 4.79 (d, $J = 16.5$ Hz, 2 H, OCH$_2$CO), 5.19 (d, $J = 12.5$ Hz, 1 H, ArCH$_2$Ar), 6.83-6.91 (m, 4 H, ArH), 6.93 (d, $J = 2.0$ Hz, 2 H, ArH), 6.99 (d, $J = 2.5$ Hz, 2 H, ArH); ^{13}C NMR (CDCl$_3$): δ 30.30, 30.60, 30.80, 31.24, 31.34, 33.90, 33.98, 53.41, 71.62, 73.63, 124.49, 125.47, 126.11, 126.19, 133.12, 133.25, 133.54, 134.94, 145.45, 146.80, 151.23, 152.71, 171.56. Anal. Calcd for C$_{52}$H$_{66}$O$_9$: C, 74.79; H, 7.97. Found: C, 74.50; H, 7.95%.

Preparation of 1,2-alternate *p-tert*-butylcalix[4]arene-1,2-crown-3 diester (**5**)

Calix[4]arene-1,2-crown-3 (**2**) (6.00 g, 8.34 mmol) in 60 mL of THF was added dropwise to a mixture of KH (4.17 g, 40% in mineral oil, 41.7 mmol) in 60 mL of THF at room temperature. After stirring for 2 h, ethyl bromoacetate (8.34 g, 50.04 mmol) was added and the reaction mixture was stirred for 3 days at room temperature. The reaction was quenched by careful addition of 0.01 N hydrochloric acid. The mixture was washed with 0.01 N HCl and water, dried over MgSO$_4$, and evaporated in vacuo. Chromatographic purification on silica gel with hexane–EtOAc (1:19) as eluent gave a white solid (3.60 g, 48%) with mp 205–206 °C. IR (deposit from CH$_2$Cl$_2$ solution on a NaCl plate) v_{max}/cm^{-1} 1760 (C=O), 1205 and 1132 (C–O); ^{1}H NMR (CDCl$_3$): δ 1.09 (t, $J = 7.0$ Hz, 6 H, SO$_2$CH$_3$), 1.31 (s, 18 H, CH$_3$), 1.33 (s, 18 H, CH$_3$), 2.48, (t, $J = 10.0$ Hz, 2 H, OCH$_2$CH$_2$O), 3.15, (d, $J = 12.5$ Hz, 1 H, ArCH$_2$Ar), 3.30–3.44 (m, 3 H, ArCH$_2$Ar, OCH$_2$CH$_2$O), 3.53–3.65 (m, 6 H, OCH$_2$CH$_2$O, OCH$_2$CO), 3.83 (d, $J = 17.0$ Hz, 2 H, OCH$_2$CO), 3.89–4.04 (m, 6 H, OCH$_2$CH$_3$, OCH$_2$CO), 4.07 (d, $J = 16.5$ Hz, 2 H, ArCH$_2$Ar), 4.54 (d, $J = 12.0$ Hz, 1 H, ArCH$_2$Ar), 4.77 (d, $J = 13.5$ Hz, 1 H, ArCH$_2$Ar), 6.97 (d, $J = 2.5$ Hz, 2 H, ArH), 7.07 (d, $J = 2.0$ Hz, 2 H, ArH), 7.32 (d, $J = 2.5$ Hz, 2 H, ArH), 7.42 (d, $J = 2.0$ Hz, 2 H, ArH); ^{13}C NMR (CDCl$_3$): δ 14.12, 29.20, 31.54, 31.58, 31.73, 34.07, 34.10, 39.14, 60.14, 69.37, 73.01, 74.43, 125.12, 125.43, 125.73, 125.89, 132.47, 133.06, 134.20, 135.24, 144.57, 145.57, 152.84, 152.96, 170.14. Anal. Calcd for C$_{56}$H$_{74}$O$_9$: C, 75.47; H, 8.37. Found: C, 75.50; H, 8.06%.

