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Synthesis and metal ion extraction of calix[4]arene mono- and diacids with 2-methoxyethoxy pendant groups

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Abstract A mono-ionizable calix[4]arene-based ligand with three 2-methoxyethoxy pendant groups is synthesized. A di-ionizable analogue with two 2-methoxyethoxy pendant groups is also prepared. Competitive solvent extractions of alkali metal cations and of alkaline earth metal cations by these ligands are performed, as are single species extractions of Hg^{2+} and of Pb^{2+}. The number of proton-ionizable groups in the ligand is found to influence the metal ion binding behavior.

Keywords Mono-ionizable calixarene · Di-ionizable calixarene · Ionic recognition · Metal ion extraction · Solvent extraction

Introduction

Calixarenes have been widely utilized as building blocks for synthesizing receptors for ions and neutral molecules over the past 30 years [1, 2]. Some calixarene-based ligands are among the most effective synthetic ionophores for selective metal cation binding [3–5]. Incorporation of proton-ionizable groups (PIGs) can improve metal ion extraction efficiencies [6, 7]. The presence of PIGs eliminates the need to transport the counter anion into the organic phase by losing a proton upon formation of the ligand–metal ion complex. Carboxylic acid groups were the first acidic function to be attached to calix[4]arene. For a recent review, see [1], pp. 154–158. Proton-ionizable

calixarenes exhibit enhanced cation binding affinity and selectivity compared to non-ionizable analogues, such as calixarenes bearing ketone, ester or amide functions [8].

Previously, we have reported the synthesis and solvent extraction study results of some mono-ionizable calix[4]-arene-based ligands (Fig. 1). Compound **1** is a calix[4]ar-ene carboxylic acid with three methoxy groups on the lower rim [9]. Since methyl is small enough to rotate through the central cavity of calix[4]arene, ligand **1** is conformationally mobile. An NMR spectroscopic study of ligand **1** and Li^+ revealed that the complex mainly adopted a cone conformation. The conformationally rigid monoacid **2** in a locked cone conformation [10] has a better "preor-ganized" structure for Li^+ complexation and exhibits high selectivity for Li^+ over Na^+ and K^+.

Compared to butoxy groups, lower-rim 2-methoxyethoxy pendant groups could provide additional binding sites and influence the metal ion binding behavior of the ligand. In this article, we describe the synthesis of tri(2-methoxyeth-oxy)calix[4]arene mono(carboxylic acid) **3** (Fig. 2) and its metal ion extraction properties towards alkali metal cations (AMC) and alkaline earth metal cations (AEMC), as well as
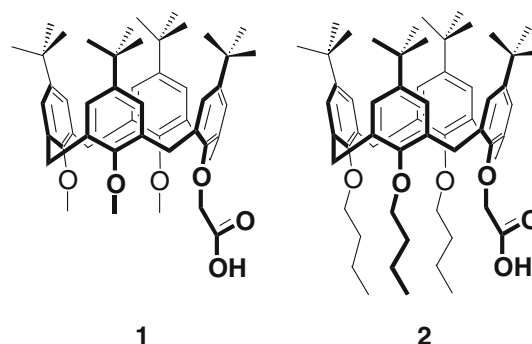
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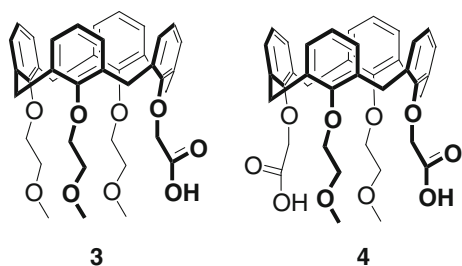Texas Tech University, Lubbock, TX 79409-1061, USA
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Fig. 1 Structures of two calix[4]arene mono(carboxylic acids)

Fig. 2 Structures of calix[4]arene mono(carboxylic acid) **3** and di(carboxylic acid) analogue **4**

Hg^{2+} and Pb^{2+}. The di-ionizable analogue diacid **4** is also prepared and solvent extractions of the same metal ion species are performed. The extraction data are compared to evaluate the influence of the number of proton-ionizable groups in the ligand on its metal ion complexation behavior.

Experimental

General

Reagents were purchased from commercial suppliers and used directly, unless noted otherwise. Calix[4]arene (**5**) was obtained from Eburon Organics International, Inc., of Lubbock, TX. 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 solutions onto NaCl plates. 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 (now Columbia Analytical Services) of Tucson, AZ.

