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ORIGINAL ARTICLE

Effect of conformation on metal ion extraction by calix[4]arene dicarboxylic acids

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Abstract Synthetic routes to four calix[4]arene stereoisomers with two distal methoxycarboxy groups and two distal butoxy groups are reported. Conformations of cone, partial cone (butyl up), partial cone (acid up), and 1,3-alternate were established by ^{1}H and ^{13}C-NMR spectroscopy. To probe the influence of ligand conformation on metal ion complexation, extractions from aqueous solutions into 1,2-dichloroethane were performed. These included competitive alkali metal cation extractions, competitive alkaline earth metal cation extractions, and single species extractions of Pb^{2+} and of Hg^{2+}. Comparisons are also made with the results for a conformationally mobile analogue in which the two butoxy groups are replaced with methoxy groups.

Keywords Di-ionizable calixarene ligand · Calix[4]arene dicarboxylic acid · Metal ion extraction · Conformations

Introduction

Calix[*n*]arenes are employed as building blocks for ionic and molecular receptors [1–9]. Calixarene molecules may adopt different conformations by rotation of the phenolic units. For calix[4]arene compounds, the four limiting conformations are cone, partial cone, 1,3-alternate and 1,2-alternate (Fig. 1). Attachment of groups larger than ethyl to the phenolic oxygens in calix[4]arene restricts rotation of the phenolic units and gives rise to stereoisomers [10]. Of these, the 1,2-alternate conformation [11] is the least commonly encountered. In the preparation of host molecules for metal ion recognition, cone conformations of calix[4]arenes were utilized initially as scaffolds to which a variety of functional groups were attached, including amides, esters, ethers, etc. As other conformational isomers became available, the influence of conformation upon the complexation properties was assessed. For certain metal cations, the 1,3-alternate and/or partial cone isomers were found to possess higher affinities than the cone isomers [12, 13].

With one or more acidic groups attached to the calixarene, proton-ionizable calixarene ligands are formed [14]. When utilized in metal ion extractions, such ligands are more efficient than non-ionizable analogues since concomitant transfer of one of more aqueous phase anions into the organic medium is no longer required.

We now report synthetic routes to stereoisomers **1**–**4** (Fig. 2) of calix[4]arene with two distal methoxylcarboxy groups and two distal butyl groups attached to the four phenolic oxygens. For these di-ionizable calix[4]arene stereoisomers, the conformations are cone, partial cone (butyl up), partial cone (acid up), and 1,3-alternate, respectively. The influence of conformation on the metal ion complexing abilities of these four calix[4]arene dicarboxylic acid stereoisomers is probed by solvent extraction and compared with results for the conformationally mobile analogue **5** [15] in which the two butoxy groups have been replaced by methoxy units.

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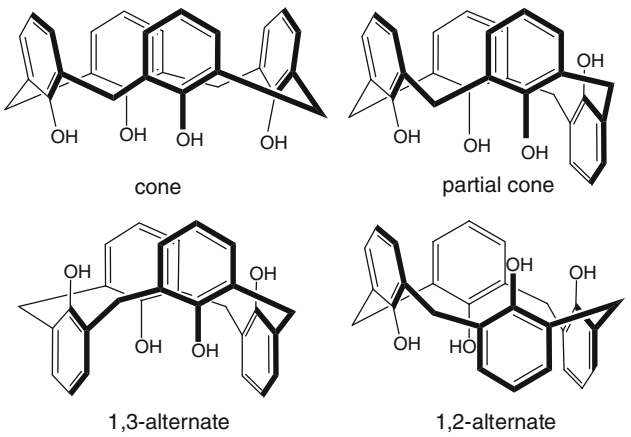


Fig. 1 The four limiting conformations of calix[4]arene

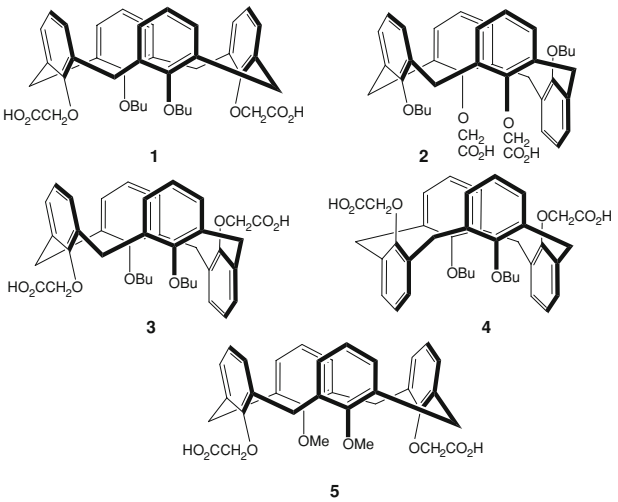


Fig. 2 Structures of calix[4]arene dicarboxylic acids locked in the cone (**1**), partial cone (butyl up) (**2**), partial cone (acid up) (**3**), and 1,3-alternate (**4**) conformations and of the conformationally flexible analogue **5**

Experimental

Chemicals

Reagents were purchased from commercial suppliers and used as received unless indicated otherwise. THF was dried over sodium with benzophenone as indicator and distilled immediately before use. DMF was stirred over CaO overnight and the mixture was filtered. The filtrate was refluxed with CaH_2 for 2 h and distilled under vacuum. The distillate was stored over 4 Å molecular sieves. Benzene, MeCN, toluene and hexanes were stored over 4 Å molecular sieves. K_2CO_3 and Cs_2CO_3 were activated by heating at 150 °C for 2–3 h under high vacuum immediately before use. Calix[4]arene (**6**) was prepared by a reported method [16]. Calix[4]arene dicarboxylic acid **5** was synthesized by a literature procedure [15]. For the solvent extraction experiments, reagent-grade 1,2-dichloroethane was washed with water, distilled, and saturated with water.

Apparatus

Melting points were determined with a Mel-Temp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 1600 FT-IR spectrophotometer as films deposited from CH_2Cl_2 solutions onto NaCl plates and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C-NMR spectra were recorded with an IBM AF 300 (^1H 300 MHz and ^{13}C 75 MHz) or Varian 500 MHz FT-NMR (^1H 500 MHz and ^{13}C 126 MHz) spectrometer with $CDCl_3$ as the solvent, unless specified otherwise. The ^1H-NMR chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and the ^{13}C-NMR chemical shifts (δ; in ppm) are referenced to $CDCl_3$. Elemental analysis was performed by Desert Analytics Laboratory/Columbia Analytical Services of Tucson, Arizona.