Preparation of 1,2-alternate *p-tert*-butylcalix[4]arene-1,2-crown-3 diacid (**6**)

The ^{13}C NMR spectra for compound **6** showed peaks at both 31 ppm and 38 ppm, revealing that the benzene rings have both *syn*- and *anti*-arrangements. In the ^{1}H NMR spectra for this compound, the bridging methylene protons are split into three pairs of doublets, with the integration ratio being 1:1:2. The *p-tert*-butylcalix[4]arene-1,2-crown-3 diester (4.00 g, 4.07 mmol) in 150 mL of THF and 150 mL of 10% Me$_4$NOH was refluxed overnight. The solvent was evaporated in vacuo and the residue was dissolved in 200 mL of CH$_2$Cl$_2$. 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 (3.60 g, 96%) with mp > 300 °C. IR (deposit from CH$_2$Cl$_2$ solution on a NaCl plate) v_{max}/cm^{-1} 3391 (O–H), 1760 (C=O), 1207 and 1128 (C–O); ^{1}H NMR (CDCl$_3$): δ 1.30 (s, 18 H, CH$_3$), 1.33 (s, 18 H, CH$_3$), 2.38, (t, $J = 11.0$ Hz, 2 H, OCH$_2$CH$_2$O), 3.19, (d, $J = 12.5$ Hz, 1 H, ArCH$_2$Ar), 3.24, (d, $J = 13.0$ Hz, 1 H, ArCH$_2$Ar), 3.49, (t, $J = 10.0$ Hz, 2 H, OCH$_2$CH$_2$O), 3.54–3.66 (m, 4 H, OCH$_2$CH$_2$O), 3.85 (d, $J = 17.5$ Hz, 2 H, ArCH$_2$Ar), 3.92 (d, $J = 17.0$ Hz, 1 H, ArCH$_2$Ar), 3.96 (d, $J = 17.0$ Hz, 1 H, ArCH$_2$Ar), 4.09 (d, $J = 15.5$ Hz, 2 H, OCH$_2$CO), 4.15 (d, $J = 16.0$ Hz, 2 H, OCH$_2$CO), 4.55 (d, $J = 12.0$ Hz, 1 H, ArCH$_2$Ar), 4.71 (d, $J = 12.5$ Hz, 1 H, ArCH$_2$Ar), 6.98 (d, $J = 2.0$ Hz, 2 H, ArH), 7.00 (d, $J = 2.0$ Hz, 2 H, ArH), 7.34 (d, $J = 2.5$ Hz, 2 H, ArH), 7.38 (d, $J = 2.0$ Hz, 2 H, ArH); ^{13}C NMR (CDCl$_3$): 29.54, 31.40, 31.59, 34.13, 34.20, 38.98, 68.32, 72.80, 74.47, 124.40, 125.22, 125.57, 126.54, 131.40, 131.86, 134.18, 134.84, 146.49, 146.52, 151.45,152.13, 170.37. Anal. Calcd for C$_{52}$H$_{66}$O$_9$·1.0C$_6$H$_6$: C, 76.29; H, 7.95. Found: C, 76.28; H, 8.11%.

Synthesis of cone calix[4]thiacrown-3

The *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 (**7**) was synthesized following the method used for making compound **2** (Fig. 2). Under Mitsunobu reaction conditions, *p-tert*-butylcalix[4]arene (**1**) was treated with triphenylphosphine (TPP) and diethylazodicarboxilate (DEAD) and reacted with 2,2′-thiodiethanol to form compound **7** in 29% yield.

Preparation of cone *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 (**7**)

To the mixture of *p-tert*-butylcalix[4]arene (**4**) (23.00 g, 35.49 mmol), 2,2′-thiodiethanol (6.49 g, 53.24 mmol) and TPP (27.92 g, 106.47 mmol) in 600 mL of toluene, a 40% solution of DEAD (46.35 g, 106.47 mmol) in toluene was added dropwise and the mixture was stirred at room temperature for 3 h. After reaction the solution was evaporated to dryness and the residue was extracted with hexane (3 × 300 mL). After filtration, the solvent was evaporated in vacuo. Purification by 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 (deposit from CH_2Cl_2 solution on a NaCl plate) v_{max}/cm^{-1} 3338 (O–H), 1247 (C–O); ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 18 H, CH_3), 1.21 (s, 18 H, CH_3), 3.17–3.26 (m, 2 H, OCH_2CH_2S), 3.29–3.41 (m, 6 H, $ArCH_2Ar$, OCH_2CH_2S), 3.93 (t, $J = 10.0$ Hz, 2 H, OCH_2CH_2S), 4.33 (d, $J = 13.0$ Hz, 2 H, $ArCH_2Ar$), 4.35 (d, $J = 13.5$ Hz, 1 H, $ArCH_2Ar$), 3.62–4.68 (m, 2 H, OCH_2CH_2S), 5.05 (d, $J = 12.0$ Hz, 1 H, v), 6.99 (d, $J = 2.5$ Hz, 2 H, ArH), 7.01 (d, $J = 2.5$ Hz, 2 H, ArH), 7.02 (d, $J = 2.5$ Hz, 2 H, ArH), 7.14 (d, $J = 2.5$ Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 31.21, 31.28, 31.49, 32.68, 33.00, 33.90, 34.17, 36.90, 53.36, 125.28, 125.54, 125.90, 126.36, 128.78, 128.90, 133.57, 134.75, 142.92, 147.48, 149.04, 150.19. Anal. Calcd for $C_{48}H_{62}O_4S$: C, 78.43; H, 8.50. Found: C, 78.75; H, 8.41%.