Synthesis of cone 25-benzyloxy-26,27, 28-trihydroxycalix[4]arene (6)

Synthesis of calix[4]arene monobenzyl ether **6** was performed by adaptation of a literature procedure [11]. A slurry of calix[4]arene (**5**) (2.12 g, 5.00 mmol) and $NaOCH_3$ (0.32 g, 5.9 mmol) in MeCN (150 mL) was refluxed for 0.5 h before benzyl bromide (2.16 g, 12.60 mmol) was added. The mixture was refluxed for an additional 8 h. The solvent was removed in vacuo and the residue was recrystallized from $CHCl_3$–MeOH to afford **6** (1.54 g) in 58% yield

as a white solid with mp 228–230 °C (Lit mp [11]: 234–235 °C). IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3305 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.43 (2d, $J = 13.5$ Hz, 4H, $ArCH_2Ar$), 4.22 (d, $J = 13.5$ Hz, 2H, $ArCH_2Ar$), 4.35 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 5.19 (s, 2H, OCH_2Ar), 6.63–6.68 (m, 3H, ArH), 6.90 (t, $J = 7.5$ Hz, 1H, ArH), 6.96–7.01 (m, 4H, ArH), 7.02–7.05 (m, 2H, ArH), 7.10 (d, $J = 7.5$ Hz, 2H, ArH), 7.45–7.49 (m, 1H, ArH), 7.51–7.55 (m, 2H, ArH), 7.72–7.74 (m, 2H, ArH), 9.21 (s, 2H, OH), 9.56 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 31.6, 31.8, 79.3, 120.9, 121.9, 126.3, 128.3, 128.4, 128.7, 128.8, 129.0, 129.4, 134.3, 135.5, 149.1, 150.8, 151.2.

Synthesis of cone 25-benzyloxy-26,27,28-tris(2-methoxyethoxy)calix[4]arene (7)

Compound **6** (0.50 g, 0.97 mmol) was dissolved in DMF (50 mL). To the solution, NaH (0.28 g, 11.64 mmol) was added. The mixture was stirred at room temperature for 0.5 h. A solution of 2-methoxyethyl tosylate (1.34 g, 5.82 mmol) in DMF (50 mL) was added dropwise. The reaction was continued at room temperature for 4 days. The mixture was poured into cold aqueous 10% HCl (150 mL) and the solid was filtered. The filter cake was washed with water (200 mL) and then dissolved in CH_2Cl_2 (50 mL). The organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo to give the crude product, which was purified by chromatography on silica gel with hexanes-EtOAc (50:1–4:1 gradient) as eluent. Compound **7** (0.32 g) was obtained in 47% yield as a white solid with mp 92–94 °C. ^1H NMR ($CDCl_3$): δ 3.08 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 3.15 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 3.29 (s, 6H, OCH_3), 3.41 (s, 3H, OCH_3), 3.68–3.76 (m, 4H, OCH_2CH_2O), 3.83 (t, $J = 5.0$ Hz, 2H, OCH_2CH_2O), 4.03–4.13 (m, 6H, OCH_2CH_2O), 4.36 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 4.48 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 4.91 (s, 2H, OCH_2Ar), 6.45–6.51 (m, 6H, ArH), 6.66 (t, $J = 8.0$ Hz, 2H, ArH), 6.71–6.76 (m, 4H, ArH), 7.31-7.38 (m, 3H, ArH), 7.43–7.47 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 30.8, 30.9, 58.6, 58.7, 71.7, 71.9, 72.7, 73.1, 76.7, 122.2, 127.9, 128.0, 128.2, 128.4, 129.5, 134.5, 134.8, 135.4, 135.5, 137.8, 155.0, 155.8, 156.7. Calc. for $C_{44}H_{48}O_7$: C, 76.72%; H, 7.02%. Found: C, 76.47%; H, 7.17%.

Synthesis of cone 25-hydroxy-26,27, 28-tris(2-methoxyethoxy)calix[4]arene (8)

Compound **7** (2.40 g, 3.48 mmol) was dissolved in THF (30 mL) and 10% Pd/C (0.25 g) and absolute EtOH (30 mL) were added. The hydrogenolysis was carried out under 70 psi hydrogen pressure at room temperature overnight with a Parr pressure reaction shaker apparatus.

The catalyst was filtered and the filtrate was evaporated in vacuo to give **8** (1.77 g, 2.96 mmol) in 85% yield as a white solid with mp 125–128 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3538 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.22 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 3.31 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 3.45 (s, 6H, OCH_3), 3.46 (s, 3H, OCH_3), 3.76 (t, $J = 5.0$ Hz, 4H, OCH_2CH_2O), 3.94–4.04 (m, 4H, OCH_2CH_2O), 4.07–4.11 (m, 2H, OCH_2CH_2O), 4.14–4.18 (m, 2H, OCH_2CH_2O), 4.41 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 4.50 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 4.89 (s, 1H, OH), 6.38–6.45 (m, 6H, ArH), 6.77 (t, $J = 8.0$ Hz, 1H, ArH), 6.97 (t, $J = 8.0$ Hz, 1H, ArH), 7.10 (d, $J = 8.0$ Hz, 2H, ArH), 7.16 (d, $J = 8.0$ Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 30.6, 30.7, 58.8, 58.9, 71.2, 71.6, 71.7, 74.4, 119.1, 123.2, 123.3, 127.9, 128.1, 128.4, 129.2, 130.6, 132.7, 133.5, 136.9, 153.2, 154.0, 156.6. Calc. for $C_{37}H_{42}O_7$: C, 74.22%; H, 7.07%. Found: C, 74.00%; H, 6.94%.