For the solvent extraction experiments, vortexing was performed with a Glas-Col Multi-Pulse Vortex Mixer and centrifugation was conducted with a Clay Adams Compact II Centrifuge. Alkali metal cation concentrations were determined with a Dionex DX-120 ion chromatograph with a CS12A column with conductivity detector and a self-regenerating cation suppressor (CSRS-II 4 mm). The pH was measured with a Fisher Accumet AR25 pH meter with a Corning 476157 combination electrode.

Ligand synthesis

25,27-Dibutoxy-26,28-dihydoxycalix[4]arene in the cone conformation (7)

To a solution of calix[4]arene (**6**) (11.10 g, 24.55 mmol, complexed with 0.26 equivalent of CH_2Cl_2) and K_2CO_3 (13.66 g, 98.2 mmol) in DMF (190 mL), 1-bromobutane (13.54 g, 98.2 mmol) was added. The reaction mixture was stirred at 90 °C for 48 h under nitrogen. Additional 1-bromobutane (6.77 g, 49.1 mmol) was added and the reaction mixture was stirred for 24 h under the same conditions. Additional 1-bromobutane (3.39 g, 24.55 mmol) was added and the reaction mixture was stirred for 24 h under the same conditions. A small amount of water was added and the DMF was removed by vacuum distillation

to give a brown solid. The solid was dissolved in CH_2Cl_2 (200 mL) and the resulting solution was washed with 1 N HCl (2 × 80 mL) and H_2O (30 mL), dried over $MgSO_4$, and evaporated in vacuo to produce a yellow solid. Chromatography on silica gel with CH_2Cl_2 as eluent gave a white solid, which was recrystallized from CH_2Cl_2-MeOH to give **7** as a white solid (8.15 g, 62%) with mp 244–247 °C. IR (deposit from a CH_2Cl_2 solution on a NaCl plate): 3286 (O–H) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.09 (t, $J = 7.4$ Hz, 6H), 1.75–1.82 (m, 4H), 2.01–2.15 (m, 4H), 3.38 (d, $J = 12.9$ Hz, 4H), 4.01 (t, $J = 6.4$ Hz, 4H), 4.32 (d, $J = 12.9$ Hz, 4H), 6.64 (t, $J = 7$ Hz, 2H), 6.74 (t, $J = 7$ Hz, 2H), 6.92 (d, $J = 7$ Hz, 4H), 7.05 (d, $J = 7$ Hz, 4H), 8.27 (s, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.08, 19.39, 31.41 ($ArCH_2Ar$), 32.25, 76.52, 118.93, 125.25, 128.15, 128.39, 128.88, 133.46, 151.95, 153.34. Anal. Calcd. for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.81; H, 7.68.

*25,27-Dibutoxy-26,28-bis[(methoxycarbonyl)-methoxy]calix[4]arene in the cone conformation (**8**)*

To a solution of **7** (4.77 g, 8.89 mmol) in DMF (50 mL) under nitrogen, NaH (0.91 g, 35.6 mmol) and DMF (10 mL) were added. The mixture was stirred for 1 h at room temperature and a solution of methyl bromoacetate (5.44 g, 35.6 mmol) in DMF (10 mL) was added. The mixture was stirred at 80 °C for 48 h under nitrogen. After cooling, a small amount of water was added carefully and then the DMF was removed by distillation under vacuum. The brown residue was dissolved in CH_2Cl_2 (80 mL). The solution was washed with H_2O (50 mL), dried over $MgSO_4$, and evaporated in vacuo to give a yellow solid, which was chromatographed on a short column of alumina with EtOAc as eluent to give a white solid. (This crude product was used directly in the synthesis of diacid **1**. Only for characterization was further purification performed.)

Recrystallization from CH_2Cl_2-MeOH gave **8** as a white solid with mp 110–112 °C. IR (deposit from CH_2Cl_2 on a NaCl plate): 1765 and 1741 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz. $CDCl_3$): δ 0.99 (t, $J = 7.4$ Hz, 6H), 1.44–1.51 (m, 4H), 1.82–1.88 (m, 4H), 3.21 (d, $J = 13.7$ Hz, 4H), 3.75 (s, 6H), 3.83 (t, $J = 7.2$ Hz, 4H), 4.66 (d, $J = 13.7$ Hz, 4H), 4.75 (s, 4H), 6.30 (d, $J = 7$ Hz, 4H), 6.37 (dd, $J = 8$, 6 Hz, 2H), 6.81 (t, $J = 7$ Hz, 2H), 6.92 (d, $J = 7$ Hz, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.07, 19.35, 31.19 ($ArCH_2Ar$), 32.11, 51.34, 70.46, 75.04, 122.22, 122.56, 127.72, 128.91, 133.75, 135.78, 155.75, 156.44, 170.59. Anal. Calcd. for $C_{42}H_{48}O_8$: C, 74.10; H, 7.11. Found: C, 74.00; H, 7.12.

*25,27-Dibutoxy-26,28-bis[(methoxycarbonyl)methoxy]-calix[4]arenes in the partial cone (carbonyl-up) (**9**) and 1,3-alternate (**10**) conformations*

To a suspension of KH (6.42 g, 35% dispersion in mineral oil, 55.9 mmol, washed with dry hexanes) in THF (80 mL) under nitrogen, a solution of **7** (6.00 g, 11.2 mmol) in THF (80 mL) was added at room temperature. The mixture was stirred for 1 h and a solution of methyl bromoacetate (6.84 g, 44.7 mmol) in THF (20 mL) was added. The mixture was stirred for 3 days at room temperature and then a small amount of water was added dropwise. The THF was evaporated in vacuo. To the residue CH_2Cl_2 (100 mL) and 1 N HCl (50 mL) were added. The organic layer was separated, washed with H_2O (50 mL), dried over $MgSO_4$, and evaporated in vacuo to produce a pale yellow solid. The ^{1}H-NMR spectrum of this solid indicated the relative ratio of isomers was partial cone (carboxyl up) (65%) and 1,3-alternate (35%). The solid was chromatographed on silica gel with hexanes and EtOAc-hexanes (1:10), (1:8), (1:5) as eluents to give two major products. The first-eluted product was a white solid (4.00 g, partial cone (carbonyl up) diester **9**) and the second-eluted product was a white solid (2.15 g, 1,3-alternate diester **10**). (These products were used directly in the synthesis of diacids **3** and **4**. Only for characterization was further purification performed.)

