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Di-ionizable calix[4]arene-1,3-crown-4 ligands in 1,3-alternate, cone, and partial-cone conformations: synthesis and metal ion extractions

Yanfei Yang [a], Xiaodan Cao [a], David W. Purkiss [a], John F. Cannon [b], Richard A. Bartsch [a,*]

[a] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA
[b] Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700, USA

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ABSTRACT

Di-ionizable calix[4]arene-1,3-crown-4 compounds locked in 1,3-alternate, cone, and partial-cone conformations are synthesized for evaluation in metal ion separations. The ionizable functions include carboxylic acid and *N*-(X)sulfonyl carboxamide groups in which the acidity is tuned by variation of the electron-withdrawing ability of X. Similar synthetic routes were employed for preparation of the cone and 1,3-alternate ligand series. A different preparative route utilizing protection and deprotection was required to obtain the partial-cone analogues. Ligand conformations were confirmed by their proton and/or carbon NMR spectra. X-ray diffraction verified an unusual 1,2-alternate conformation in the solid-state for one synthetic intermediate. Effects of ligand conformation and ionizable group variations on competitive solvent extractions of alkali and alkaline earth metal cations from aqueous solutions into chloroform were assessed. Single species solvent extractions of Hg^{2+} and Pb^{2+} were also performed.

1. Introduction

In calixarene–crown ethers, also called calixcrowns, a calixarene platform is linked to a polyether unit by connecting two phenolic oxygens of the former with a polyether chain.[1–6] More commonly encountered are calix[4]arene-1,3-crown ethers in which a calix[4]arene scaffold is bridged by a polyether fragment connecting two distal phenolic oxygens. The first example of this ligand family, *p-tert*-butylcalix[4]arene-1,3-crown-6, was reported in 1984 by Ungaro and co-workers.[7] Metal ion complexation studies have focused mainly on dialkylated, 1,3-bridged calix[4]arene-crown ethers, which have been found to exhibit high binding affinity and selectivity in alkali and alkaline earth metal cation extractions.[8–10] In such calix[4]arene–crown compounds, the bridging polyether unit may lock the calixarene framework in cone, 1,3-alternate, or partial-cone conformations.[1]

Of particular interest to our metal ion separations research program are 1,3-disubstituted calix[4]arene-crown compounds with pendant acidic groups on the two remaining phenolic oxygens. (The initial example of such a di-ionizable calixcrown compound, a cone *p-tert*-butylcalix[4]arene-1,3-crown-5 dicarboxylic acid, was reported by Ungaro and co-workers.)[10] Such ligands provide efficient extraction of divalent metal ions from aqueous solutions into organic media. The extraction proceeds by an ion-exchange process to form an electroneutral di-ionized calixcrown–divalent metal ion complex in the organic phase, thereby avoiding the need for concomitant transfer of a hydrophilic anion from the aqueous phase.

In addition to oxyacetic acid functions, we have employed *N*-(X) sulfonyl oxyacetamide groups with X=methyl, phenyl, *p*-nitrophenyl, and trifluoromethyl groups.[11,12] Variation of X is used to 'tune' the ligand acidity.[13] Also, we have observed that the *N*-(X) sulfonyl oxyacetamide groups produce ligands with greater solubility in organic extraction solvents than corresponding carboxylic acids.

In earlier work, we have evaluated the effect of conformational variation upon the efficiency and selectivity of alkaline earth metal ion solvent extractions by di-ionizable *p-tert*-butylcalix[4]arene-1,3-crown-6 ligands.[14] To probe the effect of shortening the polyether unit, the preparation of di-ionizable *p-tert*-butylcalix[4]arene-1,3-crown-4 ligands was proposed. However, synthetic difficulties arose, which made it impossible to obtain a full set of ligands.[15]

Further investigation revealed that with removal of the *p-tert*-butyl groups the desired series of di-ionizable calix[4]arene-1,3-crown-4 ligands could be realized. We now report the synthesis of these new ligands in 1,3-alternate (**1a**–**e**), cone (**2a**–**e**), and partial-cone (**3a**–**e**) conformations (Fig. 1). Their metal ion complexation properties have been evaluated in competitive solvent extractions of alkali metal cations and of alkaline earth metal cations from aqueous solutions into chloroform. Single species solvent extractions of Hg^{2+} and Pb^{2+} were also conducted.