Synthesis of cone 25-(ethoxycarbonylmethoxy)-26,27,28-tris(2-methoxyethoxy)calix[4]arene (9)

A mixture of **8** (0.30 g, 0.50 mmol) and NaH (0.08 g, 2.50 mmol) in DMF (50 mL) was stirred under nitrogen at room temperature for 1 h and ethyl bromoacetate (0.20 g, 1.10 mmol) was added. The mixture was stirred at 50 °C for 3 days. The mixture was poured into cold 10% aqueous HCl (150 mL) and the solid was filtered. The solid was washed with water (100 mL) and air dried. The crude product was chromatographed on silica gel with hexanes-EtOAc (20:1–2:1 gradient) to give monoester **9** (0.31 g) in 88% yield as a white solid with mp 94-96 °C. IR (deposit from CH_2Cl_2 solution on NaCl plate): 1759 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 3.16 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 3.20 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 3.41 (s, 9H, OCH_3), 3.80–3.90 (m, 6H, OCH_2CH_2O), 4.05–4.14 (m, 6H, OCH_2CH_2O), 4.22 (q, $J = 7.0$ Hz, 4H, OCH_2CH_3), 4.49 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 4.68 (d, $J = 14.0$ Hz, 2H, $ArCH_2Ar$), 4.73 (s, 2H, OCH_2), 6.50–6.58 (m, 6H, ArH), 6.62-6.67 (m, 2H, ArH), 6.71 (d, $J = 8.0$ Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 14.2, 30.7, 31.0, 58.6, 60.4, 71.0, 71.8, 71.9, 72.8, 73.2, 122.3, 122.6, 128.1, 128.2, 128.3, 128.5, 134.5, 134.7, 135.0, 135.3, 155.8, 156.0, 156.5, 170.2. Calc. for $C_{41}H_{48}O_9$: C, 71.91%; H, 7.06%. Found: C, 71.99%; H, 7.14%.

Synthesis of cone 25-(carbonylmethoxy)-26,27,28-tris(2-methoxyethoxy)calix[4]arene (3)

A solution of **9** (0.31 g, 0.44 mmol), 25 mL of 10% aqueous Me_4NOH and 25 mL of THF was refluxed for 24 h. After evaporation of the THF in vacuo, 20 mL of 6 N HCl was added to the residue. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (2 × 50 mL), dried over $MgSO_4$, and evaporated in vacuo to give 0.24 g (82%) of **3** as a white solid with mp 44–46 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3423 (OH), 1757 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.21 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 3.26 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 3.34 (s, 3H, OCH_3), 3.44 (s, 6H, OCH_3), 3.66-3.71 (m, 2H, OCH_2CH_2O), 3.76–3.83 (m, 4H, OCH_2CH_2O), 3.86–3.91 (m, 2H, OCH_2CH_2O), 4.05–4.10 (m, 2H, OCH_2CH_2O), 4.34 (t, $J = 6.0$ Hz, 2H, OCH_2CH_2O), 4.44 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 4.55 (d, $J = 13.0$ Hz, 2H, $ArCH_2Ar$), 4.74 (s, 2H, OCH_2), 6.39–6.43 (m, 4H, ArH), 6.48–6.51 (m, 2H, ArH), 6.91 (t, $J = 8.0$ Hz, 1H, ArH), 6.99 (t, $J = 8.0$ Hz, 1H, ArH), 7.11–7.17 (m, 4H, ArH), 11.06 (s, 1H, COOH). ^{13}C NMR ($CDCl_3$): δ 30.3, 30.6, 58.5, 58.8, 71.2, 71.3, 71.9, 73.7, 74.9, 123.0, 123.4, 124.3, 128.0, 128.5, 128.6, 129.3, 132.9, 133.8, 135.6, 136.2, 153.0, 155.2, 157.1, 170.7. Calc. for $C_{39}H_{44}O_9$: C, 71.32%; H, 6.75%. Found: C, 71.34%; H, 6.81%.

Synthesis of cone 25,27-bis(2-methoxyethoxy)-26,28-di(benzyloxy)calix[4]arene (11)

A mixture of **10** [12] (5.00 g, 8.30 mmol) and NaH (1.60 g, 66.20 mmol) in DMF (100 mL) was stirred under nitrogen at room temperature for 30 min. A solution of 2-methoxyethyl tosylate (7.61 g, 33.1 mmol) in DMF (50 mL) was added dropwise. After reaction at room temperature for 3 days, the mixture was poured into cold aqueous 10% HCl and stirred for 30 min. The solid was filtered and dissolved in CH_2Cl_2 (200 mL). The solution was washed with water (2 × 100 mL), dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was chromatographed on silica gel with CH_2Cl_2–hexanes (1:1) as eluent to give **11** (4.90 g, 82%) as a white solid with mp 158–160 °C. ^1H NMR ($CDCl_3$): δ 3.08 (d, $J = 13.5$ Hz, 4H, $ArCH_2Ar$), 3.14 (s, 6H, CH_3O), 3.60 (t, $J = 6.1$ Hz, 4H, OCH_2CH_2O), 4.05 (t, $J = 6.1$ Hz, 4H, OCH_2CH_2O), 4.38 (d, $J = 13.4$ Hz, 4H, $ArCH_2Ar$), 4.88 (s, 4H, OCH_2), 6.35 (d, $J = 7.2$ Hz, 4H, ArH), 6.37–6.44 (m, 2H, ArH), 6.70–6.79 (m, 2H, ArH), 6.85 (d, $J = 7.4$ Hz, 4H, ArH), 7.29–7.38 (m, 6H, ArH), 7.43–7.49 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 30.9, 58.5, 71.5, 72.5, 77.0, 122.2, 122.4, 127.8, 127.9, 128.2, 128.6, 129.3, 134.2, 135.8, 137.8, 154.8, 157.2. Calc. for $C_{48}H_{48}O_6$: C, 79.97%; H, 6.71%. Found: C, 79.98%; H, 6.82%.

