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Proton di-ionizable *p-tert*-butylcalix[4]arene-crown-6 compounds in cone, partial-cone and 1,3-alternate conformations: synthesis and alkaline earth metal cation extraction†

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Novel proton di-ionizable *p-tert*-butylcalix[4]arene-crown-6 compounds in cone, partial-cone and 1,3-alternate conformations are synthesized to compare the efficiency and selectivity with which they extract alkaline earth metal ions. In these ligands, a crown-6 polyether unit links alternate aromatic rings of the calix[4]arene framework. To the remaining lower-rim positions are attached oxyacetic acid or *N*-(X)sulfonyl oxyacetamide groups. Changing the conformation varies the spatial relationship between a polyether-complexed divalent metal ion and the ionized side arms of the ligands. This is found to markedly affect the efficiency and selectivity in competitive solvent extraction of alkaline earth metal ions from aqueous solutions into chloroform by the di-ionizable calix[4]arene-crown-6 ligands.

Introduction

Calixarenes are cyclic oligomers derived from condensation reactions of phenols and formaldehyde under basic or acidic conditions. These molecules have been studied extensively since the establishment of facile synthetic procedures by Gutsche and coworkers.[1] In the calixarene family, calix[4]arenes are the most popular because their more rigid, vase-like structure makes them ideal candidates for the complexation of neutral molecules or cations.[2] The parent calix[4]arene can be easily modified with functional groups at either the wide and narrow rims, or both, which not only greatly increases the solubility in organic solvents, but also enhances the binding ability and/or selectivity for guest molecules or ions.

Among the calix[4]arene derivatives, calix[4]arene-crown ethers, also called calix[4]crowns, have been found to be efficient cation extractants. Early studies showed that the conformation of mobile calix[4]arene-crowns is controlled by the complexed cations. For example, 1,3-dimethoxycalix[4]arene-crown-6 exists in a cone conformation both in the solid-state and in solution. Although the complex with Na^+ retains the cone conformation, the Cs^+ complex adopts a 1,3-alternate conformation. The ^1H-NMR spectrum and X-ray crystal structure of this complex showed that binding involves participation of both the crown ether moiety and two rotated aromatic nuclei (cation–π-interaction).[3] These studies led to the synthesis of conformationally rigid calix[4]arene-crowns for selective cation recognition. Among them, 1,3-alternate conformers have been studied more extensively due to their high Cs^+/Na^+ selectivity.[3–8] Calix[4]arene-crowns with other conformations have also been prepared.[5,9] However, metal ion complexation behavior studies are rare except for one that reports a partial cone isomer with a K^+/Na^+ selectivity of 1.18×10^4, the highest observed to date for a synthetic ionophore.[9]

Incorporation of pendant proton-ionizable groups, such as carboxylic acid, into calix[4]arenes increases their metal ion extraction efficiencies compared to their non-ionizable analogues.[10] A novel type of proton-ionizable function, the *N*-(X)sulfonyl carboxamide group, whose acidity is "tunable" by changing the X group from methyl to trifluoromethyl, was also incorporated into calix[4]arenes.[11] These di-ionizable calix[4]arenes show an unexpectedly high extraction efficiency and selectivity for some soft metal ions, such as Pb^{2+} and Hg^{2+}.

The first example of a proton-ionizable calix[4]arene-crown ether was recorded in 1984, when *p-tert*-butylcalix[4]crown-5-di(oxyacetic acid) was reported by Ungaro *et al.*[10a] This ligand exhibited a quite high extraction efficiency from aqueous solutions into dichloromethane of divalent metal cations (except Mg^{2+}). In addition, this ligand showed better selectivities for Ca^{2+} and Pb^{2+} than the non-ionizable analogues studied. Recently, Chen and coworkers prepared the crown-6 analog and found it to exhibit high selectivity for Ra^{2+} over the light alkaline earth metal cations.[12] For these two earlier studies, the di-ionizable calix[4]arene ligands were in the cone conformation.

In this paper, we report the preparation of three series of proton di-ionizable *p-tert*-butylcalix[4]arene-crown-6 compounds in the cone, partial-cone and 1,3-alternate conformations (Fig. 1). Alkaline earth metal cation complexation by these di-ionizable calix[4]arene-crown-6 ligands is evaluated in competitive solvent extraction from aqueous solutions into chloroform.

Results and discussion

Synthesis of cone di-ionizable *p-tert*-butylcalix[4]arene-crown-6 ligands

Crown ether ring formation (Scheme 1) by reaction of *p-tert*-butylcalix[4]arene[13] (**4**), pentaethylene glycol ditosylate and a base was more difficult than anticipated. It was reported that direct ring formation by reaction of **4** with pentaethylene glycol ditosylate and *t*-BuOK in benzene gave only 38% yield.[9] An alternative route was employed for the synthesis of calix[4]arene-crown-6.[14] However, when we attempted to adapt this alternative route, which involves cleavage of the methyl ether protecting groups in 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown-5, we found that the crown ether ring was also cleaved under this condition. Similar results have been reported by Ferguson and coworkers.[15] Kim *et al.* report that refluxing calix[4]arene and tetra- and pentaethylene glycol ditosylates in MeCN using exactly one equivalent of K_2CO_3 gave calix[4]arene-crown-5 and -crown-6, respectively, in 70–75% yields.[16] When this method was utilized with **4** as the calix[4]arene reactant, *p-tert*-butylcalix[4]arene-crown-6 (**5**) was obtained in 82% yield.

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† Electronic supplementary information (ESI) available: IR, ^1H-NMR and ^{13}C-NMR spectra for compounds **1a–e**, **2a–e**, **3a–e** and compounds **5–7**. See http://www.rsc.org/suppdata/ob/b5/b501822f/

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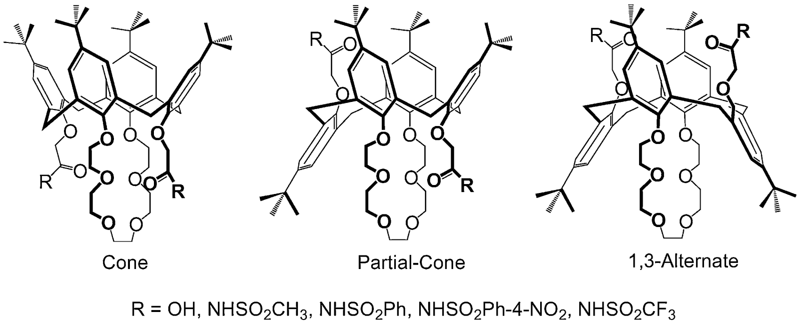
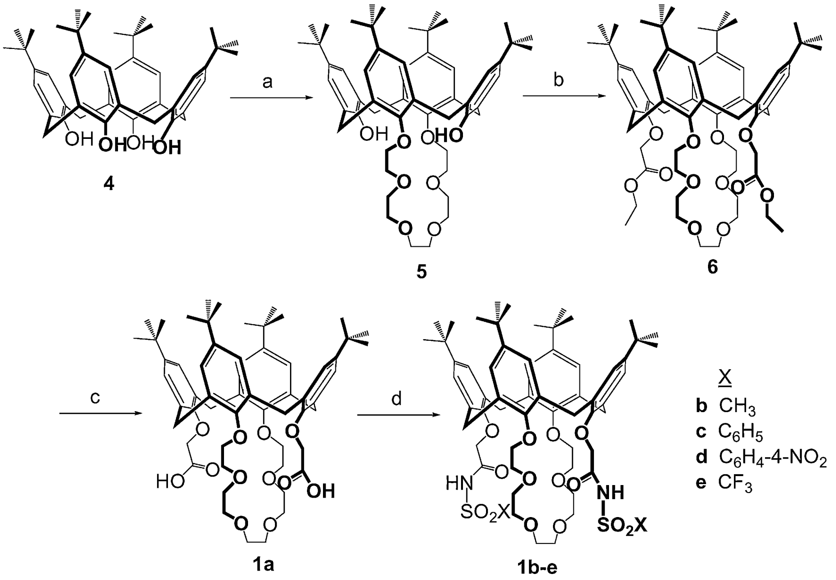


Fig. 1 Conformationally rigid, di-ionizable *p-tert*-butylcalix[4]arene-crown-6 compounds in the cone, partial-cone and 1,3-alternate conformations.