* Corresponding author. Tel.: +1 806 742 3069; fax: +1 806 742 1289; e-mail address: richard.bartsch@ttu.edu (R.A. Bartsch).

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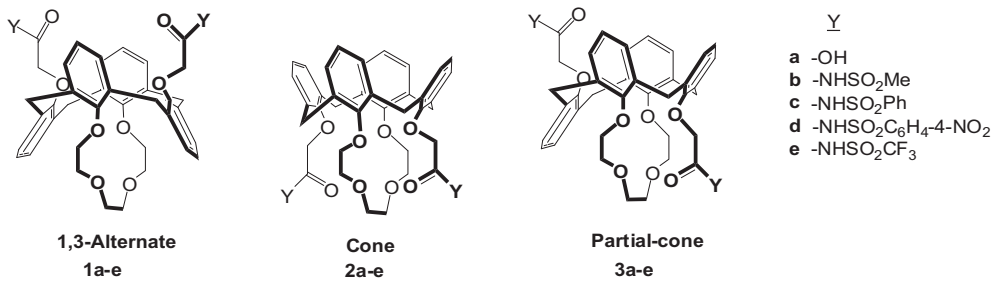


Fig. 1. Conformationally locked, di-ionizable calix[4]arene-1,3-crown-4 ligands in 1,3-alternate (**1a**–**e**), cone (**2a**–**e**), and partial-cone (**3a**–**e**) conformations.

2. Results and discussion

2.1. Synthesis of 1,3-alternate di-ionizable calix[4]arene-1,3-crown-4 ligands

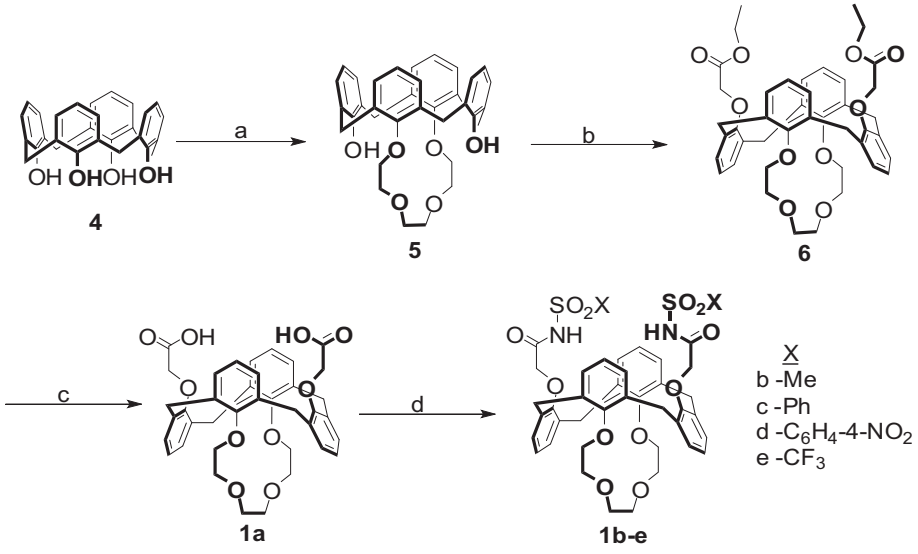
Yamato and Shinkai[16] reported the synthesis of calix[4]arene-1,3-crown-4 in 71% yield by reaction of calix[4]arene with triethylene glycol ditosylate and Na_2CO_3 in refluxing MeCN.[18] Our synthesis of the 1,3-alternate calix[4]arene-1,3-crown-4 ligands (Scheme 1) began with the preparation of calix[4]arene-1,3-crown-4 (**5**) from calix[4]arene (**4**) by this reported method. Then calixcrown **5** was treated with KH in THF followed by addition of ethyl bromoacetate to produce diester **6** in 65% yield. Di(carboxylic acid) **1a** was realized in 95% yield by hydrolysis of diester **6** with Me_4NOH (TMAOH) in aq THF. Di(carboxylic acid) **1a** was converted into the corresponding di(acid chloride) by reaction with oxalyl chloride in refluxing benzene. The crude di(acid chloride) was used directly without further purification. The appropriate, commercially available sulfonamide was converted into its sodium salt by reaction with NaH in THF. Then the di(acid chloride) was added and the reaction was allowed to proceed at room temperature overnight to give **1b**–**e** in 67–85% yields.