Synthesis of cone 25,27-bis(2-methoxyethoxy)-26,28-dihydroxycalix[4]arene (12)

Compound **11** (4.85 g, 6.70 mmol) was mixed with 10% Pd/C (1.00 g), MeOH (150 mL) and THF (50 mL) in a

glass pressure reaction vessel. The hydrogenolysis was carried out under 70 psi of hydrogen pressure at room temperature overnight with a Parr pressure reaction shaker apparatus. The catalyst was filtered and the filtrate was evaporated in vacuo to give **12** (3.56 g, 99%) as a white solid with mp 218–220 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3356 (OH) cm^{-1}. ^1H NMR (CDCl$_3$): δ 3.36 (d, $J = 13.1$ Hz, 4H, ArCH$_2$Ar), 3.56 (s, 6H, CH$_3$O), 3.86–3.96 (m, 4H, OCH$_2$CH$_2$O), 4.12–4.22 (m, 4H, OCH$_2$CH$_2$O), 4.40 (d, $J = 13.1$ Hz, 4H, ArCH$_2$Ar), 6.65 (t, $J = 7.4$ Hz, 2H, ArH), 6.72 (t, $J = 7.6$ Hz, 2H, ArH), 6.89 (d, $J = 7.6$ Hz, 4H, ArH), 7.05 (d, $J = 7.4$ Hz, 4H, ArH), 7.83 (s, 2H, OH). ^{13}C NMR (CDCl$_3$): δ 31.2, 59.3, 71.4, 75.5, 118.9, 125.3, 128.2, 128.4, 128.9, 133.4, 151.9, 153.2. Calc. for $C_{34}H_{36}O_6$: C, 75.53%; H, 6.71%. Found: C, 75.08%; H, 6.62%.

Synthesis of cone 25,27-bis(ethoxycarbonylmethoxy)-26,28-bis(2-methoxyethoxy)calix[4]arene (13)

A mixture of **12** (3.50 g, 6.50 mmol) and NaH (0.62 g, 25.90 mmol) in DMF (100 mL) was stirred under nitrogen at room temperature for 0.5 h. Ethyl bromoacetate (1.58 mL, 14.20 mmol) was added dropwise. After reaction at room temperature overnight, the mixture was poured into cold aqueous 10% HCl and stirred for 0.5 h. The precipitate was filtered and the filter cake was dissolved in CH_2Cl_2 (200 mL). The organic phase was washed with water (2 × 100 mL), dried over MgSO$_4$, and evaporated in vacuo to produce the crude product which was recrystallized from CH_2Cl_2–MeOH giving **13** (3.69 g, 80%) as a white solid with mp 121–123 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1758 (C=O) cm^{-1}. ^1H NMR (CDCl$_3$): δ 1.29 (t, $J = 7.1$ Hz, 6H, OCH$_2$CH$_3$), 3.19 (d, $J = 13.5$ Hz, 4H, ArCH$_2$Ar), 3.40 (s, 6H, CH$_3$O), 3.81 (t, $J = 5.1$ Hz, 4H, OCH$_2$CH$_2$O), 4.09 (t, $J = 5.1$ Hz, 4H, OCH$_2$CH$_2$O), 4.22 (q, $J = 7.1$ Hz, 4H, OCH$_2$CH$_3$), 4.72 (d, $J = 13.4$ Hz, 4H, ArCH$_2$Ar), 4.74 (s, 4H, OCH$_2$), 6.50 (s, 6H, ArH), 6.65–6.73 (m, 2H, ArH), 6.77 (d, $J = 7.3$ Hz, 4H, ArH). ^{13}C NMR (CDCl$_3$): δ 31.0, 58.6, 60.4, 70.9, 72.0, 73.3, 122.4, 122.6, 128.1, 128.6, 134.4, 135.2, 155.9, 156.0, 170.3. Calc. for $C_{42}H_{48}O_{10}$: C, 70.77%; H, 6.79%. Found: C, 70.40%; H, 6.72%.