Preparation of cone *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 diester (**8**)

p-tert-butylcalix[4]arene-1,2-crown-3 (**7**) was treated with sodium hydride in THF and reacted with ethyl bromoacetate at room temperature overnight to form *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 diester **8** in the cone conformation in 61% yield. The synthesis is presented in Fig. 2. The resulting diester **8** was hydrolyzed with aqueous tetramethylammonium hydroxide in THF under reflux to give diacid **9** in 91% yield. *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 (**7**) (2.00 g, 2.72 mmol) in 40 mL of THF was added dropwise to a mixture of NaH (0.96 g, 8.16 mmol) in 40 mL of THF. After stirring for 2 h, ethyl bromoacetate (2.72 g, 16.32 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was monitored by TLC. The reaction was quenched with 0.01 N HCl, washed with 0.01 N HCl and water, dried over $MgSO_4$, and evaporated in vacuo. Chromatographic purification on silica gel with 3% EtOAc in hexanes gave a white solid (1.13 g, 46%) with mp 61–63 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) v_{max}/cm^{-1} 1759 (C=O), 1248 and 1128 (C–O); ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 18 H, CH_3), 1.12 (s, 18 H, CH_3), 1.34 (t, $J = 7.0$ Hz, 6 H, CH_2CH_3), 3.02–3.09 (m, 2 H, OCH_2CH_2S), 3.12 (d, $J = 12.5$ Hz, 1 H, $ArCH_2Ar$), 3.17 (d, $J = 12.5$ Hz, 2 H, $ArCH_2Ar$), 3.25 (d, $J = 12.5$ Hz, 1 H, $ArCH_2Ar$), 3.46–3.54 (m, 2 H, OCH_2CH_2S), 3.72–3.79 (m, 2 H, OCH_2CH_2S), 4.24–4.32 (m, 4 H, OCH_2CH_3), 4.50 (d, $J = 13.0$ Hz, 1 H, $ArCH_2Ar$), 4.52 (d, $J = 16.0$ Hz, 2 H, OCH_2CO), 4.71–4.77 (m, 2 H, OCH_2CH_2S), 4.78 (d, $J = 12.5$ Hz, 2 H, $ArCH_2Ar$), 4.90 (d, $J = 16.0$ Hz, 2 H, OCH_2CO), 5.29 (d, $J = 12.0$ Hz, 1 H, $ArCH_2Ar$), 6.78 (d, $J = 2.5$ Hz, 2 H, ArH), 6.80 (d, $J = 2.5$ Hz, 2 H, ArH), 6.86 (d, $J = 2.5$ Hz, 2 H, ArH), 6.90 (d, $J = 2.5$ Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.33, 30.91, 31.33, 31.42, 31.50, 31.66, 31.76, 33.82, 33.89, 34.99, 60.70, 72.14, 75.87, 124.75, 125.17, 125.45, 125.60, 132.45, 133.96, 134.17, 134.97, 144.99, 145.44, 152.67, 152.95, 170.21. 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%.