Scheme 1 Synthesis of cone di-ionizable *p-tert*-butylcalix[4]arene-crown-6 ligands **1a–e**. *Reagents and conditions*: a) TsO(CH$_2$CH$_2$O)$_5$Ts, K$_2$CO$_3$, MeCN, reflux; b) BrCH$_2$CO$_2$Et, NaH, THF, rt; c) 10% aqueous NMe$_4$OH, THF, reflux; d) i) (COCl)$_2$, C$_6$H$_6$, reflux; ii) XSO$_2$NH$_2$, NaH, THF, rt.

The ^{1}H-NMR spectrum of **5** showed a cone conformation according to the ArCH$_2$Ar signals, which appear as two doublets at 4.35 and 3.29 ppm.

The *p-tert*-butylcalix[4]arene-crown-6 (**5**) was reacted with ethyl bromoacetate and NaH in THF at room temperature to give the cone conformer of 1,3-di(ethoxycarbonylmethoxy)-*p-tert*-butylcalix[4]arene-crown-6 (**6**) in 82% yield. The ^{1}H-NMR spectrum of **6** verified this conformation. Subsequent hydrolysis with tetramethylammonium hydroxide (TMAOH) in aqueous THF gave cone 1,3-di(carboxymethoxy)-*p-tert*-butylcalix[4]arene-crown-6 (**1a**) quantitatively. Di(carboxylic acid) **1a** was treated with oxalyl chloride in benzene to give the corresponding di(acid chloride), which was reacted with the sodium salt forms of appropriate sulfonamides to give final products **1b–e** in 47–74% yields.

The cone conformation for products **1b–e** was confirmed by their ^{1}H- and ^{13}C-NMR spectra. For the former, a typical AB pattern was observed for the methylene bridge (ArCH$_2$Ar) protons that is two widely separated doublets at δ 4.08–4.51 and 2.84–3.27 ($J = 12.6 \sim 12.9$ Hz). In the ^{13}C-NMR spectra, the four methylene bridge carbons have one peak with a chemical shift around 31 ppm, which is typical for the bridge carbons in the *syn*-orientation. The OCH$_2$C(O) protons for cone conformers **1b–e** gave singlets at δ 4.97–5.23 (Table 1).

Table 1 Chemical shifts (ppm) of the OCH$_2$C(O)R protons for the three conformers

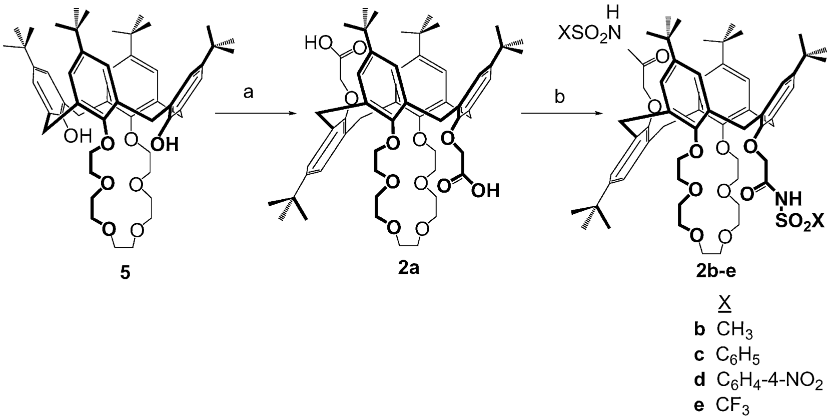
	Cone	Partial-cone		1,3-Alternate
R	*Syn-*[a]	*Syn-*	*Anti-*[a]	*Anti-*
OH	4.97	4.87	3.79	4.07
NHSO$_2$CH$_3$	5.17	4.70	2.08	3.54
NHSO$_2$C$_6$H$_5$	5.02	4.53	1.47	3.16
NHSO$_2$C$_6$H$_4$-4-NO$_2$	5.07	4.56	1.44	3.21
NHSO$_2$CF$_3$	5.23	4.76	1.60	3.45

[a] To the crown ether ring.

Synthesis of partial cone di-ionizable *p-tert*-butylcalix[4]arene-crown-6 compounds

During our attempts to synthesize 1,3-alternate conformers, we observed that reaction of *p-tert*-butylcalix[4]arene-crown-5 with ethyl bromoacetate and KH (instead of NaH) in THF at room temperature, followed by hydrolysis with NaOH in aqueous EtOH, gave a 90% yield of partial cone 1,3-di(carboxymethoxy)-*p-tert*-butylcalix[4]arene-crown-5. No other isomers were isolated. When we applied these reaction conditions to *p-tert*-butylcalix[4]arene-crown-6 (**5**), partial cone 1,3-di(carboxymethoxy)-*p-tert*-butyl-calix[4]arene-crown-6 (**2a**) was obtained in 72% yield after a simple recrystallization (Scheme 2). In this case, cone conformer **1a** was also isolated in 6% yield. Di(carboxylic acid) **2a** was converted into the corresponding di(acid chloride) using oxalyl chloride, followed by reaction with the sodium salt forms of appropriate sulfonamides to give ligands **2b–2e** in 46–90% yields.

The ^{1}H-NMR spectra of the partial cone conformers exhibited two sets of doublets for the ArCH$_2$Ar protons, one set was very close together and buried in the signals for the crown ring protons. The ^{13}C-NMR spectra showed two signals for the ArCH$_2$Ar carbons. One at around 31 ppm corresponds to the bridges in the *syn*-orientation, as in the cone



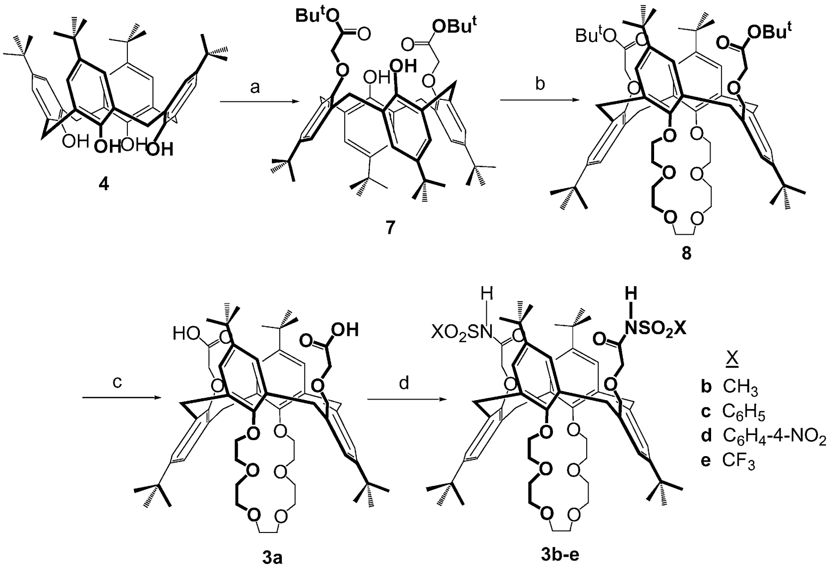
Scheme 2 Synthesis of partial cone di-ionizable *p*-*tert*-butylcalix[4]arene-crown-6 ligands **2a**–**e**. *Reagents and conditions*: a) i) $BrCH_2CO_2Et$, KH, THF, rt; ii) NaOH, aqueous EtOH, reflux; c) i) $(COCl)_2$, C_6H_6, reflux; ii) XSO_2NH_2, NaH, THF, rt.

conformers, and the other at around 38 ppm corresponds to the methylene bridges in the *anti*-orientation, as in the 1,3-alternate conformers (*vide infra*).

A distinguishing features in the ^{1}H-NMR spectra of the partial cone isomers is a small upfield shift for the *syn*-$OCH_2C(O)$ protons on the same side as the crown ether ring and a large upfield shift for the *anti*-$OCH_2C(O)$ protons on the side opposite to the crown ether ring, which is caused by the shielding effects of the aromatic rings. As shown in Table 1, while the di(carboxylic acid) derivative **2a** exhibits only a slight upfield shift for the *syn*-$OCH_2C(O)$ protons, the di-*N*-(X)sulfonylcarboxamides **2b**–**e** show a somewhat larger upfield shift of 0.47–0.51 ppm, which could result from shielding by the aromatic ring at the 3-position. The *anti*-$OCH_2C(O)$ protons exhibit very large upfield shifts for **2b**–**e** in the range of 3.09–3.73 ppm. Even for the dicarboxylic acid **2a**, an upfield shift of 1.18 ppm was observed for the *anti*-OCH_2CO protons. This indicates that the *anti*-$OCH_2C(O)$ groups in the partial cone isomers are buried deeply in the hydrophobic pocket formed by the three aromatic rings. In addition to electronegativity, it appears that the size of the ionizable group influences the magnitude of upfield shift (Table 1). The larger the X group in $OCH_2C(O)NHSO_2X$, the greater is the upfield shift for the *anti*-$OCH_2C(O)$ protons.