Synthesis of cone 25,27-bis(carboxymethoxy)-26,28-bis(2-methoxyethoxy)calix[4]arene (4)

A solution of **13** (3.50 g, 4.90 mmol), THF (200 mL), 25% aqueous Me$_4$NOH (100 mL), and water (50 mL) was refluxed overnight. The THF was evaporated in vacuo and the resulting aqueous solution was cooled in an ice-bath and acidified with 6 N HCl. The mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL), dried over MgSO$_4$, and evaporated in vacuo to give the crude product which recrystallized from CH_2Cl_2–MeOH to give **4** (2.90 g, 90%) as a white solid with mp 240–242 °C. IR (deposit from CH_2Cl_2 solution on NaCl plate): 3400–2900 (CO$_2$H), 1758, 1736 (C=O) cm^{-1}. ^1H NMR (CDCl$_3$): δ 3.27 (d, $J = 13.3$ Hz, 4H, ArCH$_2$Ar), 3.47 (s, 6H, CH$_3$O), 3.70–3.83 (m, 4H, OCH$_2$CH$_2$O), 3.92–4.04 (m, 4H, OCH$_2$CH$_2$O), 4.56 (d, $J = 13.2$ Hz, 4H, ArCH$_2$Ar), 4.80 (s, 4H, OCH$_2$), 6.36–6.49 (m, 6H, ArH), 7.01 (t, $J = 7.5$ Hz, 2H, ArH), 7.17 (d, $J = 7.4$ Hz, 4H, ArH), 9.99 (br s, 2H, CO$_2$H). ^{13}C NMR (CDCl$_3$): δ 30.4, 58.8, 70.9, 72.2, 75.8, 123.7, 124.3, 128.5, 129.3, 133.0, 135.3, 135.5, 152.3, 156.1, 171.0. Analysis calculated for $C_{38}H_{40}O_{10}$: C, 69.50%; H, 6.14%. Found: C, 69.44% ; H, 6.16%.

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 step 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 [13].

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

The procedure for single species extraction of Pb^{2+} was the same as that reported previously [13], except that a Shimadzu AA-6300 atomic absorption spectrophotometer was utilized.

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

An aqueous solution (3.0 mL) of 0.25 mM Hg(NO$_3$)$_2$ with Me$_4$NOH or HNO$_3$ for pH adjustment and 3.0 mL of 0.25 mM ligand solution in chloroform in a capped 15-mL polypropylene 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 sample was added to 100 mL of 1.0 N H$_2$SO$_4$ 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$_2$·H$_2$O 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 KMnO$_4$ in 5% H$_2$SO$_4$.

Results and discussion

Synthesis of the tri(2-methoxyethoxy)calix[4]arene mono (carboxylic acid) 3 is depicted in Scheme 1. Monobenzylation of calix[4]arene (5) was performed by modification of a reported procedure [11] to produce the monobenzyloxycalix[4]arene 6 in 58% yield. Compound 6 was reacted with NaH and 2-methoxyethyl tosylate in DMF to give the monobenzylated tris(2-methoxyethoxy)calix [4]arene 7 in 47% yield. Catalytic hydrogenolysis of 7 over Pd/C in EtOH/THF gave the monohydroxy tri(2-methoxyethoxy)calix[4]arene 8 in 85% yield. Monoester 9 was obtained in 88% yield by reaction of 8 with NaH and ethyl bromoacetate in DMF. Subsequent hydrolysis of 9 with Me$_4$NOH in aqueous THF gave an 82% yield of mono(carboxylic acid) 3.

Di(2-methoxyethoxy)calix[4]arene di(carboxylic acid) 4 was prepared using a similar synthetic strategy (Scheme 2). Although it was reported that 25,27-bis(2-methoxyethoxy)-calix[4]arene (12) could be obtained in 43% yield by reaction of calix[4]arene (5) with 2-methoxyethyl tosylate in refluxing MeCN with 2.0 equivalents of K$_2$CO$_3$ as the base [14], in our hands, this reaction produced a mixture of mono-, di- and tetra-substituted products. Therefore, an alternate pathway was adopted. A mixture of calix[4]arene 5, benzyl bromide, K$_2$CO$_3$, and MeCN gave 25,27-dibenzyloxycalix[4]arene 10 in 92% yield. Compound 10 was reacted with NaH and an excess of 2-methoxyethyl tosylate in DMF to give tetraether 11 in 82% yield. Catalytic hydrogenolysis of 11 cleaved the two benzyl groups to give 25,27-bis(2-methoxyethoxy)-26,28-dihydroxycalix[4]arene 12 quantitatively. Reaction of 12 with NaH and an excess of BrCH$_2$CO$_2$Et in DMF provided diester 13 in 80% yield. Subsequent hydrolysis of 13 with 10% aqueous NMe$_4$OH gave a 90% yield of di(carboxylic acid) 4.

Structures of new calix[4]arene ligands 3 and 4 and their synthetic precursors were verified by ^{1}H and ^{13}C NMR spectroscopy, IR spectrophotometry, and combustion analysis. By ^{1}H NMR spectroscopy, the cone conformations of the calix[4]arene frameworks were confirmed.