Preparation of cone *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 diacid (**9**)

There are no peaks at 35–40 ppm in the ^{13}C NMR spectra for compound **9**, revealing that all four benzene rings have *syn*-arrangements. In the ^{1}H NMR spectra for this compound, the bridging methylene group protons are split into three pairs of doublets, with the integration ratio of 1:2:1. *p-tert*-butylcalix[4]arene diester (**8**) (1.13 g, 1.25 mmol) in 30 mL of THF and 30 mL of 10% Me_4NOH was refluxed overnight. The solvent was evaporated in vacuo and the residue was dissolved in 100 mL of CH_2Cl_2. The organic solution was washed with 1 N HCl solution until pH 1, and then with brine (100 mL) and water (100 mL), dried over $MgSO_4$, and the solvent was evaporated in vacuo to give a white solid (0.90 g, (85%) with mp 202–205 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) v_{max}/cm^{-1} 3217 (O–H), 1760 (C=O), 1246 and 1127 (C–O); ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 18 H, CH_3), 1.12 (s, 18 H, CH_3), 3.07–3.14 (m, 2 H, OCH_2CH_2S), 3.15 (d, $J = 12.5$ Hz, 1 H, $ArCH_2Ar$), 3.27 (d, $J = 13.0$ Hz, 2 H, $ArCH_2Ar$), 3.31 (d, $J = 13.0$ Hz, 1 H, $ArCH_2Ar$), 3.67–3.75 (m, 2 H, OCH_2CH_2S), 4.33 (d, $J = 13.0$ Hz, 2 H, $ArCH_2Ar$), 4.49 (d, $J = 13.0$ Hz, 1 H, $ArCH_2Ar$), 4.58 (d, $J = 16.5$ Hz, 2

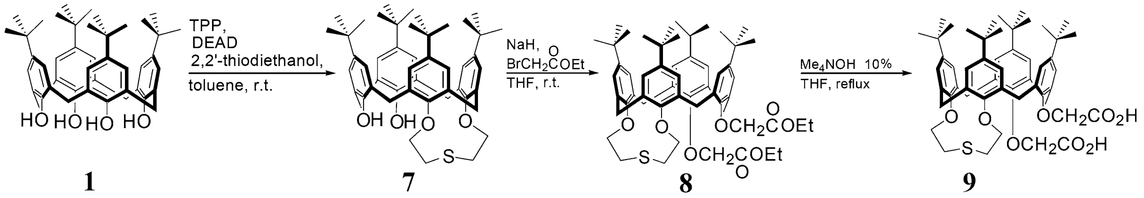


Fig. 2 Synthesis of *p-tert*-butylcalix[4]arene-1,2-thiacrown-3 di-carboxylic acid (**9**)

H, OCH_2CO), 4.59–4.66 (m, 2 H, OCH_2CH_2S), 4.78 (d, $J = 16.0$ Hz, 2 H, OCH_2CO), 5.29 (d, $J = 12.0$ Hz, 1 H, $ArCH_2Ar$), 5.59 (d, $J = 12.5$ Hz, 1 H, $ArCH_2Ar$), 6.86 (d, $J = 2.0$ Hz, 2 H, ArH), 6.88 (d, $J = 2.5$ Hz, 2 H, ArH), 6.91 (d, $J = 2.5$ Hz, 2 H, ArH), 6.97 (d, $J = 2.5$ Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 25.59, 30.63, 31.25, 31.35, 31.47, 31.60, 33.92, 33.97, 36.04, 67.96, 71.70, 77.59, 109.88, 124.80, 125.48, 125.93, 126.10, 133.09, 133.22, 133.33, 135.15, 145.64, 146.77, 151.40, 152.46, 171.58. Anal. Calcd for $C_{52}H_{66}O_8S$: C, 73.38; H, 7.82. Found: C, 73.12; H, 7.54%.

Experimental

Standard solutions

Lithium chloride (99%), rubidium chloride (99+ %) and cesium chloride (99+ %) were obtained from Alfa Aesar (Ward Hill, MA). Potassium chloride (99%) and sodium chloride (99%) were purchased from Mallinckrodt (Phillipsburg, NJ). Magnesium chloride hexahydrate (99%), calcium chloride dihydrate (98%), barium chloride dihydrate (99%) and strontium chloride hexahydrate (99%) were obtained from Aldrich. Lithium hydroxide was purchased from Fisher Scientific (Fair Lawn, NJ). Barium hydroxide octahydrate (98%) was purchased from MCB, hydrochloric acid (1.0 N) from J. T. Baker, and sulfuric acid (2.0 N) was obtained from Mallinckrodt. Chloroform was purchased from EM Science and was shaken with deionized water to remove the stabilizing ethanol and stored in the dark.