Synthesis of 1,3-alternate di-ionizable *p*-*tert*-butylcalix[4]arene-crown-6 compounds

Since it is well known that the 1,3-alternate conformation can be obtained using Cs^+ as a template cation, this principle was followed.[5,14] In this case, it was necessary to perform the *O*-alkylation first, followed by the crown ether ring formation. To reduce hydrolysis during the reaction, *tert*-butyl bromoacetate was used instead of ethyl bromoacetate. Thus, *p*-*tert*-butylcalix[4]arene (**4**) was reacted with *tert*-butyl bromoacetate and K_2CO_3 in refluxing MeCN to produce 88% yield of 1,3-di(*tert*-butoxycarbonylmethoxy)-*p*-*tert*-butylcalix[4]arene (**7**) (Scheme 3). Compound **7** was reacted with pentaethylene glycol ditosylate and two equivalents of Cs_2CO_3 in refluxing MeCN to provide 57% yield of 1,3-alternate 1,3-di(*tert*-butoxycarbonylmethoxy)-*p*-*tert*-butylcalix[4]arene-crown-6 (**8**). Diester **8** was hydrolyzed with NaOH in aqueous EtOH. After acidification, 1,3-alternate 1,3-di(carboxymethoxy)-*p*-*tert*-butylcalix[4]arene-crown-6 (**3a**) was obtained in 97% yield. Dicarboxylic acid **3a** was converted into the final products **3b**–**e** under the same reaction conditions as those employed for the cone and partial-cone isomers. Yields of di-ionizable *p*-*tert*-butylcalix[4]arene-crown-6 were in the range 52–86%.

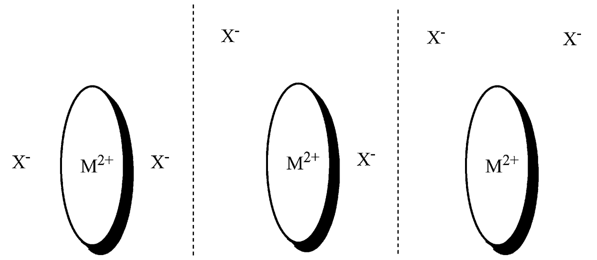


Scheme 3 Synthesis of 1,3-alternate di-ionizable *p*-*tert*-butylcalix[4]arene-crown-6 ligands **3a**–**e**. *Reagents and conditions*: a) $BrCH_2CO_2Bu^t$, K_2CO_3, MeCN, reflux; b) $TsO(CH_2CH_2O)_5Ts$, Cs_2CO_3, MeCN, reflux; c) NaOH, aqueous EtOH, reflux; d) i) $(COCl)_2$, C_6H_6, reflux; ii) XSO_2NH_2, NaH, THF, rt.

The ^{1}H-NMR spectra of the 1,3-alternate isomers exhibit a singlet or two closely spaced doublets for the $ArCH_2Ar$ protons at around 4.0 ppm. The ^{13}C-NMR spectra show one signal for the $ArCH_2Ar$ carbons at around 39 ppm, which corresponds to the bridges in the *anti*-orientation. The two *anti*-$OCH_2C(O)$ protons show a singlet at δ 3.02–4.07, which is an upfield shift of 0.90–2.03 ppm compared to the cone isomers, resulting from the shielding effect of two aromatic rings (Table 1).

Competitive solvent extraction of alkali metal cations by di-ionizable calix[4]arene-crown-6 ligands 1a–e, 2a–e and 3a–e

Upon ionization of the new ligands **1a–e**, **2a–e** and **3a–e**, fixed conformations for the calix[4]arene units control the spatial relationship for a crown-complexed divalent metal ion with respect to the two anionic centers required for electroneutrality of the extraction complex (Fig. 2). Upon ionization, the cone di-ionizable calix[4]arene-crown-6 compounds **1a–e** form complex **9** with an anionic center over each side of the crown unit. Alternatively, the partial cone di-ionizable calix[4]arene-crown-6 compounds **2a–e** produce complex **10** with one anionic center in close proximity to the complexed divalent metal ion and one in a remote location. Finally the 1,3-alternate di-ionizable calix[4]arene-crown-6 compounds **3a–e** form complex **11** in which anionic centers are remote from the complexed divalent metal ion. To probe the influence of these differing spatial arrangements upon the efficiency and selectivity of divalent metal ion complexation, competitive solvent extraction of alkaline earth metal cations from aqueous solutions into chloroform by ligands **1a–e**, **2a–e** and **3a–e** were performed.



9 **10** **11**

Fig. 2 Depiction of spatial relationships between a crown-complexed divalent metal ion and the anionic centers formed by ionization of ligands **1a–e**, **2a–e** and **3a–e**.

Earlier studies of solvent extraction by proton-ionizable lariat ethers demonstrated that the selectivity in competitive metal ion extraction may be quite different from that obtained by extrapolating the results of single species extractions.[17] Therefore, competitive solvent extractions of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} were utilized in the present investigation.

For competitive solvent extractions of aqueous alkaline earth metal cation (10.0 mM in each) solutions by 1.0 mM solutions of di-ionizable calix[4]arene ligands **1a–e**, **2a–e** and **3a–e** in chloroform, plots of metal ion loading of the organic *vs.* the equilibrium pH of the aqueous phase are presented in Figs. 3–6.

Fig. 3 records the results of competitive alkaline earth metal ion solvent extraction by calix[4]arene-crown-6 di(carboxylic acids) **1a**, **2a** and **3a** in the cone, partial cone and 1,3-alternate conformations, respectively. Cone ligand **1a** exhibits very high extraction selectivity for Ba^{2+} over the other three alkaline earth metal ion species and 100% maximum metals loading (for formation of a 1 : 1 metal ion–ligand complex). The Ba^{2+} selectivity observed in competitive solvent extraction is much higher than would be expected from the single species extraction results reported by Chen *et al.*[12] Both the extraction efficiency and selectivity are markedly affected by ligand conformation in the order: cone ≫ 1,3-alternate ≫ partial cone. The 1,3-alternate ligand is a much weaker extractant than the corresponding cone ligand and the selectivity is $Ba^{2+} > Ca^{2+} \gg Sr^{2+}, Mg^{2+}$. The partial

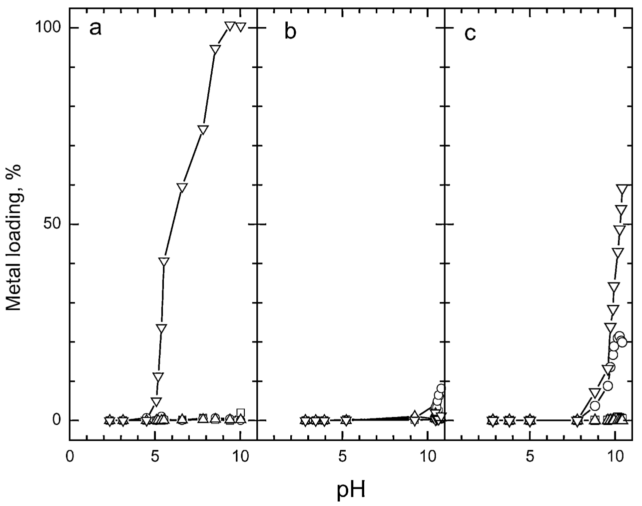


Fig. 3 Percent metals loading *vs.* equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by *tert*-butylcalix[4]arene-crown-6 dicarboxylic acids; a) **1a**, b) **2a**, and c) **3a** (☐ = Mg^{2+}, ○ = Ca^{2+}, △ = Sr^{2+}, ▽ = Ba^{2+}).

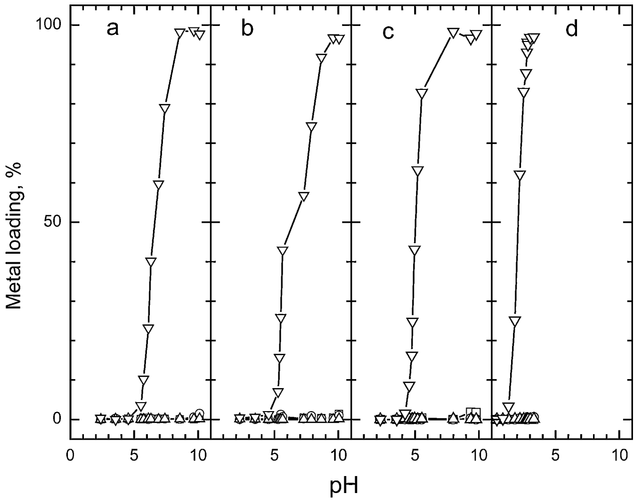


Fig. 4 Percent metal loading *vs.* equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by *tert*-butylcalix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamides); a) **1b**, b) **1c**, c) **1d** and d) **1e** (☐ = Mg^{2+}, ○ = Ca^{2+}, △ = Sr^{2+}, △ = Ba^{2+}).