For competitive solvent extraction of AMC, aqueous solutions containing Li$^+$, Na$^+$, K$^+$, Rb$^+$, and Cs$^+$
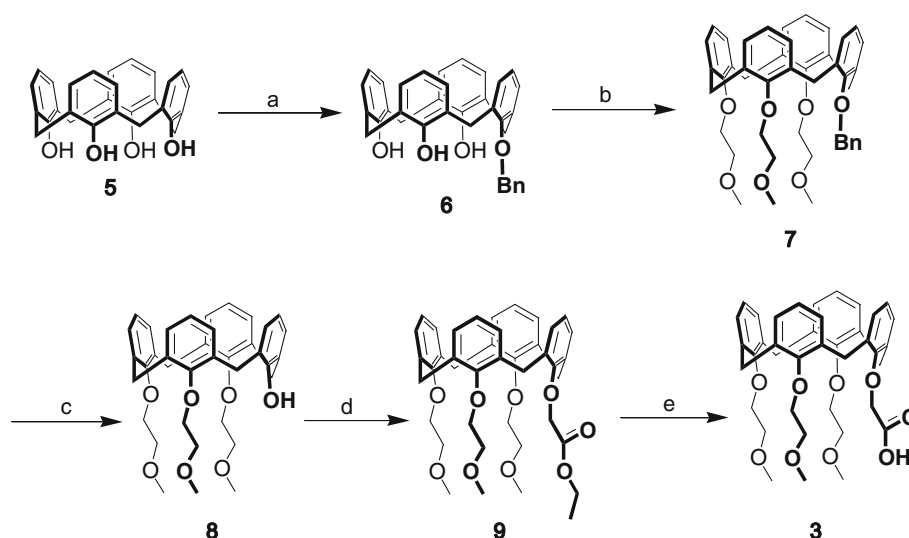
Scheme 1 Synthesis of tri(methoxyethoxy)calix[4]arene mono(carboxylic acid) 3. Reagents and conditions: a BnBr, NaOCH$_3$, MeCN, reflux; b CH$_3$OCH$_2$CH$_2$OTs, NaH, DMF, r.t.; c H$_2$, Pd/C, EtOH/THF, r.t.; d BrCH$_2$CO$_2$Et, NaH, DMF, r.t.; e Me$_4$NOH, aqueous THF, reflux

Scheme 2 Synthesis of di(methoxyethoxy)calix[4]arene di(carboxylic acid) **4**. Reagents and conditions: **a** BnBr, K$_2$CO$_3$, MeCN, reflux; **b** MeOCH$_2$CH$_2$OTs, NaH, DMF, r.t.; **c** H$_2$, Pd/C, THF/MeOH; **d** BrCH$_2$CO$_2$Et, NaH, DMF, r.t.; **e** 10% aqueous NMe$_4$OH, THF, reflux
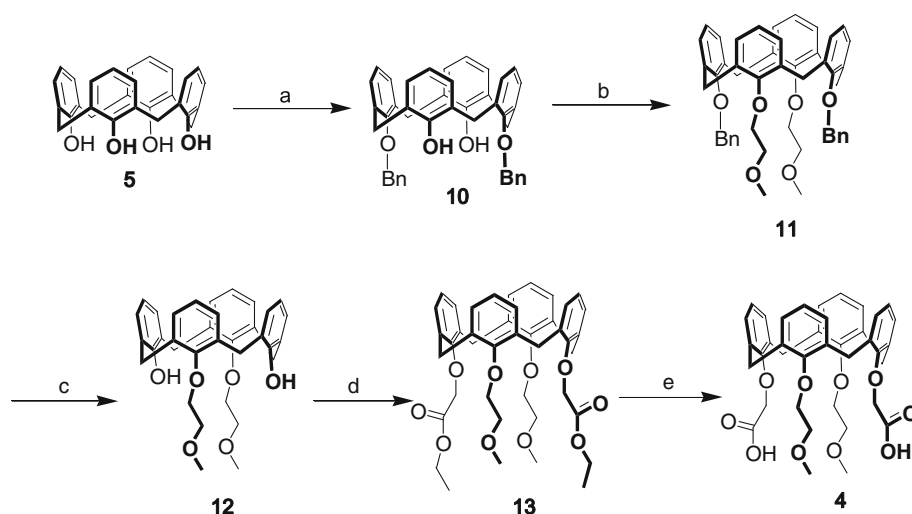
(10.0 mM in each) chlorides were extracted with 1.0 mM solutions of ligands **3** and **4** in chloroform. Plots of metal ion loadings of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 3. Note that the theoretical total metal loadings for ligands **3** and **4** are different. For diacid **4**, the maximal total loading for monovalent cations is 200%, but 100% is the maximal total loading for monoacid **3**. In low pH regions, no deprotonation occurs for the proton-ionizable groups in ligands **3** and **4** and the metal ion loading is negligible. This shows that the non-ionized forms of the ligands are ineffective

extractants. Observed maximal total AMC loadings for ligands **3** and **4** are 80 and 160%, respectively. This suggests that the two carboxylic acid groups in ligand **4** are operating independently in AMC extraction.