After recrystallization from CH_2Cl_2-MeOH, diester **9** was obtained as a white solid with mp 146–148 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1763 and 1740 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.00 (t, $J = 7.3$ Hz, 6H), 1.46–1.54 (m, 4H), 1.78–1.85 (m, 4H), 3.15 (d, $J = 14$ Hz, 2H), 3.59 (s, 3H), 3.62–3.70 (m + d, $J = 12.8$ Hz, 4H), 3.76–3.80 (m + d, $J = 12.8$ Hz, 4H), 3.84 (s, 3H), 3.94 (s, 2H), 4.32 (d, $J = 14$ Hz, 2H), 4.39 (s, 2H), 6.25 (t, $J = 7$ Hz, 2H), 6.47 (t, $J = 7$ Hz, 2H), 6.87 (t, $J = 7$ Hz, 1H), 6.96 (t, $J = 7$ Hz, 1H), 7.04–7.07 (m, 4H), 7.28 (d, $J = 7.0$ Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.07, 19.41, 31.68, 32.59, 35.11 ($ArCH_2Ar$), 50.91, 51.82, 66.67, 70.06, 74.25, 122.15, 122.18, 128.48, 128.84, 129.17, 130.59, 131.89, 133.34, 133.94, 136.34, 154.80, 155.80, 156.63, 169.89, 170.98. Anal. Calcd. for $C_{42}H_{48}O_8$: C, 74.10; H, 7.11. Found: C, 74.36; H, 7.29.

After recrystallization from MeOH, diester **10** was obtained as a white solid with mp 109–112 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1765 and 1755 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.0$ Hz, 6H), 1.22–1.30 (m, 8H), 3.45 (s, 4H), 3.53 (t, $J = 7.3$ Hz, 4H), 3.62 (s, 6H), 3.76 (d, $J = 15.3$ Hz, 4H), 3.98 (d, $J = 15.3$ Hz, 4H), 6.78 (t, $J = 7.5$ Hz, 4H), 7.04 (d, $J = 7.5$ Hz, 4H), 7.09 (d, $J = 7.5$ Hz, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.17, 19.02, 31.41, 37.39

($ArCH_2Ar$), 51.29, 68.54, 71.36, 122.50, 122.55, 130.06, 130.19, 133.67, 134.56, 155.29, 157.19, 170.55. Anal. Calcd. for $C_{42}H_{48}O_8$: C, 74.10; H, 7.11. Found: C, 74.38; H, 7.16.

*25,27-Dibutoxy-26,28-bis(carboxymethoxy)calix[4]arene in the cone conformation (**1**)*

A mixture of crude diester **8** (6.22 g, 9.14 mmol), THF (150 mL), and 10% Me_4NOH (150 mL) was refluxed for 17 h and the THF was evaporated in vacuo. The resulting aqueous solution was acidified with 6 N HCl and extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were washed with H_2O (100 mL) and evaporated in vacuo to afford a pale yellow solid, which was recrystallized from CH_2Cl_2-hexanes to give **1** as a white solid (4.66 g, 73% overall yield for two steps from **7**) with mp 245–247 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3500–2700 (CO_2H); 1759 and 1740 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.4$ Hz, 6H), 1.33–1.40 (m, 4H), 1.81–1.92 (m, 4H), 3.33 (d, $J = 13.4$ Hz, 4H), 3.89 (t, $J = 7.8$ Hz, 4H), 4.36 (d, $J = 13.4$ Hz, 4H), 4.71 (s, 4H), 6.34–6.43 (m, 6H), 7.05 (t, $J = 7$ Hz, 2H), 7.19 (d, $J = 7$ Hz, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.85, 18.96, 30.91 ($ArCH_2Ar$), 31.05, 72.00, 77.32, 123.62, 124.44, 128.34, 129.54, 132.61, 135.28, 152.25, 156.24, 169.90. Anal. Calcd. for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.72; H, 6.79.

*25,27-Dibutoxy-26,28-bis(carboxymethoxy)calix[4]arene in the partial cone (acid up) conformation (**3**)*

Using the same procedure as described above for the hydrolysis of **8** to form **1** but with refluxing for 30 h, diester **9** was converted into diacid **3** in 51% yield (overall for two steps from **7**) as a white solid with mp 205–208 °C. IR (deposit from CH_2Cl_2 solutions onto a NaCl plate): 3500–2800 (CO_2H), 1766 and 1759 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.3$ Hz, 6H), 1.33–1.41 (m, 4H), 1.70–1.84 (m, 4H), 3.26 (d, $J = 13$ Hz, 2H), 3.65–3.70 (m + d, $J = 15$ Hz, 4H), 3.87–3.96 (m + d, $J = 15$ Hz, 4H), 4.08 (d, $J = 13$ Hz, 2H), 4.21 (s, 2H), 4.31 (s, 2H), 6.69 (t, $J = 7$ Hz, 2H), 6.74 (dd, $J = 8$, 1 Hz, 2H), 6.85 (dd, $J = 7$, 1 Hz, 2H), 7.06 (t, $J = 7$ Hz, 1H), 7.21 (d, $J = 7$ Hz, 2H), 7.25–7.27 (m, 1H), 7.31 (d, $J = 7$ Hz, 2H), 9.32 (br s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.89, 19.13, 30.54 ($ArCH_2Ar$), 31.78, 37.31 ($ArCH_2Ar$), 66.20, 70.57, 75.06, 123.54, 125.27, 125.82, 128.71, 129.48, 129.61, 131.08, 132.97, 133.53, 133.83, 135.36, 152.33, 153.53, 154.27, 168.04, 169.08. Anal. Calcd. for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.41; H, 6.61.

*25,27-Dibutoxy-26,28-bis(carboxymethoxy)calix[4]arene in the 1,3-alternate conformation (**4**)*

Using the same procedure as described above for the hydrolysis of **8** to form **1** but with refluxing for 30 h, diester **10** was converted into diacid **4** in 12% yield (overall for two steps from **7**) as a white solid with mp 290–291 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3400–2300 (CO_2H), 1732 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.83 (t, $J = 7.3$ Hz, 6H), 1.05–1.12 (m, 4H), 1.16–1.22 (m, 4H), 3.53 (t, $J = 7.1$ Hz, 4H), 3.78 (d, $J = 16.4$ Hz, 4H), 3.93 (d, $J = 16.4$ Hz, 4H), 4.09 (s, 4H), 6.89 (t, $J = 7$ Hz, 2H), 6.95 (t, $J = 7$ Hz, 2H), 7.03 (d, $J = 7$ Hz, 4H), 7.10 (d, $J = 7$ Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.24, 19.00, 31.72, 37.80 ($ArCH_2Ar$), 67.31, 70.37, 124.04, 124.29, 129.35, 130.06, 133.41, 133.74, 153.41, 156.73, 168.09. Anal. Calcd. for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.85; H, 6.90.