The 1,3-alternate conformation for products **1a**–**e** was readily established by their ^1H and ^{13}C NMR spectra (Table 1) according to the 'De Mendoza' rule.[17] Since the aromatic units are alternately *anti* to each other, the differential between the *equatorial* protons H_e and *axial* protons H_a on the methylene bridge should be minimized. As a result, a singlet is generally observed in the ^1H NMR spectrum. However, the methylene bridge ($ArCH_2Ar$) protons appeared as an AB pattern for calix[4]arene-1,3-crown-4 di(carboxylic acid) **1a** at δ 3.93. These protons in **1b**–**e** were singlets. These proton signals all correlated with single carbon signals at 38 ppm. This verified that the conformations of **1a**–**e** were 1,3-alternate.

2.2. Synthesis of cone di-ionizable calix[4]arene-1,3-crown-4 ligands

Formation of the di-ionizable calix[4]arene-1,3-crown-4 series ligands in the cone conformation followed a similar synthetic route (Scheme 2). Calix[4]arene-1,3-crown-4[16] (**5**) was reacted with NaH and then ethyl bromoacetate in THF to form diester **7** in the cone conformation as the major product in 50% yield. Di(carboxylic acid) **2a** was prepared from **7** in 97% yield by hydrolysis with TMAOH in refluxing aq THF. By reaction with oxalyl chloride in refluxing benzene, di(carboxylic acid **2a**) was converted into corresponding di(acid chloride), which was used in the subsequent reaction without purification. A commercially available sulfonamide was treated with NaH in THF followed by room temperature reaction of the corresponding sodium salt with the di(acid chloride) in THF. Products **2b**–**e** were realized in 40–73% yields.

The conformations for **2a**–**e** were deduced from their ^1H and ^{13}C NMR spectra. Selected ^1H and ^{13}C NMR chemical shifts are listed in Table 1. The *syn* arrangement of all aromatic units of the calix[4]arene framework makes the *equatorial* protons H_e and *axial* protons H_a diastereotopic to each other. The methylene bridge ($ArCH_2Ar$) protons appeared as a pair of widely separated (by at least 1 ppm) doublets, which is a typical AX pattern for calix[4]arene compounds in the cone conformation. The corresponding carbon signals were located at 30–31 ppm,[17] which further confirms the cone conformation. The –NH protons in **2b**–**e** were located around



Scheme 1. Synthesis of 1,3-alternate di-ionizable calix[4]arene-1,3-crown-4 ligands **1a**–**e**. Reagents and conditions: (a) $TsO(CH_2CH_2O)_3Ts$, Na_2CO_3, MeCN, reflux; (b) $BrCH_2CO_2Et$, KH, THF, rt; (c) 10% aq NMe_4OH, THF, reflux; (d) (i) $(COCl)_2$, C_6H_6, reflux; (ii) XSO_2NH_2, NaH, THF, rt.

Table 1
Selected proton and ^{13}C chemical shifts (ppm) for the 1,3-alternate and cone di-ionizable calix[4]arene-1,3-crown-4 ligands in $CDCl_3$

Ligand	NH/OH	$OCH_2C(O)$	$OCH_2C(O)$[a]	$ArCH_2Ar$	$ArCH_2Ar$[a]
1a	—	4.14	67.36	3.93 AB pair	37.76
1b	8.14	4.01	70.63	3.90 singlet	37.99
1c	8.42	3.85	70.52	3.86 singlet	37.99
1d	8.60	3.81	70.61	3.88 singlet	37.99
1e	8.50	3.95	70.47	3.93 singlet	38.01
2a	—	4.37	71.53	4.31, 3.22	30.43
2b	10.88	4.33	74.79	4.28, 3.24	30.59
2c	10.87	4.22	73.88	4.24, 3.15	30.56
2d	11.20	4.24	73.83	4.23, 3.18	30.57
2e	11.61	4.40	73.98	4.26, 3.26	30.57

[a] Chemical shifts for ^{13}C.