Sample preparation

The alkali metal cations were loaded into the aqueous solutions by adding stock solutions containing five alkali metal cations. The solutions of five alkali metal cations were made up as lithium, sodium, potassium, rubidium, and cesium chloride solutions (20.0 mM in each). The 20.0 mM lithium hydroxide and 0.01–1.0 M hydrochloric acid solutions were used to adjust the pH values of the aqueous phases.

The alkaline earth metal cations were loaded into the aqueous solutions by adding stock solutions containing 4 alkaline earth metal cations. The blend solutions of alkaline earth metal cations were made up as magnesium, calcium, barium, and strontium chloride solutions (20.0 mM in each). The pH values of the aqueous phases were adjusted using 4.0 mM barium hydroxide and 0.01 M hydrochloric acid solutions.

Extraction ability of calix[4]arene scaffolds were determined in thirteen solutions with pH range of 1.0–12.0 and 1.0–10.0 for alkali and alkaline earth cations, respectively. For each macrocyclic ligand, more than thirteen solutions for competitive solvent extraction of alkali or alkaline earth metals were prepared in 15 mL conical polypropylene centrifuge tubes. The samples contained 2.0 mL of the aqueous phase of 10.0 mM alkali or alkaline earth metals solution and 2.0 mL of 1.00 mM calixarene solution in chloroform.

Extraction procedure

In this research, the solvent extraction procedure as a sample preparation and a preconcentration method was used. The combined aqueous and organic phases were shaken for 5 min and were centrifuged for 5 min. The pH of the aqueous phase was measured using pH meter with a Corning 476157 combination pH electrode. In the stripping step, 1.5 mL of the organic phase was transferred to a capped conical centrifuge tube containing 3.0 mL of 0.10 M HCl. The stripping involved 5 min of mixing and 5 min of centrifuging. After that, 1.0 mL of the aqueous phase was diluted to 10.0 mL for analysis by ion chromatography.

Ion chromatographic analysis

Determinations of alkali or alkaline earth metals were accomplished by Dionex DX-120 ion chromatographs with a CS12A column, a conductivity detection and membrane suppression. Nitrogen pressure for the eluent was set at 50 psi. The eluent was 0.011 M sulfuric acid after filtration through a Millipore 0.22 μm filtration membrane, while the pump flow rate at 1,700 psi was about 1 mL/min. To obtain a stable baseline, the eluent was flowed through the column for 60 min and then, 2.0 mL of standard solutions were injected and they were repeated two other times. PeakNet software was used to manipulate the outputs from the ion chromatograph.

Results and discussions

Upon ionization, the di-ionizable calix[4]arene-1,2-crown-3 compounds form metal ion complexes with two anionic centers on the same side of the crown unit. Competitive solvent extractions of alkali metal cations (Li^+, Na^+, K^+, Rb^+, Cs^+) and alkaline earth metal cations (Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+}) were performed by 1.0 mM solutions of di-ionizable calix[4]arene ligands **4**, **6** and **9** in chloroform, and the plot of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase were obtained, as depicted in Figs. 3, 4 and 5, respectively.

Competitive solvent extractions by ligand **4**

For competitive extraction of such metal cations, di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-3 ligand **4** exhibit very different selectivity from their *p-tert*-butylcalix[4]arene-1,2-crown-4 and -crown-5 analogues. All five alkali metal cations and four alkaline earth metal cations were detectably extracted into the chloroform phase and the selectivity order was $Na^+ > Li^+ > K^+ \approx Rb^+ \approx Cs^+$ and $Mg^{2+} > Ca^{2+} \approx Ba^{2+} > Sr^{2+}$ for ligand **4**, respectively. The pH for half loading, $pH_{1/2}$, is a measure of the ligand acidity. For compound **4**, the $pH_{1/2}$ value was obtained to be 6 for binding to Na^+, 9.6 for binding to Li^+, K^+, Rb^+ and Cs^+. The $pH_{1/2}$ values for binding to alkaline earth metal cations were determined to be in the range of 9–9.5. Figure 3 depicted the plots of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase using ligands **4**.