*25,27-Dihydroxy-26,28-bis[(tert-butoxycarbonyl)-methoxy]calix[4]arene in the cone conformation (**11**)*

Calix[4]arene complexed with 0.26 equiv of CH_2Cl_2 (**6**, 3.00 g, 6.64 mmol) and K_2CO_3 (1.80 g, 13.28 mmol) were activated by heating at 150 °C for 2 h under oil pump vacuum and then cooled to room temperature. A solution of *tert*-butyl bromoacetate (13.94 mmol, 2.1 equiv) in MeCN (70 mL) was added and the reaction mixture was stirred at 55 °C for 24 h. A small amount of water was added and the MeCN was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and the solution was washed with 1 N HCl (100 mL) and evaporated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 and EtOAc as eluents to give a white solid, which was recrystallized from CH_2Cl_2-MeOH to afford **11** as a white solid (3.52 g, 82%), mp 199–201 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3387 (O–H); 1754 and 1731 (C=O) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.56 (s, 18H), 3.37 (d, $J = 13.1$ Hz, 4H), 4.47 (d, $J = 13.1$ Hz, 4H), 4.58 (s, 4H), 6.64 (t, $J = 7$ Hz, 2H), 6.70 (t, $J = 7$ Hz, 2H), 6.87 (d, $J = 7$ Hz, 4H), 7.04 (d, $J = 7$ Hz, 4H), 7.67 (s, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.11, 31.47 ($ArCH_2Ar$), 73.17, 82.43, 118.84, 125.41, 128.00, 128.42, 129.03, 133.03, 152.53, 153.14, 167.82. Anal. Calcd. for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.85; H, 6.83.

*25,27-Dibutoxy-26,28-bis[(tert-butoxycarbonyl)methoxy]-calix[4]arene in the partial cone (butyl up) conformation (**12**)*

A solution of diester **11** (5.00 g, 7.66 mmol), 1-bromobutane (4.00 g, 30.64 mmol), and K_2CO_3 (4.04 g, 30.64 mmol) in MeCN (150 mL) was refluxed for 24 h. An additional

portion of 1-bromobutane (4.00 g, 30.64 mmol) in CH_3CN (15 mL) was added and the mixture was refluxed for 48 h. A small amount of water was added and the MeCN was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL). The solution was washed with 1 N HCl (200 mL) and evaporated in vacuo to give a yellow solid, which was used directly for the hydrolysis step. For identification, the crude product was chromatographed on silica gel with EtOAc-hexanes (1:99) as eluent to give a white solid. The solid was recrystallized from CH_2Cl_2-MeOH to produce **12** as a white solid with mp 140–141 °C. IR (deposit from CH_2Cl_2 on a NaCl plate): 1756 and 1729 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.4$ Hz, 3H), 1.04 (t, $J = 7.4$ Hz, 3H), 1.13–1.19 (m, 2H), 1.39–1.45 (m, 2H), 1.48–1.56 (m + s, 20H), 1.88–1.94 (m, 2H), 3.09 (d, $J = 13$ Hz, 2H), 3.41 (t, $J = 8.2$ Hz, 2H), 3.64 (d, $J = 12$ Hz, 2H), 3.80 (t, $J = 7.3$ Hz, 2H), 3.86 (d, $J = 12$ Hz, 2H), 4.15 (d, $J = 13$ Hz, 2H), 4.24 (d, $J = 14.8$ Hz, 2H), 4.27 (d, $J = 14.8$ Hz, 2H), 6.20 (d, $J = 7$ Hz, 2H), 6.44 (t, $J = 7$ Hz, 2H), 6.87–6.91 (m, 2H), 6.95 (dd, $J = 7, 1$ Hz, 2H), 7.08 (d, $J = 7$ Hz, 2H), 7.47 (d, $J = 7$ Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.18, 14.20, 19.12, 19.48, 28.16, 31.07 ($ArCH_2Ar$), 31.22, 33.05, 35.10 ($ArCH_2Ar$), 72.22, 73.19, 73.67, 81.52, 121.82, 122.10, 122.20, 128.39, 129.09, 130.41, 132.27, 132.89, 133.60, 136.77, 155.29, 157.19, 157.23, 168.33. Anal. Calcd. for $C_{48}H_{60}O_8$: C, 75.36; H, 7.91. Found: C, 75.30; H, 7.82.

*25,27-Dibutoxy-26,28-bis(carboxymethoxy)calix[4]arene in the partial cone (butyl-up) conformation (**2**)*

Solutions of the crude ester **12** (4.37 g, 5.71 mmol) in EtOH (100 mL) and NaOH (2.34 g, 45.68 mmol) in H_2O (30 mL) were combined and the mixture was refluxed for 20 h. After cooling, the mixture was acidified with 6 N HCl and extracted with CH_2Cl_2 (2 × 150 mL). The extracts were combined and washed with 6 N HCl (100 mL) and then H_2O (100 mL), dried over $MgSO_4$, and evaporated in vacuo to give a pale yellow solid. The solid was recrystallized from CH_2Cl_2-hexanes and dried at 100 °C for 12 h to remove trapped solvents (CH_2Cl_2 and hexane) under high vacuum to give **2** as a white solid (3.20 g, 86%; overall 73% in two steps from **11**), mp 212–214 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3400–2400 (CO_2H); 1760 and 1735 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.16–0.22 (m, 2H), 0.30 (t, $J = 7.3$ Hz, 3H), 0.38–0.44 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H), 1.21–1.29 (m, 2H), 1.62–1.68 (m, 2H), 2.37 (t, $J = 6.0$ Hz, 2H), 3.36 (d, $J = 12$ Hz, 2H), 3.84 (t, $J = 7.9$ Hz, 2H), 3.90 (d, $J = 17.0$ Hz, 2H), 3.99 (d, $J = 17.0$ Hz, 2H), 4.28 (d, $J = 15.9$ Hz, 2H), 4.43 (d, $J = 15.9$ Hz, 2H), 4.50 (d, $J = 12$ Hz, 2H), 6.75 (t, $J = 7$ Hz, 1H), 6.93 (t, $J = 7$ Hz, 2H), 6.98–7.04 (m, 5H), 7.16 (d, $J = 7$ Hz, 2H), 7.20 (d, $J = 7$ Hz, 2H), 9.67 (br s, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 13.84, 13.90, 18.15, 18.93, 30.45 ($ArCH_2Ar$), 31.16, 31.53, 37.69 ($ArCH_2Ar$), 69.92, 70.04, 123.62, 123.99, 124.67, 128.61, 128.63, 129.81, 129.89, 132.89, 132.95, 134.13, 135.79, 153.05, 153.96, 156.89, 170.62. Anal. Calcd. for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.64; H, 6.64.