11 ppm. A clear downfield shift was observed for these –NH protons compared to those of 1,3-alternate conformer analogues **1b**–**e**. This downfield shift is rationalized as resulting from the NH protons in the cone conformers being situated in the deshielding region of the aromatic units.

2.3. Synthesis of partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands

In the preparation of cone diester **7** by reaction of calix[4]arene-1,3-crown-4 (**5**) with NaH and ethyl bromoacetate in THF, a small amount of the partial-cone conformer was observed. Subsequent attempts with various base–solvent combinations and reaction temperatures (Table 2) to substantially enhance formation of the partial-cone conformer diester were unsuccessful.

Therefore, an entirely different synthetic route (Scheme 3) involving a protection–deprotection strategy was developed for preparation of the partial-cone conformers. Reaction of calix[4]arene (**4**) with K_2CO_3 and benzyl bromide in MeCN at reflux gave dibenzyl calix[4]arene **9** in 90% yield. Reaction of **9** with KH and *tert*-butyl bromoacetate in THF at room temperature gave dibenzyl calixarene di-*tert*-butyl ester **10** in the partial-cone conformation in 55% yield. (The 1,3-alternate conformer was isolated as a minor product in 25% yield.) Steric repulsion between the benzyl and *tert*-butyl groups together with an appropriate metal cation (K^+ in this case) chelation effect with the calix[4]arene framework were postulated as key factors in controlling the conformation. The benzyl protecting groups in **10** were removed by quantitative catalytic hydrogenolysis with Pd/C in THF/EtOH.

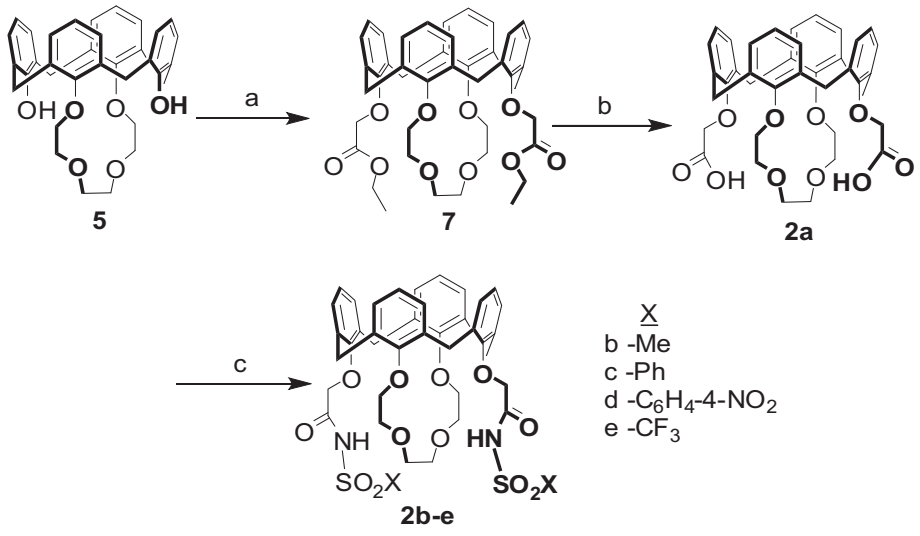
Table 2
Reactions of calix[4]arene-1,3-crown-4 (**5**) with ethyl bromoacetate and 10 equiv of base under different conditions

Base	Solvent	Reaction conditions	Diester conformation
NaH	THF	rt	Cone
NaH	THF	Reflux	Cone+partial-cone (minor)
NaH	DMF	rt	Cone+partial-cone (minor)
NaH	DMF	70 °C	Cone+partial-cone (minor)
K_2CO_3	THF	rt	No reaction
Cs_2CO_3	THF	rt	1,3-Alternate
t-BuOK	THF	rt	1,3-Alternate