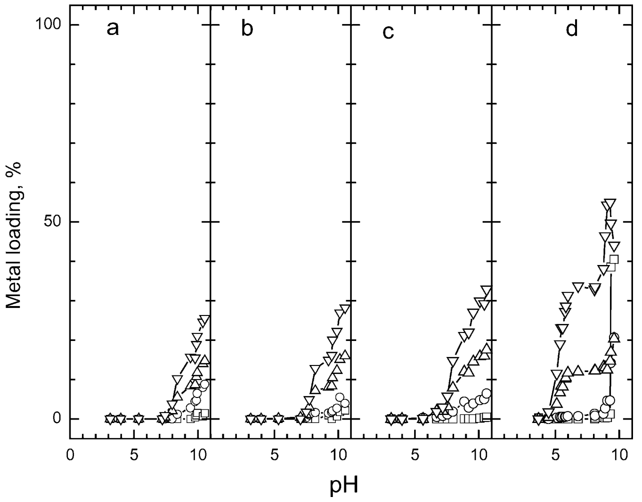


Fig. 5 Percent metal loading *vs.* equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by *tert*-butylcalix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamides); a) **2b**, b) **2c**, c) **2d** and d) **2e** (☐ = Mg^{2+}, ○ = Ca^{2+}, △ = Sr^{2+}, △ = Ba^{2+}).

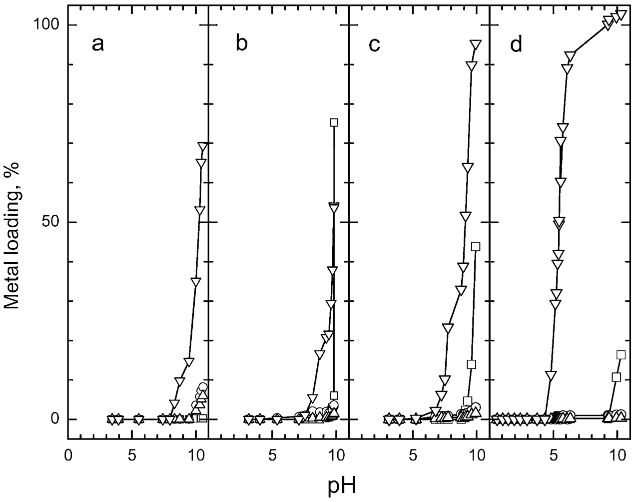


Fig. 6 Percent metal loading *vs.* equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal ions into chloroform by *tert*-butylcalix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamides); a) **3b**, b) **3c**, c) **3d** and d) **3e** (□ = Mg^{2+}, ○ = Ca^{2+}, △ = Sr^{2+}, ▽ = Ba^{2+}).

cone isomer exhibits such a weak extraction propensity that it is difficult to discern its selectivity. These results reveal an energetically most favorable arrangement when the calix[4]arene unit of the di-ionized ligand is in the cone conformation, which allows positioning of one ionized group above and the other below the plane of the crown–divalent metal ion complex (as represented in **9**). Although it might be anticipated that the one proximal and one distal ionized groups (represented by **10**) might be more energetically favorable than having two distal ionized groups (represented by **11**), this is not the case. Perhaps a greater symmetry in the latter is a counteracting factor.

To probe the effect of changing to a different class of ionizable group in which the acidity can be systematically varied, solvent extractions were performed with the calix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamide) ligands **1b–e**, **2b–e** and **3b–e**, which are in the cone, partial cone and 1,3-alternate conformations, respectively. Fig. 4 presents the results for competitive solvent extractions for alkaline earth metal cations from aqueous solution by cone ligands **1b–e** in which the X group is varied as CH_3, C_6H_5, C_6H_4-4-NO_2 and CF_3. With this group of substitutents, the ligand acidity is expected to increase in the order of $CH_3 \sim C_6H_5 < C_6H_4\text{-4-}NO_2 < CF_3$ as the electron-withdrawing power of the X group is increased. As is seen, very high Ba^{2+} extraction selectivity is observed for all four ligands with 100% maximal metal loading. The pH for half loading, $pH_{0.5}$, is a measure of the ligand acidity. For **1b–e**, the $pH_{0.5}$ values are 6.6, 6.3, 5.1 and 2.1, respectively, which is in accord with the electron-withdrawing power the X group.

Fig. 5 presents the results for competitive alkaline earth metal ion extraction by the partial-cone calix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamide) ligands **2b–e**. Both the extraction efficiency and selectivity are markedly diminished for **2b–e** compared with their cone conformation analogues **1b–e**. Although Ba^{2+} is the best extracted alkaline earth metal cation, appreciable amounts of Sr^{2+} are also transferred into the organic phase. As before, the alkaline earth metal ion extraction propensity increases as the X group is varied $CH_3 \sim C_6H_5 < C_6H_4\text{-4-}NO_2 < CF_3$.

In Fig. 6 are shown the results for competitive alkaline earth metal solvent extraction by the 1,3-alternate calix[4]arene-crown-6 di(*N*-(X)sulfonyl carboxamide) ligands **3b–e**. For ligands **3c** and **3d**, the apparent extraction of Mg^{2+} at the highest pH values is attributed to transfer of colloidal $Mg(OH)_2$ into the organic phase. At lower pHs, very high Ba^{2+} selectivity is evident with the extraction efficiency increasing in the order $CH_3 \sim C_6H_5 < C_6H_4\text{-4-}NO_2 < CF_3$. Comparison of Fig 4 and Fig. 6 shows that each of the cone ligands **1b–e** is an appreciably more efficient extractant than its 1,3-alternate analogue.

Taken together, the results obtained with the calix[4]arene-crown-6 di(carboxylic acid) and di(*N*-(X)sulfonyl carboxamide) ligands **1a–e**, **2a–e** and **3a–e** clearly demonstrate energetically most favorable extraction complexes of the type represented in **9** in which the calix[4]arene unit is in the cone conformation. This places one ionized group over and one under the polyether-complexed alkaline earth metal ion.

Experimental

General

Melting points were determined with a Mel-Temp melting point apparatus. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 1600 FT-IR spectrometer as deposits from CH_2Cl_2 solution on NaCl plates. The ^1H- and ^{13}C-NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR (^1H- 500 MHz and ^{13}C- 126 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard. Elemental analysis was performed by Desert Analytics Laboratory of Tucson, Arizona.

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 a high vacuum and then stored in a desiccator. Pentaethylene glycol ditosylate[18] and *p*-*tert*-butylcalix[4]arene (**4**)[13] were prepared by literature procedures.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis(carboxymethoxy)calix[4]arene-crown-6 (1a). A mixture of **6** (5.40 g, 5.28 mmol), THF (250 mL) and 10% Me_4NOH (250 mL) was refluxed for 12 h. The THF was evaporated *in vacuo* and the resulting aqueous mixture 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 layers were washed with water (2 × 50 mL) and dried over $MgSO_4$. After evaporation of the THF *in vacuo*, **1a** (4.54 g, 89%) was obtained as a white solid (mp 257–259 °C). ν_{max}(film)/cm^{-1} 3233 (COOH), 1756 (C=O). δ_H 10.94 (2 H, bs, CO_2H), 7.13 (4 H, s, ArH), 6.54 (4 H, s, ArH), 4.97 (4 H, s, OCH_2CO), 4.47 (4 H, d, *J* 12.9, $ArCH_2Ar$), 3.93 (4 H, m, OCH_2CH_2O), 3.87 (4 H, m, OCH_2CH_2O), 3.79 (8 H, s, OCH_2CH_2O), 3.75 (4 H, m, OCH_2CH_2O), 3.22 (4H, d, *J* 12.9, $ArCH_2Ar$), 1.34 (18 H, s, $C(CH_3)_3$), 0.83 (18 H, s, $C(CH_3)_3$). δ_C 171.11, 153.13, 151.20, 146.11, 145.38, 134.94, 131.96, 125.82, 125.09, 75.61, 71.74, 70.53, 70.51, 70.47, 69.93, 34.09, 33.63, 31.62, 31.29, 30.99. Found: C, 72.28; H, 8.03%. $C_{58}H_{78}O_{12}$ requires C, 72.02; H, 8.13%.