The two ligands have very similar binding behavior towards AMC. Both ligands show an AMC extraction order of Na$^+$ > Li$^+$ >> K$^+$, Rb$^+$, Cs$^+$ at maximal loading. Extractions of Na$^+$ and Li$^+$ by the monoacid **3** take place concurrently. On the other hand, diacid **4** exhibits high selectivity for Na$^+$ extraction at weakly acidic pH until the Li$^+$ extraction commences at neutral pH.
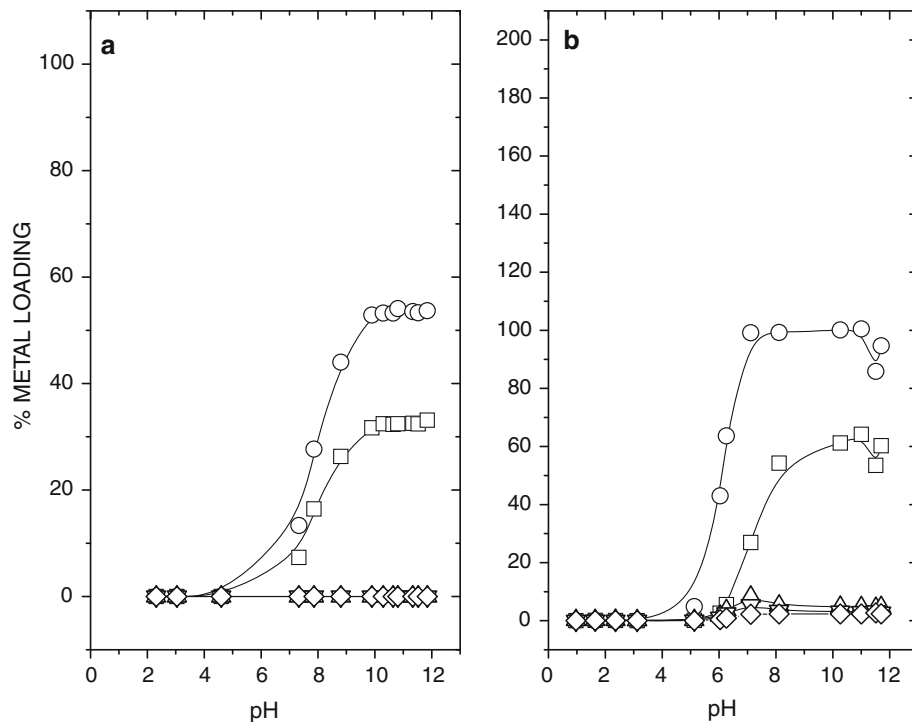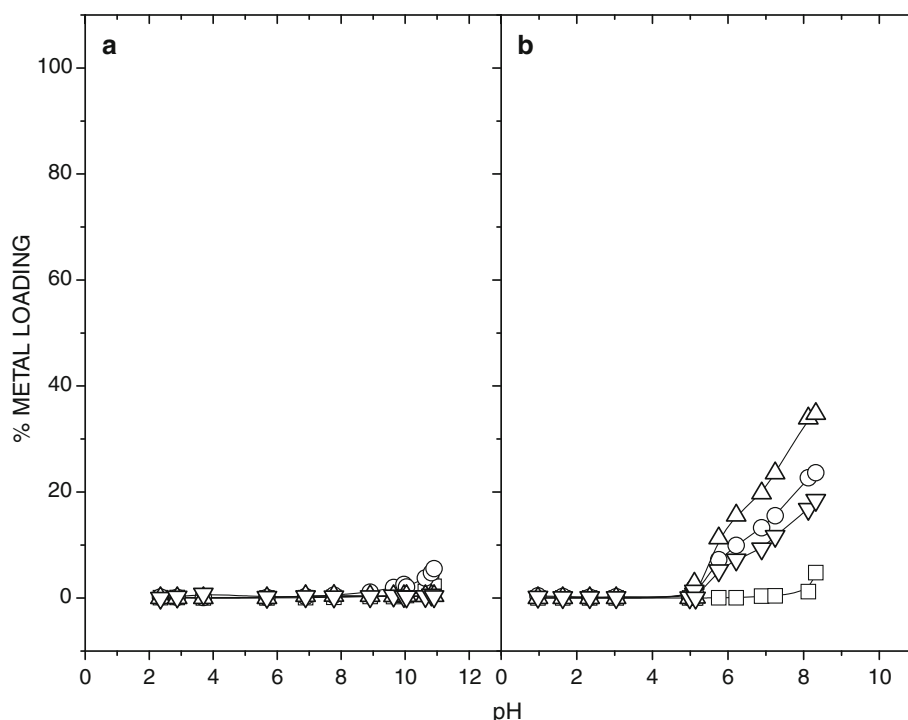
Fig. 3 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive solvent extraction of alkali metal cations into chloroform by **a** tri(2-methoxyethoxy)calix[4]arene mono(carboxylic acid) **3** and **b** di(2-methoxyethoxy)-calix[4]arene di(carboxylic acid) **4**. (*square* Li$^+$, *circle* Na$^+$, *triangle* K$^+$, *inverted triangle* Rb$^+$, *diamond* Cs)

Fig. 4 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** tri(2-methoxyethoxy) calix[4]arene mono (carboxylic acid) **3** and **b** di(2-methoxyethoxy)- calix[4]arene di(carboxylic acid) **4**. (*square* Mg^{2+}, *circle* Ca^{2+}, *triangle* Sr^{2+}, *inverted triangle* Ba^{2+})

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 **3** and **4** in chloroform. For the competitive AEMC extractions, plots of metal loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 4.