Procedure for competitive extraction of alkali metal cations

An aqueous solution of the alkali metal chlorides with NBu_4OH or HCl for pH adjustment (2.0 mL, 10.0 mM in each of the five alkali metal cation species) and 2.0 mL of a 1.0 mM ligand solution in 1,2-dichloroethane was vortexed in a capped, polypropylene, 15-mL centrifuge tube for 10 min. The tube was centrifuged 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. A portion of the aqueous phase from this stripping was diluted to 10.0 mL with deionized water and the alkali metal cation concentrations were determined by ion chromatography. The pH of the aqueous phase from the initial extraction step was measured.

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 [17], except that the diluent was 1,2-dichloroethane instead of chloroform.

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

The procedure for single species extraction of Pb^{2+} was the same as that reported previously [17], except that the diluent was 1,2-dichloroethane instead of chloroform.

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

The procedure for single species extraction of Hg^{2+} was the same as that reported previously [17], except that the diluent was 1,2-dichloroethane instead of chloroform.

Results and discussion

Ligand synthesis

The synthetic objective was to prepare calix[4]arene isomers with two distal butoxy groups and two distal

carboxymethoxy groups. This involves the introduction of the two types of substituents in different steps. Over the past decade, it has been deduced that the stereochemical outcome of such sequential dialkylation reactions of calix[4]arenes depends upon the base, solvent, reaction temperature, reactivity of the electrophile, nature of para substitutens, and the order in which the different substituents are introduced [18–20]. Fortunately, ^{1}H and ^{13}C-NMR spectroscopy is a powerful tool for verifying the conformations of the separated stereoisomers and for estimating their relative proportions in product mixtures [21].

To indicate the appropriate reaction conditions for the preparation of the calix[4]arene di(carboxylic acid)s, calix[4]arene with two distal butoxy groups (**7**) was prepared by reaction of calix[4]arene (**6**) with K_2CO_3 and 1-bromobutane in DMF at 90 °C. Test runs were conducted with 100 mg of **7**, 4.0 equivalents of methyl bromoacetate, and different base-solvent combinations. For these test runs, 4.0 equivalents of NaH and K_2CO_3, 5.0 equivalents of KH, and 15.0 equivalents of Cs_2CO_3 were utilized. Results are presented in Table 1.

On silica gel TLC, the cone and partial cone (acid up) diesters had nearly the same R_f value of 0.7 with ethyl acetate-hexanes (1:8) as eluent; but the 1,3-alternate diester had a very low R_f value of 0.2.

The preparative route to cone calix[4]arene di(carboxylic acid) **1** is shown in Scheme 1. Reaction of calix[4]-arene (**6**) with 1-bromobutane and K_2CO_3 in DMF at 90 °C gave a 62% yield of **7**. A mixture of diether **7**, methyl bromoacetate, and NaH in DMF was heated at 80 °C to give the crude diester **8**, which was hydrolyzed with NMe_4OH in aqueous THF at reflux to afford a 73% overall yield of **1** for two steps from diether **7**. (Except for structural verification of the precursor diesters to calix[4]arene di(carboxylic acid)s **1**–**4**, the crude diesters were utilized.)

The synthesis routes to partial cone (acid up) and 1,3-alternate calix[4]arene di(carboxylic acid)s **3** and **4**, respectively, are presented in Scheme 2. The room-temperature reaction of diether **7** with methyl bromoacetate and KH in THF gave a crude mixture of partial cone (acid up) and 1,3-alternate calix[4]arene diesters **9** and **10**, respectively. Due to their very different retention behavior on silica gel, these two isomers were easily separated by column chromatography, even on a large scale. Basic hydrolysis of diester **9** with NMe_4OH in aqueous THF produced partial cone (acid up) calix[4]arene di(carboxylic acid) **3** in 51% overall yield for two steps from **7**. The basic hydrolysis of diester **10**, formed in the lesser amount in the dialkylation of **7,** produced 1,3-alternate calix[4]arene di(carboxylic acid) **4** in 12% overall yield for two steps from **7**.

To obtain the partial cone (butyl up) calix[4]arene di(carboxylic acid) **2**, the order for introducing the two different types of substituents was reversed. In test runs conducted as described earlier, calix[4]arene with two –OCH_2CO_2Me groups [19] was alkylated with 1-bromobutane under different experimental conditions (Table 2). With KH-THF and K_2CO_3-MeCN, only the partial cone (butyl up) diester was apparent in the crude product. However, in some cases, hydrolysis of the diester products under the reaction conditions was evident from the ^{1}H-NMR spectra. Therefore, the diester reactant was changed to calix[4]arene with two –$OCH_2CO_2Bu^t$ groups (**11**) for the preparative-scale reactions.

The preparative route to partial cone (butyl up) calix[4]arene di(carboxylic acid) **2** is displayed in Scheme 3. Dialkylation of diester **11** with K_2CO_3 and 1-bromobutane in MeCN at reflux gave partial cone (butyl up) calix[4]arene diester **12**, which was unaffected by attempted hydrolysis with NMe_4OH in aqueous THF at reflux. Basic hydrolysis of diester **12** with NaOH in aqueous EtOH gave partial cone (butyl up) calix[4]arene di(carboxylic) acid **2** in 73% overall yield for the two steps from diester **11**.

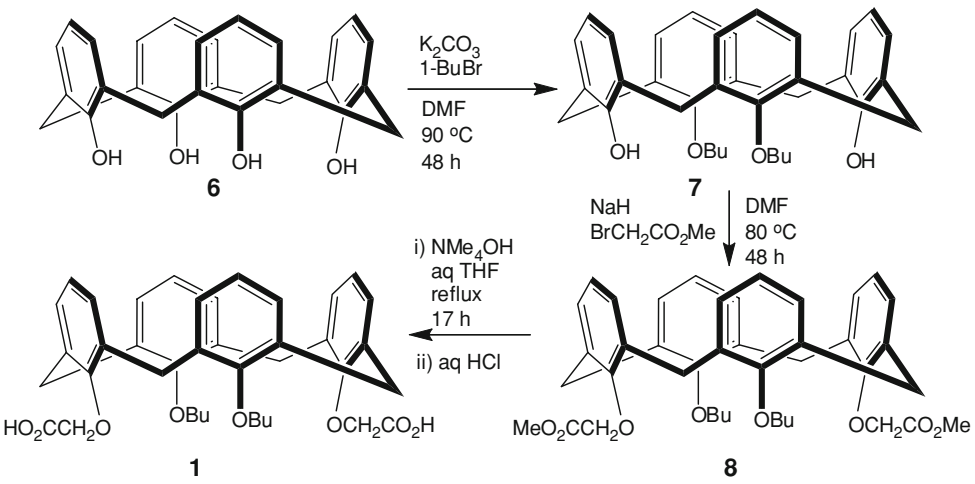
Conformations of four calix[4]arene diesters **8**–**11** and the calix[4]arene di(carboxylic acids) **1**–**4** were verified by their ^{1}H, ^{13}C, and ^{1}H-^{13}C HeteroCOSY NMR spectra. Chemical shift values and splitting patterns for the