General procedure for preparation of cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(X-sulfonyl)carbamoyl]-calix[4]arene-crown-6 compounds 1b–e. A solution of **1a** (1.50 g, 1.55 mmol) and oxalyl chloride (1.57 g, 12.37 mmol) in benzene (60 mL) was refluxed for 5 h. The solution was evaporated *in vacuo* and dried under a high vacuum for 30 min. The residue was dissolved in THF (20 mL) and added to a mixture of the appropriate sulfonamide (4.65 mmol) and NaH (0.58 g, 24.17 mmol) in THF (40 mL) under nitrogen at room temperature. The reaction mixture was stirred for 12 h (except for *p*-nitrobenzenesulfonamide, 3 h). The reaction was quenched with a small amount of water and the THF was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with 10% aqueous K_2CO_3 solution (2 × 5 0 mL), 10% HCl (50 mL) and water (2 × 50 mL). The organic layer was dried over $MgSO_4$ (except for trifluoromethyl derivatives). Evaporation of CH_2Cl_2 *in vacuo* gave the crude product, which was purified by recrystallization or chromatography.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(methanesulfonyl)carbamoyl]calix[4]arene-crown-6 (1b). Chromatography on silica gel with CH_2Cl_2–MeOH (50 : 1) as eluent, yield 73%, white solid, mp 266–268 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1734, 1718 cm^{-1} (C=O). δ_H 10.57 (2 H, s, NH), 7.11 (4 H, s, ArH), 6.45 (4 H, s, ArH), 5.17 (4 H, s, OCH_2CO), 4.58 (4 H, d, *J* 12.9, $ArCH_2Ar$), 3.92 (8 H, q, OCH_2CH_2O), 3.85 (4 H, d, OCH_2CH_2O), 3.81 (8 H, s, OCH_2CH_2O), 3.23 (4 H, d, *J* 12.9, $ArCH_2Ar$), 3.18 (6 H, s, CH_3SO_2), 1.33 (18 H, s, $C(CH_3)_3$), 0.82 (18 H, s, $C(CH_3)_3$). δ_C 170.62, 152.37, 152.20, 145.59, 144.87, 135.31, 131.57, 125.77, 124.72, 73.96, 70.41, 70.23, 69.97, 69.28, 41.35, 34.02, 33.53, 32.09, 31.61, 31.01. Found: C, 64.12; H, 7.56; N, 2.77%. $C_{60}H_{84}O_{14}N_2S_2$ requires C, 64.26; H, 7.55; N, 2.50%.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(benzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (1c). Chromatography on silica gel with EtOAc–hexanes (3 : 1) as eluent, yield 72%, white solid, mp 267–270 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1721 cm^{-1} (C=O). δ_H 10.80 (2 H, s, NH), 8.07 (4 H, m, PhH), 7.59 (2 H, m, PhH), 7.47 (4 H, m, PhH), 6.94 (4 H, s, ArH), 6.38 (4 H, s, ArH), 5.02 (4 H, s, OCH_2CO), 4.38 (4 H, d, *J* 12.9, $ArCH_2Ar$), 3.87 (4 H, m, OCH_2CH_2O), 3.81 (4 H, m, OCH_2CH_2O), 3.75 (8 H, s, OCH_2CH_2O), 3.67 (4 H, m, OCH_2CH_2O), 3.04 (4 H, d, *J* 12.9, $ArCH_2Ar$), 1.29 (18 H, s, $C(CH_3)_3$), 0.78 (18 H, s, $C(CH_3)_3$). δ_C 168.80, 152.39, 151.79, 145.16, 144.74, 139.32, 134.98, 133.44, 131.59, 128.62, 128.38, 125.65, 124.63, 73.93, 70.57, 70.48, 70.16, 69.92, 69.54, 33.94, 33.49, 31.99, 31.59, 30.98. Found: C, 67.58; H, 7.22; N, 2.48%. $C_{70}H_{88}O_{14}N_2S_2$ requires C, 67.50; H, 7.12; N, 2.25%.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(*p*-nitrobenzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (1d). Chromatography on silica gel with EtOAc–hexanes (1 : 2) as eluent, yield 52%, white solid, mp 262–265 °C. ν_{max}(film)/cm^{-1} 3104 cm^{-1} (N–H); 1737, 1731 cm^{-1} (C=O). δ_H 10.95 (2 H, s, NH), 8.27 (4 H, m, PhH), 8.21 (4 H, m, PhH), 6.95 (4 H, s, ArH), 6.37 (4 H, s, ArH), 5.07 (4 H, s, OCH_2CO), 4.38 (4 H, d, *J* 12.8, $ArCH_2Ar$), 3.90 (8 H, q, OCH_2CH_2O), 3.81 (12 H, m, OCH_2CH_2O), 3.08 (4 H, d, *J* 13.1, $ArCH_2Ar$), 1.26 (18 H, s, $C(CH_3)_3$), 0.77 (18 H, s, $C(CH_3)_3$). δ_C 169.08, 152.35, 151.73, 150.46, 145.72, 145.04, 144.53, 134.96, 131.29, 129.88, 125.73, 124.73, 123.82, 73.92, 70.46, 70.39, 70.22, 69.85, 69.40, 33.94, 33.53, 32.03, 31.54, 30.98. Found: C, 62.96; H, 6.58; N, 4.12%. $C_{70}H_{86}O_{18}N_4S_2$ requires C, 62.95; H, 6.49; N, 4.19%.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(trifluoromethanesulfonyl)carbamoyl]calix[4]arene-crown-6 (1e). Chromatography on silica gel with EtOAc–hexanes (1 : 5) as eluent, yield 68%, white solid, mp 203–206 °C. ν_{max}(film)/cm^{-1} 2800–3200 cm^{-1} (N–H); 1770 cm^{-1} (C=O). δ_H 10.97 (2 H, s, NH), 7.09 (4 H, s, ArH), 6.45 (4 H, s, ArH), 5.23 (4 H, s, OCH_2CO), 4.51 (4 H, d, *J* 12.9, $ArCH_2Ar$), 3.84–3.93 (20 H, m, OCH_2CH_2O), 3.23 (4 H, d, *J* 12.9, $ArCH_2Ar$), 1.33 (18 H, s, $C(CH_3)_3$), 0.81 (18 H, s, $C(CH_3)_3$). δ_C 168.08, 152.46, 151.45, 145.82, 145.01, 135.07, 131.48, 125.85, 124.71, 73.33, 70.35, 70.08, 69.84, 68.55, 34.04, 33.57, 32.03, 31.59, 31.00. Found: C, 58.86; H, 6.09; N, 2.51%. $C_{60}H_{78}O_{14}N_2S_2F_6$ requires C, 58.62; H, 6.39; N, 2.28%.

Partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-(carboxymethoxy)calix[4]arene-crown-6 (2a). A mixture of **5** (8.43 g, 9.91 mmol), THF (250 mL) and KH (2.50 g, 35% dispersion in mineral oil, 21.80 mmol) was stirred under nitrogen at room temperature for 1 h. Ethyl bromoacetate (4.98 g, 29.82 mmol) in THF (50 mL) was added slowly. The reaction mixture was stirred at room temperature for 12 h and then quenched with a small amount of water. The THF was evaporated *in vacuo*. To the residue was added 95% EtOH (200 mL), NaOH (2.29 g, 57.25 mmol) and H_2O (30 mL) and the solution was refluxed for 24 h. The EtOH was evaporated in *vacuo* and the resulting aqueous mixture was cooled in an ice-bath and acidified with 6 N HCl. The solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (2 × 50 mL) and dried over $MgSO_4$. After evaporation of the CH_2Cl_2 *in vacuo*, the crude product was recrystallized from CH_2Cl_2–MeOH to give **2a** (6.90 g, 72%) as a white solid with mp 244–246 °C. ν_{max}(film)/cm^{-1} 2700–3300 (COOH), 1758 (C=O). δ_H 7.5–9.0 (2 H, bs, COOH), 7.23 (2 H, s, ArH), 7.14 (2 H, s, ArH), 6.98 (2 H, d, *J* 2.44, ArH), 6.77 (2 H, d, *J* 2.32, ArH), 4.87 (2 H, s, OCH_2CO), 4.57 (2 H, d, *J* 12.6, $ArCH_2Ar$), 4.21 (2 H, m, OCH_2CH_2O), 3.88 (2 H, d, *J* 15.5, $ArCH_2Ar$), 3.79 (2 H, s, OCH_2CO), 3.64–3.77 (8 H, m, OCH_2CH_2O, $ArCH_2Ar$), 3.54–3.64 (6 H, m, OCH_2CH_2O), 3.45–3.52 (2 H, m, OCH_2CH_2O), 3.34–3.45 (4 H, m, OCH_2CH_2O), 3.12 (2 H, d, *J* 12.6, $ArCH_2Ar$), 1.50 (9 H, s, $C(CH_3)_3$), 1.33 (9 H, s, $C(CH_3)_3$), 1.10 (18 H, s, $C(CH_3)_3$). δ_C 170.34, 168.47, 152.26, 150.89, 149.79, 148.03, 146.90, 146.48, 135.66, 134.66, 133.14, 132.39, 128.03, 127.25, 125.69, 124.34, 73.64, 71.06, 70.77, 70.73, 70.55, 69.36, 66.13, 38.56, 34.34, 34.12, 33.91, 31.58, 31.52, 30.91, 30.63. Found: C, 72.38; H, 8.36%. $C_{58}H_{78}O_{12}$ requires C, 72.02; H, 8.03%;