The AEMC extraction results for the two ligands is quite different. As is readily apparent, monoacid **3** is an ineffective extractant toward all of the AEMC species. Diacid **4**, on the other hand, shows appreciable AEMC extraction at alkaline pHs. The AEMC extraction selectivity order for diacid **4** is $Sr^{2+} > Ca^{2+} > Ba^{2+} > Mg^{2+}$, with maximal metal loading near 80% under the most alkaline conditions employed. The marked difference in AEMC extraction efficiency is readily understood when the matching between the charges in the ionized ligand and the AEMC are considered. When ionized, ligand **4** produces a dianion that can form an electroneutral extraction complex with the divalent metal ion. Formation of an electroneutral extraction complex for ligand **3** would require an unfavorable 2:1 (ionized ligand:divalent metal ion) stoichiometry.

Aqueous solutions of Pb^{2+} (1.0 mM) nitrate were extracted with 0.50 mM solutions of ligands **3** and **4** in chloroform. Plots of metal loadings of the organic phase versus the equilibrium pH of the aqueous phase by ligand **3** (closed squares) and **4** (open circles) are presented in Fig. 5. The single species extraction results for the two ligands are again strikingly different. Diacid **4** is a very effective extractant for Pb^{2+} from acidic solutions with a
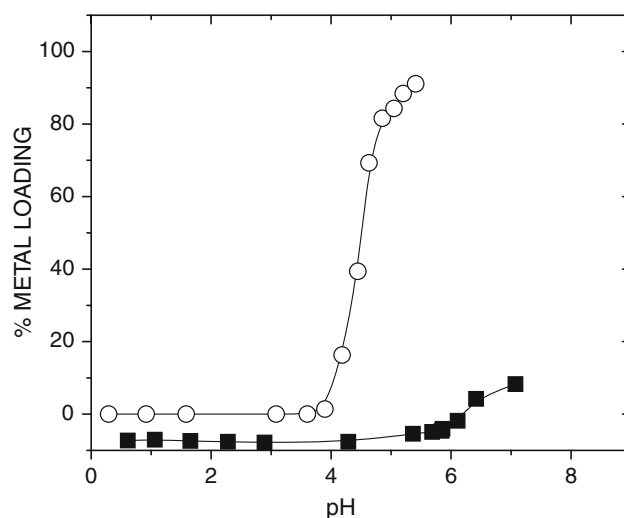

Fig. 5 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} into chloroform by **a** tri(2-methoxyethoxy)-calix[4]arene mono(carboxylic acid) **3** (*filled squares*) and **b** di(2-methoxyethoxy)calix[4]arene di(carboxylic acid) **4** (*open circles*)

maximal loading greater than 90%. In contrast, monoacid **3** is a poor extractant for the Pb^{2+} with a maximal loading of only about 10%.

Aqueous solutions of Hg^{2+} (0.25 mM) nitrate were extracted with 0.25 mM solutions of ligands **3** and **4** in chloroform. Plots of metal loadings of the organic phase versus the equilibrium pH of the aqueous phase by ligands
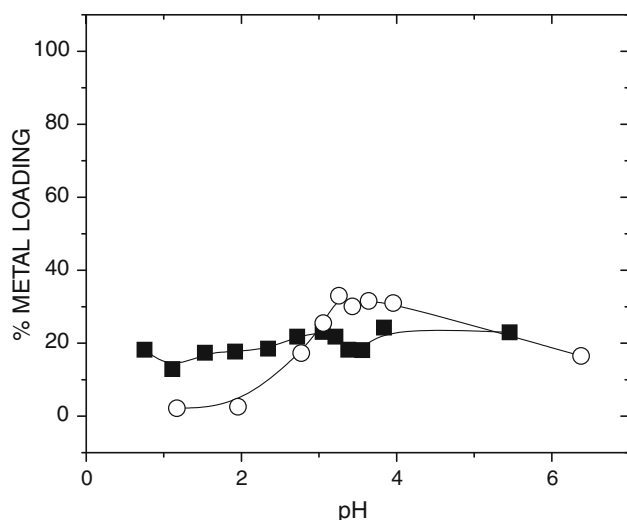
Fig. 6 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for single species solvent extraction of Hg^{2+} into chloroform by **a** tri(2-methoxyethoxy)calix[4]arene mono(carboxylic acid) **3** (*filled squares*) and **b** di(2-methoxyethoxy)calix[4]arene di(carboxylic acid) **4** (*open circles*)

3 (closed squares) and **4** (open circles) are presented in Fig. 6. Both ligands are found to be ineffective extractants for Hg^{2+}.

Presumably the difference in extraction propensities of di(carboxylic acid) ligand **4** towards the AEMC and Pb^{2+} on the one hand and Hg^{2+} on the other results from the hardness of the former divalent metal ions.

Summary

Syntheses of two new proton-ionizable calix[4]arenes with combinations of 2-methoxyethoxy and carboxymethoxy groups on the lower rims are reported. The metal ion complexation propensities of mono(carboxylic acid) ligand **3** and di(carboxylic acid) ligand **4** are compared in solvent extractions of AMC, AEMC, Pb^{2+}, and Hg^{2+} into chloroform. When extracting AMC, the two ligands exhibit similarities which reveal that two ionizable groups in **4** act independently. For extraction of the hard divalent metal ion species of AEMC and Pb^{2+}, ligand **4** is effective, but ligand **3** is not. For extraction of the soft divalent metal ion species Hg^{2+}, neither ligand is effective.

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