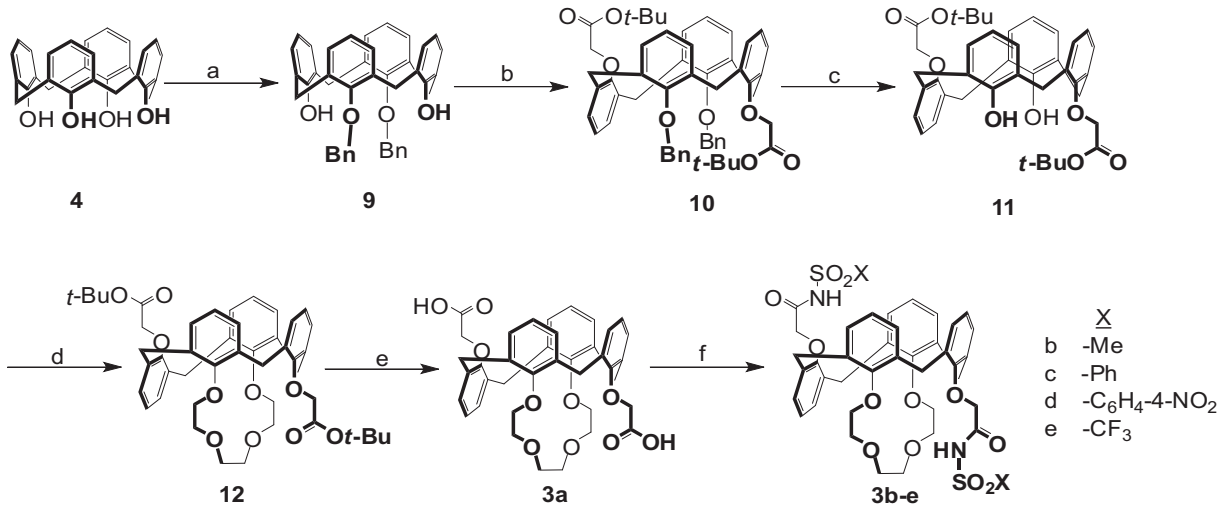
A partial-cone conformation was anticipated for di-*tert*-butyl ester **11**, since it would facilitate hydrogen bonding between the two distal hydroxyl groups. The NMR spectra of **11** in $CDCl_3$ were in agreement with this expectation. However, the solid-state structure of **11** as determined by X-ray diffraction revealed that the compound exists in a 1,2-alternate conformation in the solid-state (Fig. 2). Solid-state structures of mobile calix[4]arene ligands in 1,2-alternate conformations are rare with only a few cases reported in the literature.[18,19] As shown by the data in Table 3, the 1,2-alternate conformation structure for **11** is stabilized by hydrogen bonding of each phenolic hydroxyl group with an adjacent alkyl aryl ether oxygen.

Incorporation of the polyether segment was accomplished by reaction of **11** with K_2CO_3 and triethylene glycol ditosylate in MeCN at reflux to form diester **12** in 45% yield. Calix[4]crown-4 diacid **3a** in the partial-cone conformation was obtained in quantitative yield from **12** with NaOH in refluxing aq THF. Diacid **3a** was converted into the corresponding di(acid chloride) by reaction with oxalyl chloride in refluxing benzene. A commercially available sulfonamide in THF was treated with NaH to convert it into the sodium salt. The crude di(acid chloride) was dissolved in THF and reacted with the sodium salt of the sulfonamide at room temperature to produce partial-cone products **3b**–**e** in low yields of 15–43%.

Partial-cone conformers with two *anti*-arranged proton-ionizable groups are less symmetrical than corresponding 1,3-alternate and cone conformers. The reduced symmetry (from C_{2v} to C_s) brought extra complexity to the ^1H NMR spectra of the partial-cone conformers (Table 4). The two non-equivalent N–H protons appeared as two widely separated singlets. One was located downfield at about δ 11–12 and the other around δ 6. These very large chemical shift differences are attributed to different local magnetic environments for the proton-ionizable groups. In the



Scheme 2. Synthesis of cone di-ionizable calix[4]arene-1,3-crown-4 ligands **2a**–**e**. Reagents and conditions: (a) $BrCH_2CO_2Et$, NaH, THF, rt; (b) 10% aq NMe_4OH, THF, reflux; (c) (i) $(COCl)_2$, C_6H_6, reflux; (ii) XSO_2NH_2, NaH, THF, rt.