General procedure for preparation of partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(X-sulfonyl)carbamoyl]-calix[4]arene-crown-6 compounds 2b–e. The procedure followed that utilized for the cone isomers **1b–e**.

Partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(methanesulfonyl)carbamoyl]calix[4]arene-crown-6 (2b). Recrystallization from CH_2Cl_2–MeOH, yield 62%, white solid, mp 269–272 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1721 cm^{-1} (C=O). δ_H 10.62 (1 H, s, NH), 8.46 (1 H, s, NH), 7.22 (2 H, s, ArH), 7.09 (2 H, d, ArH), 6.98 (2 H, s, ArH), 6.91 (2 H, d, ArH), 4.70 (2 H, s, OCH_2CO), 4.54 (2 H, d, *J* 12.4, $ArCH_2Ar$), 3.93 (2 H, m, OCH_2CH_2O), 3.64–3.89 (14 H, m, $ArCH_2Ar$, OCH_2CH_2O), 3.60 (2 H, m, OCH_2CH_2O), 3.48 (2 H, m, OCH_2CH_2O), 3.25 (2 H, d, *J* 12.6, $ArCH_2Ar$), 3.05 (3 H, s, CH_3SO_2), 3.02 (3 H, s, CH_3SO_2), 2.08 (2 H, s, OCH_2CO), 1.42 (9 H, s, $C(CH_3)_3$), 1.17 (27 H, d, $C(CH_3)_3$). δ_C 170.13, 166.54, 152.46, 151.98, 151.66, 146.45, 146.06, 145.25, 136.20, 133.41, 133.09, 131.97, 127.19, 126.26, 125.54, 125.49, 74.32, 71.98, 70.94, 70.43, 70.07, 70.04, 68.85, 41.24, 40.60, 38.15, 34.07, 33.92, 33.90, 31.65, 31.20, 31.16, 30.97. Found: C, 64.42; H, 7.47; N, 2.47%. $C_{60}H_{84}O_{14}N_2S_2$ requires C, 64.26; H, 7.55; N, 2.50%.

Partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(benzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (2c). Recrystallization from CH_2Cl_2–MeOH, yield 90%, white solid, mp 165–168 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1742, 1723 cm^{-1} (C=O). δ_H 11.00 (1 H, s, NH), 8.52 (1 H, s, NH), 8.07 (2 H, m, PhH), 7.83 (2 H, m, PhH), 7.58 (1 H, m, PhH), 7.52 (1 H, m, PhH), 7.45 (2 H, m, PhH), 7.36 (2 H, m, PhH), 7.17 (2 H, s, ArH), 7.02 (2 H, d, ArH), 6.85 (2 H, d, ArH), 6.75 (2 H, s, ArH), 4.53 (2 H, s, OCH_2CO), 4.27 (2 H, d, *J* 12.4, $ArCH_2Ar$), 3.76–3.94 (8 H, m, OCH_2CH_2O, $ArCH_2Ar$), 3.70 (4 H, m, OCH_2CH_2O), 3.61 (4 H, m, OCH_2CH_2O), 3.55 (2 H, m, OCH_2CH_2O), 3.47 (2 H, m, OCH_2CH_2O), 3.32–3.42 (4 H, m, OCH_2CH_2O), 2.90 (2 H, d, *J* 12.4, $ArCH_2Ar$), 1.47 (2 H, s, OCH_2CO), 1.40 (9 H, s, $C(CH_3)_3$), 1.09 (18 H, s, $C(CH_3)_3$), 1.01 (9 H, s, $C(CH_3)_3$). δ_C 168.73, 164.44, 152.16, 152.01, 151.68, 146.62, 145.70, 145.40, 139.26, 138.46, 136.87, 133.65, 133.36, 133.29, 131.89, 131.80, 128.49, 128.47, 128.42, 128.33, 126.55, 126.13, 125.86, 125.52, 75.60, 71.64, 70.85, 70.32, 70.04, 69.64, 68.26, 38.16, 34.08, 33.82, 33.81, 31.61, 31.1, 30.98, 30.46. Found: C, 67.74; H, 7.17; N, 2.29%. $C_{70}H_{88}O_{14}N_2S_2$ requires C, 67.50; H, 7.12; N, 2.25%.

Partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(*p*-nitrobenzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (2d). Recrystallization from CH_2Cl_2–MeOH, yield 46%, light yellow solid, mp 289–291 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1}

(N–H); 1743, 1727 cm^{-1} (C=O). δ_H 11.26 (1 H, s, NH), 8.61 (1 H, s, NH), 8.25–8.33 (4 H, m, PhH), 8.18–8.25 (2 H, m, PhH), 8.00–8.06 (2 H, m, PhH), 7.19 (2 H, s, ArH), 7.04 (2 H, d, ArH), 6.84 (2 H, d, ArH), 6.76 (2 H, s, ArH), 4.56 (2 H, s, OCH_2CO), 4.29 (2 H, d, *J* 12.3, $ArCH_2Ar$), 3.77–3.92 (8 H, m, $ArCH_2Ar$, OCH_2CH_2O), 3.74 (4 H, m, OCH_2CH_2O), 3.59 (6 H, m, OCH_2CH_2O), 3.49 (2 H, m, OCH_2CH_2O), 3.30–3.42 (4 H, m, OCH_2CH_2O), 2.94 (2 H, d, *J* 12.4, $ArCH_2Ar$), 1.44 (2 H, s, OCH_2CO), 1.41 (9 H, s, $C(CH_3)_3$), 1.07 (18 H, s, $C(CH_3)_3$), 1.01 (9 H, s, $C(CH_3)_3$). δ_C 169.12, 164.84, 151.95, 151.92, 151.70, 146.93, 146.07, 145.81, 144.77, 143.86, 137.02, 133.78, 131.92, 131.86, 130.11, 129.97, 126.70, 126.25, 125.82, 125.62, 123.67, 123.61, 75.51, 71.62, 70.87, 70.33, 70.12, 69.67, 68.16, 38.28, 34.19, 33.89, 33.87, 31.67, 31.07, 30.98, 30.56. Found: C, 63.23; H, 6.69; N, 4.29%. $C_{70}H_{86}O_{18}N_4S_2$ requires C, 62.95; H, 6.49; N, 4.19%.