Table 1 Distribution of conformational isomers in alkylation of **7** with methyl bromoacetate under various reaction conditions

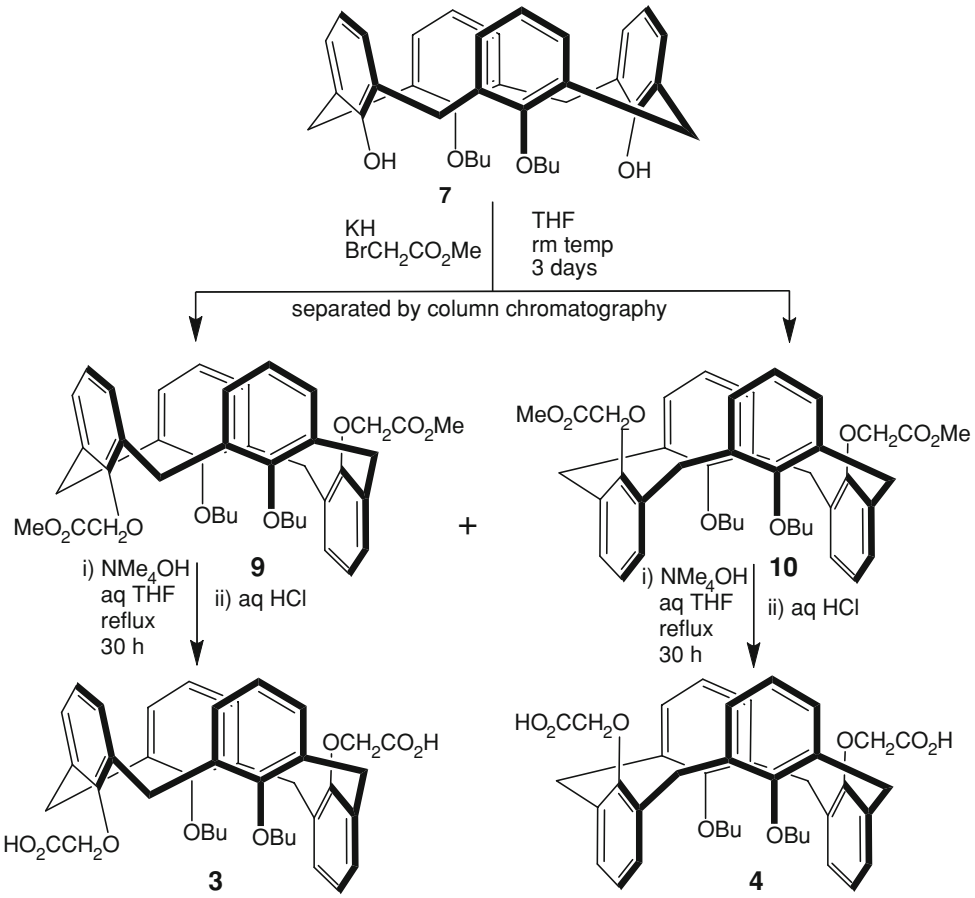
Base	Solvent (temperature, time)	Relative ratio of isomers in the crude product[a]		
		Cone	Partial cone (acid up)	1,3-alternate
NaH	THF (reflux, 72 h)	65	0	35
NaH	DMF (80 °C, 48 h)	100	0	0
KH	THF (rm temp, 72 h)	0	75	25
K_2CO_3	MeCN (reflux, 72 h)	20	55	25
Cs_2CO_3	Acetone (reflux, 36 h)	15	85	0
Cs_2CO_3	DMF (80 °C, 24 h)	20	80	0

[a] Estimated from the ^{1}H-NMR spectrum and confirmed by the TLC pattern

Scheme 1 Synthesis of cone calix[4]arene di(carboxylic acid) **1**



Scheme 2 Synthesis of partial cone (acid up) and 1,3-alternate calix[4]arene di(carboxylic acid)s **3** and **4**, respectively



methylene (–$OCH_2C(O)$–) and bridging methylene ($ArCH_2Ar$) groups are collected in Table S-1 (Supplementary Information) for the diesters and in Table 3 for the di(carboxylic acids). The cone and 1,3-alternate isomers were readily differentiated by their ^{13}C-NMR absorptions for the bridging methylene groups at 31.19 and 37.39 ppm, respectively. The bridging methylene groups of the two partial cone isomers **2** and **3**, both exhibit two sets of doublets in their ^{1}H-NMR spectra and absorptions near 31 and 37 ppm in their ^{13}C-NMR spectra. The chemical shift values are close to those reported for other calix[4]arene molecules in the same conformations [20, 21].

Table 2 Distribution of conformational isomers in alkylation of 25,27-dihydroxy-26,28-bis[(methoxycarbonyl)methoxy]calix[4]arene with 1-bromobutane under various reaction conditions

Base	Solvent (temperature, time)	Relative ratio of isomers in the crude product[a]		
		Cone	Partial cone (butyl up)	1,3-alternate
NaH	THF (reflux, 12 h)	40	60	0
KH	THF (rm temp, 24 h)	0	100	0
K_2CO_3	MeCN (reflux, 18 h)	0	100	0
Cs_2CO_3	DMF (80 °C, 24 h)	25	75	0

[a] Estimated from the ^{1}H-NMR spectrum and confirmed by the TLC pattern, after the crude product was passed through a short silica gel column to remove baseline impurities

Scheme 3 Synthesis of partial cone (butyl up) calix[4]arene di(carboxylic acid) **2**