Competitive solvent extractions by ligand **6**

For competitive solvent extractions of aqueous alkali and alkaline earth metal cation (10.0 mM in each) solutions by 1.0 mM solutions of di-ionizable *p-tert*-butylcalix[4]-arene1,2-crown-3 ligand **6** in chloroform, plots of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 4.

For competitive extraction of alkali and alkaline earth metal cations, di-ionizable *p-tert*-butylcalix[4]arene-1,2-crown-3 ligand **6** exhibit versatile selectivities for alkali and alkaline earth metal ion species. All five alkali metal cations and four alkaline earth metal cations were detectably extracted into the chloroform phase. The selectivity order was $Li^+ > Rb^+ > K^+ > Cs^+ > Na^+$ and $Ca^{2+} > Ba^{2+} > Mg^{2+} > Sr^{2+}$ for ligand **6**. For compound **6**, the $pH_{1/2}$ value was obtained to be 7 for binding to K^+, Rb^+ and Cs^+ and 9 for binding to Li^+ and Na^+. The $pH_{1/2}$ values for binding to alkaline earth metal cations were determined to be 8.5.

Competitive solvent extractions by ligand **9**

The *p-tert*-butylcalix[4]arene-1,2-thiocrown-3 ligand **9** exhibited very different selectivity from their *p-tert*-butylcalix[4]arene-1,2-crown-3 analogues in cone and 1,2-alternate conformers. All five alkali metal cations and four alkaline earth metal cations were detectably extracted into the chloroform phase and the selectivity order was $K^+ > Na^+ \gg Li^+ \approx Rb^+ \approx Cs^+$ and $Ba^{2+} \gg Mg^{2+} \approx Ca^{2+} \approx Sr^{2+}$ for ligand **9**, respectively. The loading of K^+ and Na^+ passed through a maximum value and decreased to initial values, respectively. The peak points in loading of K^+ and Na^+ by ligand 9 were determined to be 40 and 30%, respectively. These maximum loading conditions were observed in the pH range of 7–10. The $pH_{1/2}$ values were obtained to be 6 for binding to Na^+ and K^+, while the other alkali metal cations (Li^+, Rb^+ and Cs^+) showed no loading. The $pH_{1/2}$ values for binding to alkaline earth metal cations were determined to be 9. Figure 5 shows the plots of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase using ligands **9**.

The effect of calix[4]crown-3 conformation (cone and 1,2-alternate scaffolds) and inserting the sulfur atom in the crown ring of calix[4]crown-3 in the presence of two di-ionizable carboxylic acid moieties on the sensitivity (extraction efficiency), selectivity and $pH_{1/2}$ values of five alkali metals and four alkaline earth metals were determined and compared. Base upon the results, alternation of calix[4]crown-3 conformation from the cone to the 1,2-alternate led to changing the selectivity and the extraction efficiency. Calix[4]crown-3 in the 1,2-alternate conformation enhanced the overall extractions but declined the selectivity for both alkaline and alkaline earth metals. Such enhancements were referred to this fact that 1,2-alternate complexes can be formed by both inclusions at the upper (crown moiety) and the lower (acid moieties) sides; while in the case of cone conformers, the lower-rim position is the only inclusion space. Introducing the sulfur atom in the crown ring declined the overall extraction

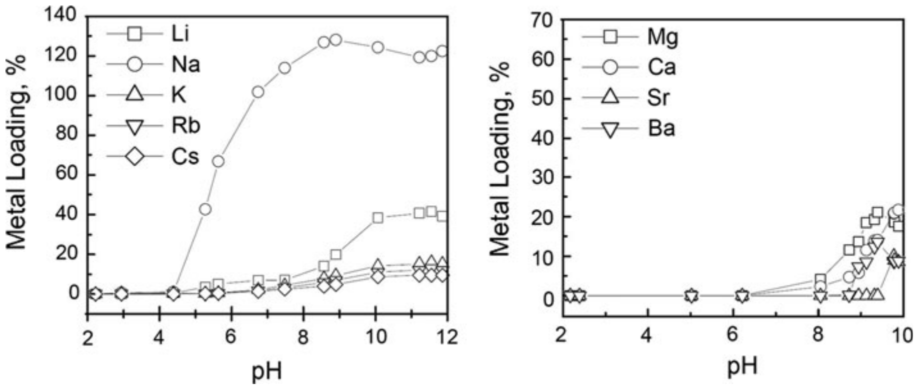


Fig. 3 Percent of metals loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkali and alkaline earth metal ions into chloroform by conformer **4**