Partial cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(trifluoromethanesulfonyl)carbamoyl]calix[4]arene-crown-6 (2e). Recrystallization from CH_2Cl_2–MeOH, yield 66%, white solid, mp 214–216 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1773, 1750 cm^{-1} (C=O). δ_H 11.47 (1 H, bs, NH), 8.64 (1 H, s, NH), 7.24 (2 H, d, ArH), 7.22 (2 H, s, ArH), 6.96 (2 H, s, ArH), 6.92 (2 H, d, ArH), 4.76 (2 H, s, OCH_2CO), 4.52 (2 H, d, *J* 12.4, $ArCH_2Ar$), 3.81–4.00 (8 H, m, $ArCH_2Ar$, OCH_2CH_2O), 3.71–3.81 (4 H, m, OCH_2CH_2O), 3.42–3.71 (12 H, m, OCH_2CH_2O), 3.28 (2 H, d, *J* 12.3, $ArCH_2Ar$), 1.60 (2 H, s, OCH_2CO), 1.41 (9 H, s, $C(CH_3)_3$), 1.22 (18 H, s, $C(CH_3)_3$), 1.12 (9 H, s, $C(CH_3)_3$). δ_C 168.71, 162.90, 151.91, 151.60, 151.45, 147.47, 146.68, 146.21, 137.50, 134.09, 131.96, 131.79, 126.81, 126.59, 125.93, 125.68, 76.12, 71.51, 71.01, 70.58, 70.03, 69.58, 68.28, 38.46, 34.23, 34.06, 34.02, 31.65, 31.15, 31.03, 30.59. Found: C, 58.62; H, 6.48; N, 2.25%. $C_{60}H_{78}O_{14}N_2S_2F_6$ requires C, 58.62; H, 6.39; N, 2.28%.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-(carboxymethoxy)calix[4]arene-crown-6 (3a). A mixture of diester **8** (6.09 g, 5.55 mmol), NaOH (1.78 g, 44.4 mmol), EtOH (100 mL) and water (30 mL) was refluxed for 12 h. The EtOH was evaporated *in vacuo* and the resulting aqueous solution was cooled in an ice-bath and acidified with 6 N HCl. The solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with water (2 × 50 mL) and dried over $MgSO_4$. After evaporation of the CH_2Cl_2 *in vacuo*, **3a** was obtained (5.21 g, 97%) as a white solid, mp 265–268 °C. ν_{max}(film)/cm^{-1} 3416 (CO_2H), 1760 (C=O). δ_H 7.67 (2 H, bs, COOH), 7.10 (4 H, s, ArH), 7.03 (4 H, s, ArH), 4.07 (4 H, s, OCH_2CO), 3.96 (4 H, d, *J* 16.9, $ArCH_2Ar$), 3.90 (4 H, d, *J* 16.9, $ArCH_2Ar$), 3.55 (4 H, s, OCH_2CH_2O), 3.50 (8 H, s, OCH_2CH_2O), 3.34 (4 H, t, OCH_2CH_2O), 3.03 (4 H, t, OCH_2CH_2O), 1.35 (18 H, s, $C(CH_3)_3$), 1.23 (18 H, s, $C(CH_3)_3$). δ_C 169.27, 169.24, 153.63, 151.98, 146.60, 146.31, 146.30, 132.75, 132.42, 126.20, 126.09, 71.19, 71.09, 70.98, 70.03, 68.41, 67.26, 38.61, 34.10, 33.86, 31.54, 31.16. Found: C, 72.17; H, 7.94%. $C_{58}H_{78}O_{12}$ requires C, 72.02; H, 8.13%.

General procedure for preparation of 1,3-alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[*N*-(X-sulfonyl)carbamoyl]-calix[4]arene-crown-6 compounds 3b–e. The procedure followed that utilized for the cone isomers **1b–e**.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(methanesulfonyl)carbamoyl]calix[4]arene-crown-6 (3b). Chromatography on silica gel with CH_2Cl_2–MeOH (20 : 1) as eluent, yield 77%, white solid, mp 278–280 °C. ν_{max}(film)/cm^{-1} 3200 cm^{-1} (N–H); 1706 cm^{-1} (C=O). δ_H 8.81 (2 H, s, NH), 7.12 (4 H, s, ArH), 7.11 (4 H, s, ArH), 3.93–4.00 (8 H, t, $ArCH_2Ar$), 3.54 (4 H, s, OCH_2CO), 3.50–3.54 (12 H, m, OCH_2CH_2O), 3.43 (4 H, m, OCH_2CH_2O), 3.16 (6 H, s, CH_3SO_2), 2.69 (4 H, m, OCH_2CH_2O), 1.35 (18 H, s, $C(CH_3)_3$), 1.27 (18 H, s, $C(CH_3)_3$). δ_C 169.64, 154.08, 153.39, 146.70, 146.19, 132.92, 132.26, 126.77, 126.54, 71.45, 70.66, 70.64, 70.25, 69.31, 68.55, 41.25, 38.72, 34.11, 34.06, 31.46, 31.22. Found: C, 64.58; H, 7.73; N, 2.61%. $C_{60}H_{84}O_{14}N_2S_2$ requires C, 64.26; H, 7.55; N, 2.50%.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(benzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (3c). Chromatography on silica gel with CH_2Cl_2-MeOH (50:1) as eluent, yield 78%, white solid, mp 264–267 °C. ν_{max}(film)/cm^{-1} 3345 cm^{-1} (N–H); 1726, 1711 cm^{-1} (C=O). δ_H 9.20 (2 H, s, NH), 8.01 (4 H, m, PhH), 7.60 (2 H, m, PhH), 7.49 (4 H, m, PhH), 7.08 (4 H, s, ArH), 7.03 (4 H, s, ArH), 3.92 (8 H, t, $ArCH_2Ar$), 3.57 (4 H, s, OCH_2CH_2O), 3.52 (8 H, m, OCH_2CH_2O), 3.42 (4 H, m, OCH_2CH_2O), 3.16 (4 H, s, OCH_2CO), 2.69 (4 H, t, OCH_2CH_2O), 1.33 (18 H, s, $C(CH_3)_3$), 1.11 (18 H, s, $C(CH_3)_3$). δ_C 168.62, 153.91, 153.28, 146.88, 146.02, 138.61, 133.77, 133.09, 132.47, 128.94, 128.33, 126.82, 126.68, 71.47, 71.08, 70.72, 70.29, 69.16, 68.64, 38.83, 34.06, 33.94, 31.48, 31.07. Found: C, 67.75; H, 7.28; N, 2.46%. $C_{70}H_{88}O_{14}N_2S_2$ requires C, 67.50; H, 7.12; N, 2.25%.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(*p*-nitrobenzenesulfonyl)carbamoyl]calix[4]arene-crown-6 (3d). Recrystallization from CH_2Cl_2–MeOH, yield 63%, light yellow solid, mp 273–275 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1727, 1714 cm^{-1} (C=O). δ_H 9.43 (2 H, s, NH), 8.34 (4 H, m, PhH), 8.23 (4 H, m, PhH), 7.11 (4 H, s, ArH), 7.02 (4 H, s, ArH), 3.88 (4 H, d, *J* 17.0, $ArCH_2Ar$), 3.94 (4 H, d, *J* 17.0, $ArCH_2Ar$), 3.57 (4 H, s, OCH_2CH_2O), 3.52 (8 H, m, OCH_2CH_2O), 3.42 (4 H, m, OCH_2CH_2O), 3.21 (4 H, bs, OCH_2CO), 2.70 (4 H, m, OCH_2CH_2O), 1.34 (18 H, s, $C(CH_3)_3$), 1.13 (18 H, s, $C(CH_3)_3$). δ_C 169.10, 153.97, 153.31, 150.76, 146.92, 146.51, 143.97, 133.24, 132.53, 129.77, 126.87, 126.73, 124.27, 71.50, 71.19, 70.73, 70.35, 69.43, 68.53, 38.70, 34.11, 33.98, 31.46, 31.01. Found: C, 62.96; H, 6.63; N, 4.25%. $C_{70}H_{86}O_{18}N_4S_2$ requires C, 62.95; H, 6.49; N, 4.19%.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-[*N*-(trifluoromethanesulfonyl)carbamoyl]calix[4]arene-crown-6 (3e). Chromatography on silica gel with CH_2Cl_2–EtOAc (50 : 1) as eluent, yield 52%, white solid, mp 232–234 °C. ν_{max}(film)/cm^{-1} 3300–2800 cm^{-1} (N–H); 1760 cm^{-1} (C=O). δ_H 9.35 (2 H, bs, NH), 7.12, 7.10 (8 H, s, ArH), 3.98 (8 H, q, $ArCH_2Ar$), 3.58 (4 H, s, OCH_2CH_2O), 3.53 (8 H, m, OCH_2CH_2O), 3.45 (8 H, m, OCH_2CH_2O, OCH_2CO), 2.74 (4 H, m, OCH_2CH_2O), 1.35 (18 H, s, $C(CH_3)_3$), 1.25 (18 H, s, $C(CH_3)_3$). δ_C 167.54, 153.99, 152.75, 147.07, 146.53, 133.16, 132.59, 126.83, 71.46, 70.76, 70.38, 69.12, 68.72, 38.84, 34.11, 33.99, 31.47, 31.02. Found: C, 58.98; H, 6.58; N, 2.32%. $C_{60}H_{78}O_{14}N_2S_2F_6$ requires C, 58.62; H, 6.39; N, 2.28%.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-dihydroxycalix-[4]arene-crown-6 (5). Under nitrogen, a solution of *p*-*tert*-butylcalix[4]arene (**4**·toluene) (5.00 g, 6.75 mmol), pentaethylene glycol ditosylate (4.18 g, 7.64 mmol) and K_2CO_3 (1.06 g, 7.64 mmol) in MeCN (300 mL) was refluxed for 24 h. The mixture was filtered and the MeCN was evaporated *in vacuo*. To the residue CH_2Cl_2 (200 mL) and water (100 mL) was added. The organic phase was separated and washed with 10% aqueous HCl (50 mL) and twice with water, dried over $MgSO_4$ and evaporated *in vacuo* to give the crude product, which was purified by chromatography on silica gel with EtOAc–hexanes (1 : 5) as eluent to give **5** (4.71 g, 82%) as a white solid, mp 229–231 °C, ref. 9 236–237 °C. ν_{max}(film)/cm^{-1} 3405 (OH). δ_H 7.06 (4 H, s, ArH), 6.98 (2 H, s, OH), 6.73 (4 H, s, ArH), 4.35 (2 H, d, *J* 13.1, $ArCH_2Ar$), 4.10 (4 H, m, OCH_2CH_2O), 4.00 (4 H, m, OCH_2CH_2O), 3.93 (4 H, m, OCH_2CH_2O), 3.84 (4 H, m, OCH_2CH_2O), 3.76 (4 H, s, OCH_2CH_2O), 3.28 (2 H, d, *J* 13.1, $ArCH_2Ar$), 1.31 (18 H, s, $C(CH_3)_3$), 0.91 (18 H, s, $C(CH_3)_3$). δ_C 150.65, 149.92, 146.73, 141.19, 132.36, 127.79, 125.40, 124.96, 76.26, 71.67, 71.05, 70.10, 69.93, 33.82, 33.79, 31.70, 31.28, 30.95. Found: C, 76.15; H, 8.81%. $C_{54}H_{74}O_8$ requires C, 76.20; H, 8.76%.