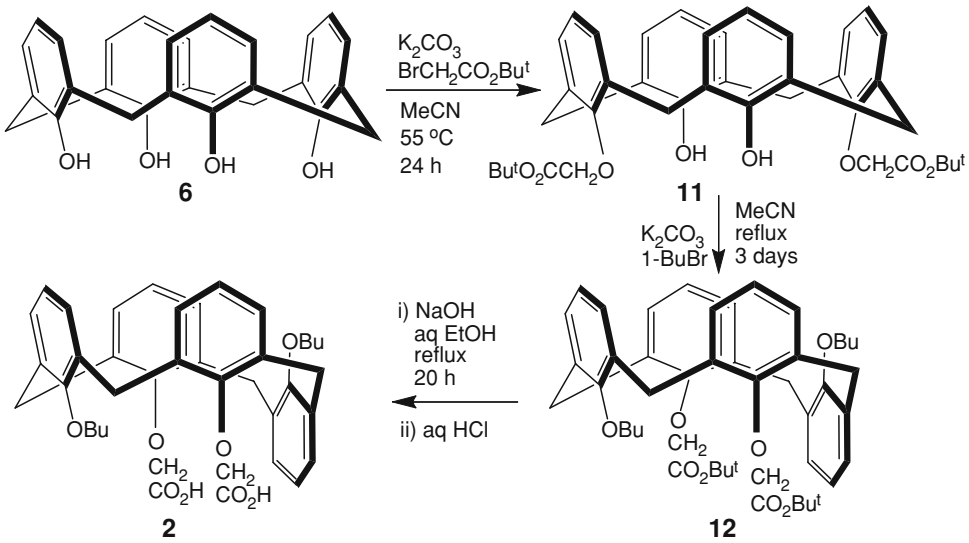


Table 3 Chemical shift values (in ppm) and splitting patterns in the ^{1}H and ^{13}C-NMR spectra for the methylene (–$OCH_2C(O)$–) and bridging methylene ($ArCH_2Ar$) groups in calix[4]arene di(carboxylic acid)s **1–4**

Isomer	–$OCH_2C(O)$–		$ArCH_2Ar$	
	^{1}H[a]	^{13}C[a]	^{1}H[a]	^{13}C[a]
1-cone	4.71 (s)	72.00	3.33 (d, J = 13.4 Hz)	30.91
			4.36 (d, J = 13.4 Hz)	
2-partial	4.28 (d, J = 15.9 Hz)	70.04	3.36 (d, J = 12 Hz)	30.45
cone (butyl up)	4.43 (d, J = 15.9 Hz)		3.90 (d, J = 17.0 Hz)	37.69
			3.99 (d, J = 17.0 Hz)	
			4.50 (d, J = 12 Hz)	
3-partial	4.21 (s)	66.20	3.26 (d, J = 13 Hz)	30.54
cone (acid up)	4.31 (s)	70.57	3.26 (d, J = 15 Hz)	37.31
			3.95 (d, J = 15 Hz)	
			4.08 (d, J = 13 Hz)	
4-1,3-alternate	4.09 (s)	67.31	3.78 (d, J = 16.4 Hz)	37.80
			3.93 (d, J = 16.4 Hz)	

[a] Connection was confirmed by the ^{1}H–^{13}C HeteroCOSY NMR spectrum

Interestingly, the methylene protons (–$CH_2C(O)$) show different splitting patterns in the ^{1}H-NMR spectrum depending upon the conformation. They are chemically equivalent in the cone and 1,3-alternate conformations, chemically non-equivalent in the partial cone (acid up) conformation, and magnetically non-equivalent in the

partial cone (butyl up) conformation. In the ^{13}C-NMR spectra, the methylene carbons appear as one signal in the cone, partial cone (butyl up), and 1,3-alternate conformations, but as two signals (i.e., chemically non-equivalent) in the partial cone (acid up) conformation.

Structures of isomeric calix[4]arene di(carboxylic acid) isomers **1–4** and their precursors were verified by IR spectrophotometry, ^{1}H and ^{13}C-NMR spectroscopy, and combustion analysis. Confirming solid-state structures of diesters **9**, **11** and **12** and di(carboxylic acid) **2** have been obtained (R.D. Rogers and S.T. Griffin, The University of Alabama (unpublished results)).

Metal ion extraction

To probe the influence of conformation of the isomeric calix[4]arene di(carboxylic acid)s **1–4** and conformationally mobile analogue **5** upon their metal ion complexation abilities, solvent extractions of metal ions from aqueous solutions into 1,2-dichloroethane were performed. (This diluent was utilized due to the limited solubility of the ligands in chloroform.) 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.

Aqueous solutions containing Li^+, Na^+, K^+, Rb^+, and Cs^+ (10.0 mM in each) chlorides were extracted with 1.00 mM solutions of ligands **1–5** in 1,2-dichloroethane. The pH of the aqueous solutions was adjusted by addition of HCl or NBu_4OH. 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 AMC 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 should be 200%. The maximal AMC loadings for isomeric calix[4]arene di(carboxylic acid)s **1–4** decreased in the order: 1,2-alternate (100%) ~partial cone (butyl up) (97%) ~cone (96%) >partial cone (acid up) (16%). In comparison, the maximal metal loading obtained with conformationally flexible ligand **5** was 89%. It is proposed that mono-ionization of the di(carboxylic acid) gives an AMC-carboxylate complex that hydrogen bonds intramolecularly to a non-ionized carboxylic acid group. In agreement, the extraction efficiency plummets for the partial cone (acid up) isomer **3** in which the two carboxylic acid groups are well separated.

With regard to the selectivity for AMC extraction into 1,2-dichloroethane by ligands **1–5**, excellent Na^+ selectivity was observed with the cone, partial cone (butyl up), and flexible ligands. For the cone isomer **1**, the Na^+ selectivity was the highest with only Na^+ and Li^+ being

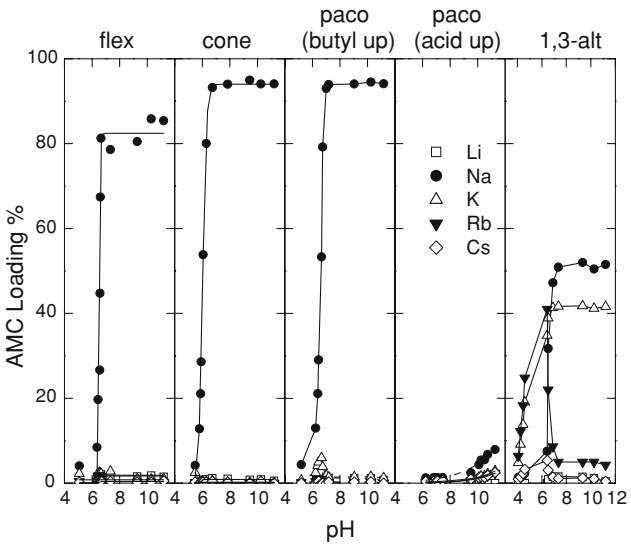


Fig. 3 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive alkali metal cation extraction into 1,2-dichloroethane by ligands **1–5**

transported into the organic diluent and a Na^+/Li^+ selectivity of greater than 100. For the partial cone (butyl up) isomer, the second best extracted AMC was K^+. Since the second best extracted AMC was Li^+ for both cone isomer **1** and the flexible analogue **5**, it is postulated that the latter adopts a cone conformation in extracting AMC into 1,2-dichloroethane.