Fig. 4 Percent of metals loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkali and alkaline earth metal ions into chloroform using conformer **6**

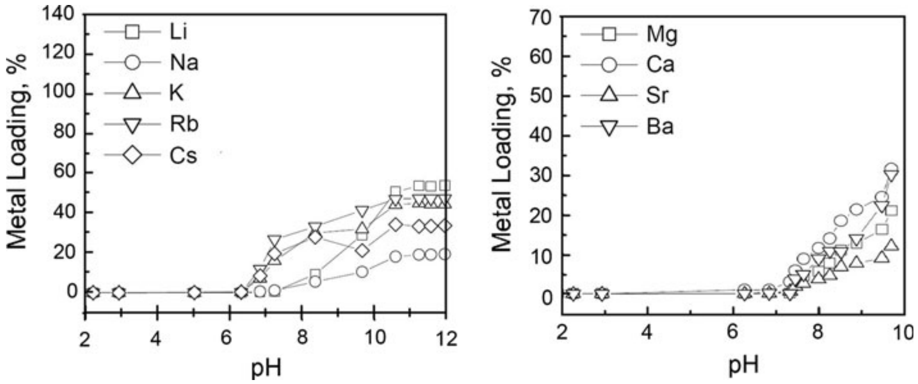
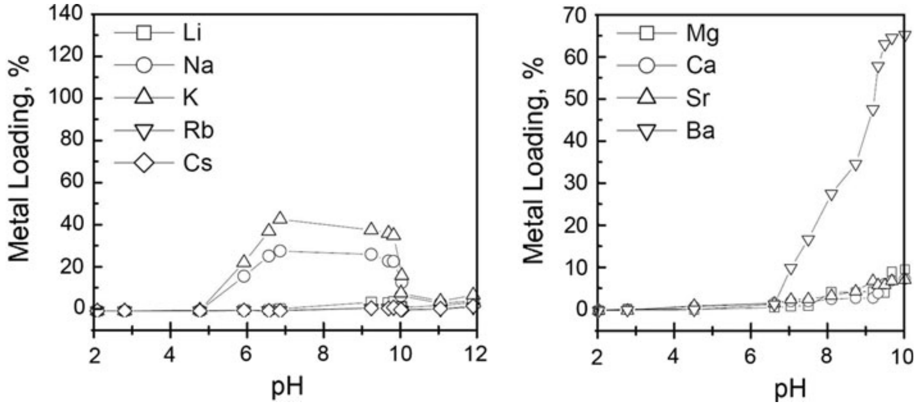


Fig. 5 Percent of metals loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkali and alkaline earth metal ions into chloroform using conformer **9**



efficiency but improved the selective extraction of Ba^{2+}. This high selectivity was attributed to enhanced binding of soft atoms (sulfur and barium).

Conclusions

The proton di-ionizable *p*-*tert*-butylcalix[4]arene-1,2-crown-3 in the cone and the 1,2-alternate conformation, as well as the *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-3 in the cone conformation, were synthesized as potential metal ion extractants and were verified by ^{1}H and ^{13}C NMR, IR and elemental analysis. The experiments carried out via the solvent extraction procedure as a preconcentration or a sample preparation method. Inserting the soft element of sulfur in the crown ether ring enhanced the loading percent of soft cations (Ba^{2+}). The $pH_{1/2}$ values not only depended to the conformer's structure but also were a function of the trapped cation. *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diacid in cone conformation showed selective extraction towards Na^{+} in $pH = 8$, while the *p*-*tert*-butylcalix[4]arene-1,2-crown-3 diacid in 1,2-alternate conformation was not selective to any cations of alkali or alkaline earth metals in the full pH range. *p*-*tert*-butylcalix[4]arene-1,2-thiacrown-3 diacid in cone conformation didn't show any selectivity towards alkali metals and was selective for Ba^{2+} extraction in $pH = 10$.

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