Cone 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis[(ethoxycarbonylmethoxy]calix[4]arene-crown-6 (6). A mixture of **5** (4.89 g, 5.75 mmol), THF (250 mL) and NaH (0.96 g, 28.76 mmol) was stirred under nitrogen at room temperature for 30 min. Ethyl bromoacetate (5.76 g, 34.49 mmol) in THF (50 mL) was added slowly. The mixture was stirred at room temperature for 12 h and quenched with a small amount of water (added dropwise). The THF was evaporated *in vacuo* and CH_2Cl_2 (200 mL) and 10% HCl (50 mL) were added to the residue. The organic layer was washed with water (50 mL) twice, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography on alumina with EtOAc–hexanes (1 : 5) as eluent to give **6** (4.83 g. 82%) as a white solid, mp 152–154 °C. ν_{max}(film)/cm^{-1} 1760, 1735 cm^{-1} (C=O). δ_H 7.01 (4 H, s, ArH), 6.55 (4 H, s, ArH), 4.59 (4 H, s, OCH_2CO), 4.52 (4 H, d, *J* 12.6, $ArCH_2Ar$), 4.24 (8 H, m, $OCH_2(CH_3)$, OCH_2CH_2O), 4.15 (4 H, t, OCH_2CH_2O), 3.74–3.82 (8 H, m, OCH_2CH_2O), 3.73 (4 H, s, OCH_2CH_2O), 3.16 (4 H, d, *J* 12.8, $ArCH_2Ar$), 1.27–1.32 (6 H, m, $(OCH_2)CH_3$), 1.25 (18 H, s, $C(CH_3)_3$), 0.89 (18 H, s, $C(CH_3)_3$). δ_C 169.86, 167.23, 154.28, 152.18, 144.98, 144.78, 134.87, 132.23, 125.44, 124.88, 72.72, 71.93, 70.98, 70.75, 70.52, 69.93, 62.32, 60.65, 33.98, 33.64, 31.61, 31.26, 31.14, 25.93, 14.23, 13.99. Found: C, 72.14; H, 8.14%. $C_{62}H_{86}O_{12}\cdot 0.1\ CH_2Cl_2$ requires C, 72.29; H, 8.14%.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-bis(*p-tert*-butoxycarbonylmethoxy)calix[4]arene (7). A solution of **4**·toluene (10.00 g, 13.50 mmol) and K_2CO_3 (2.10 g, 15.20 mmol) in MeCN (150 mL) was heated to reflux for 0.5 h and *tert*-butyl bromoacetate (6.14 g, 31.48 mmol) was added dropwise. The mixture was refluxed for 24 h. The MeCN was removed *in vacuo* and CH_2Cl_2 (300 mL) and water (100 mL) were added to the residue. The organic layer was separated and washed with 10% HCl (100 mL) and twice with water (100 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Chromatography on silica gel with CH_2Cl_2–EtOAc (15 : 1) as eluent gave **7** (10.42 g, 88%) as a white solid, mp 180–182 °C. ν_{max}(film)/cm^{-1} 3438 cm^{-1} (OH), 1754, 1732 cm^{-1} (C=O). δ_H 7.14 (2 H, s, OH), 7.02 (4 H, s, ArH), 6.79 (4 H, s, ArH), 4.58 (4 H, s, OCH_2CO), 4.44 (4 H, d, *J* 13.1, $ArCH_2Ar$), 3.29 (4 H, d, *J* 13.2, $ArCH_2Ar$), 1.54 (18 H, s, $C(CH_3)_3$), 1.27 (18 H, s, $OC(CH_3)_3$), 0.91 (18 H, s, $C(CH_3)_3$). δ_C 168.23, 150.81, 150.47, 146.85, 141.18, 132.39, 127.75, 125.61, 124.99, 82.20, 73.08, 33.87, 33.77, 31.80, 31.66, 31.00, 28.14. Found: C, 76.86; H, 8.86%. $C_{56}H_{76}O_8$ requires C, 76.68; H, 8.73%.

1,3-Alternate 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis-(*tert*-butoxycarbonylmethoxy)calix[4]arene-crown-6 (8). A solution of **7** (10.00 g, 11.40 mmol), pentaethylene glycol ditosylate (6.83 g, 12.48 mmol), Cs_2CO_3 (5.57 g, 17.10 mmol) and MeCN (600 mL) was refluxed for 24 h. The MeCN was evaporated *in vacuo* and CH_2Cl_2 (300 mL) and water (100 mL) were added to the residue. The organic layer was separated and washed with 10% HCl (100 mL) and twice with water (100 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give the crude product, which was purified by chromatography (alumina with CH_2Cl_2–EtOAc, 50 : 1, as eluent) to give **8** (7.01 g, 57%) as a white solid, mp 182–185 °C. ν_{max}(film)/cm^{-1} 1756, 1727 cm^{-1} (C=O); δ_H 7.14 (4 H, s, ArH), 7.04 (4 H, s, ArH), 4.08 (4 H, d, *J* 15.9, $ArCH_2Ar$), 3.84 (4 H, s, OCH_2CO), 3.83 (4 H, d, *J* 16.0, $ArCH_2Ar$), 3.53–3.60 (12 H, m, OCH_2CH_2O), 3.02 (4 H, t, OCH_2CH_2O), 2.89 (4 H, t, OCH_2CH_2O), 1.36 (18 H, s, $C(CH_3)_3$), 1.33 (18 H, s, $C(CH_3)_3$), 1.24 (18 H, s, $C(CH_3)_3$); δ_C 169.23, 154.42, 153.76, 144.24, 143.80, 133.23, 133.16, 127.30, 126.35, 80.69, 77.26, 77.00, 76.75, 71.48, 71.11, 70.80, 70.76, 69.00, 68.95, 38.62, 33.90, 33.76, 31.55, 31.38, 27.97. Found: C, 73.56; H, 8.68%. $C_{66}H_{94}O_{12}$ requires C, 73.44; H, 8.78%.

Extraction procedure

An aqueous solution of the alkaline earth metal chlorides with hydroxides for pH adjustment (for **1e**, **2e** and **3e**, 0.10 M HCl was utilized for pH adjustment) (2.0 mL, 10.0 M in each alkaline earth metal cation species) and 2.0 mL of 1.0 mM ligand in chloroform in a metal-free, capped, polypropylene, 15 mL centrifuge tube was vortexed with a Glas-Col Multi-Pulse Vortexer for 10 min at room temperature. The tube was centrifuged for 10 min for phase separation with a Becton-Dickinson Clay Adams Brand® Centrifuge. 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 alkaline earth metal cation concentrations in the aqueous phase from stripping were determined with a Dionex DX-120 Ion Chromatograph with a CS12A column. 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.

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