Aqueous solutions containing Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} (2.00 mM in each) chlorides were extracted with 1.00 mM solutions of calix[4]arene di(carboxylic acid)s **1–5** in 1,2-dichloroethane. For the competitive alkaline earth metal cation (AEMC), plots of the metal loading of the organic phase versus the pH of the aqueous phase are presented in Fig. 4. For cone and partial cone (butyl up) isomers, **1** and **2**, respectively, and the conformationally flexible analog **5**, the maximal AMEC loadings were 91 ± 2%. This is consistent with formation of 1:1 divalent metal ion-di-ionized ligand extraction complexes.

The change from cone isomer **1** to partial cone (butyl up) isomer **2** produces a marked change in the extraction selectivity order from $Ba^{2+} > Ca^{2+} \sim Sr^{2+} > Mg^{2+}$ to $Ca^{2+} > Ba^{2+} > Sr^{2+}$, Mg^{2+}, respectively. Similarities in the extraction profiles for partial cone (butyl up) isomer **2** and the flexible analogue **5** strongly indicates that the latter adopts a partial cone (butyl up) conformation in its extraction complex.

Aqueous solutions of Pb^{2+} (1.00 mM) nitrate were extracted with 0.50 mM solutions of isomeric calix[4]arene di(carboxylic acid)s **1–4** and flexible analogue **5** in 1,2-dichloroethane. For these single species extractions, plots of the metal loading of the organic phase versus the pH of the aqueous phase are shown in Fig. 5. For all of the

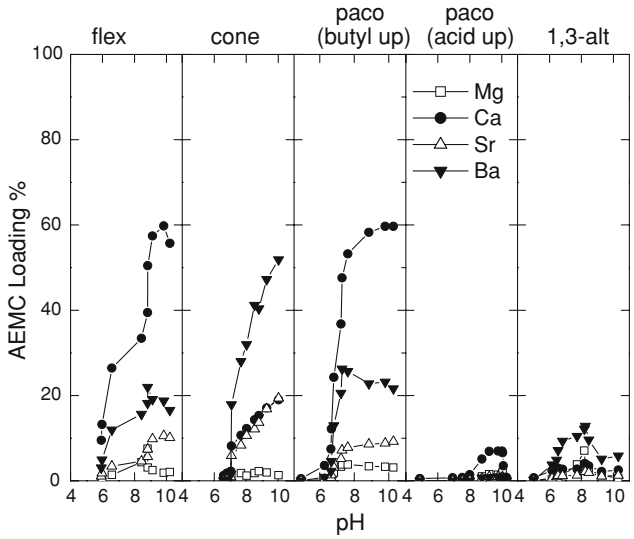


Fig. 4 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for competitive alkaline earth metal cation extraction into 1,2-dichloroethane by ligands **1**–**5**

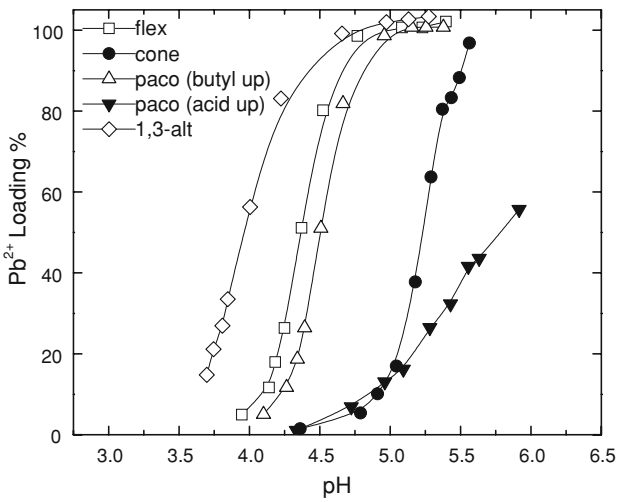


Fig. 5 Percent metal loading of the organic phase versus the equilibrium pH of the aqueous phase for Pb^{2+} extraction into 1,2-dichloroethane by ligands **1**–**5**

ligands except partial cone (acid up) **4**, the Pb^{2+} extraction was quantitative or nearly so. The strength of Pb^{2+} binding by the four di(carboxylic acid) isomers decreased in the order: 1,3-alternate > partial cone (butyl up) > cone > partial cone (acid up). The very similar nature of the extraction profiles for the partial cone (butyl up) isomer **2** and the flexible analogue **5** suggests that the latter assumes a partial cone (butyl up) conformation in its extraction complex with Pb^{2+}.

Aqueous solutions of Hg^{2+} (0.25 mM) nitrate were extracted with 0.25 mM solutions of ligands **1**–**5** in 1,2-dichloroethane. No appreciable extraction of Hg^{2+} was detected from aqueous solutions of pH = 0–3. Apparently the hard nature of the ether and/or carboxylic acid oxygen donor sites are incompatible with the soft nature of Hg^{2+}.

Summary

Four stereoisomers of calix[4]arene with two distal methoxycarboxy groups and two distal butoxy groups are synthesized. These di-ionizable calix[4]arene ligands are locked in the cone, 1,3-alternate, and two different partial cone conformations. The influence of ligand conformation on metal ion complexation is deduced by metal ion extractions from aqueous solutions into 1,2-dichloroethane solutions of the for ligands. Also studied was a conformationally mobile analogue in which the two butoxy groups are replaced with methoxy groups. For competitive AMC extraction, the cone, partial cone (butyl up), and flexible ligands exhibited high selectivity for Na^{+} extraction with the highest selectivity for the cone isomer. For competitive AEMC extraction, the cone, partial cone (butyl up) and flexible ligands gave high metal loadings, but with Ba^{2+}-selective extraction for the cone isomer compared with Ca^{2+}-selective extraction for the other two ligands. Similarity of the extraction profiles obtained with the partial cone (butyl up) and flexible ligands indicates that the conformationally mobile ligand adopts a partial cone (butyl up) conformation for its extraction complexes with AEMC. For extraction of Pb^{2+}, the 1,3-alternate, partial cone (butyl up) and flexible ligands are the most effective. Similarity of the extraction profiles for the partial cone (butyl up) and flexible ligands suggests that the latter assumes a partial cone (butyl up) conformation in its extraction complex with Pb^{2+}. Of the four calix[4]arene di(carboxylic acid) stereoisomers, the partial cone (acid up) is the least effective metal ion extractant. Presumably this results from the spatial separation of the two carboxylic acid functions.

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