Scheme 3. Synthesis of partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands **3a**–**e**. Reagents and conditions: (a) BnBr, K_2CO_3, MeCN, reflux; (b) KH, $BrCH_2CO_2$-*t*-Bu, THF, rt; (c) Pd/C, H_2, THF/EtOH, rt; (d) $TsO(CH_2CH_2O)_3Ts$, K_2CO_3, MeCN, reflux; (e) NaOH, aq THF, reflux; (f) (i) $(COCl)_2$, C_6H_6, reflux; (ii) XSO_2NH_2, NaH, THF, rt.

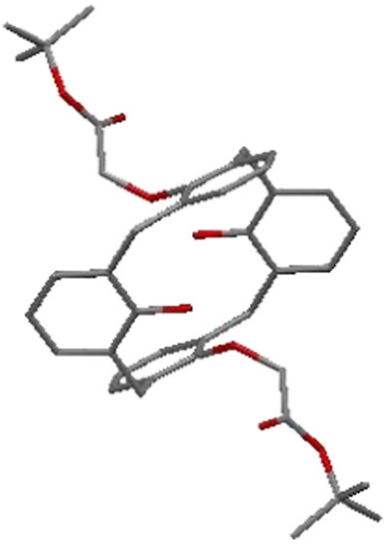


Fig. 2. Solid-state structure of intermediate **11** in a 1,2-alternate conformation.

Table 3
Hydrogen bonds for intermediate **11**

D–H···A	d(D–H) Å	d(H···A) Å	d(D···A) Å	<(DHA) °
O(3)–H(3A)···O(1)#1[a]	0.82	2.03	2.8233(15)	165.1

[a] Symmetry transformations used to generate equivalent atoms: #1 $-x+1, y+2, z$.

Table 4
Selected proton and ^{13}C chemical shifts (ppm) for the partial-cone di-ionizable ligands **3a**–**e** in $CDCl_3$

Ligand	NH/OH	$OCH_2C(O)$	$OCH_2C(O)$[a]	$ArCH_2Ar$	$ArCH_2Ar$[b]
3a	—	4.64, 3.16	1.48	4.42, 3.39; 3.99, 3.89	37.76, 30.18
3b	11.48, 6.26	4.63, 2.46	2.17	4.39, 3.42; 3.94, 3.90	30.21, 37.37
3c	11.53, 6.39	4.50, 2.28	2.22	4.21, 3.13; 3.83	30.02, 37.24
3d	11.82, 6.36	4.55, 2.60	1.95	4.27, 3.24; 3.88, 3.83	30.19, 37.44
3e	12.20, 6.38	4.71, 2.35	2.36	4.36, 3.44; 3.92	30.02, 37.40

[a] $\Delta\delta$ value for the two $OCH_2C(O)$ group protons.
[b] Chemical shifts for ^{13}C.

partial-cone conformers, two distal aromatic units are linked by the crown ether ring. The other two aromatic units bearing the proton-ionizable groups are arranged *anti* to each other. The three *syn*-arranged aromatic units cause strong deshielding of the N–H protons in the *syn*-arranged proton-ionizable group, while less deshielding affects the proton-ionizable group linked to the *anti*-arranged aromatic unit. This rationalization agrees with the trend observed for the 1,3-alternate and cone analogues. Based on an earlier NMR study,[20] the proton-ionizable group, that is, *syn* to the crown ether ring has its acidic proton appearing relatively downfield and vice versa. Similar results were observed for the $OCH_2C(O)$ protons and are caused by the same effects. A pair of widely separated (>1 ppm) doublets (AX pattern) and a pair of closely spaced doublets (for diacid) or a singlet (for sulfonamides) (AB patterns) were observed for the methylene bridge ($ArCH_2Ar$) protons. The AX system correlated with *syn*-orientated bridge carbons at about 30 ppm and the AB system correlated with *anti*-orientated bridge carbons at around 38 ppm. These data confirm the partial-cone conformations for ligands **3a**–**e**.

2.4. Effects of ligand conformation and ionizable group variation on metal ion extractions

The effects systematic structural variations in di-ionizable calix[4]arene-1,3-crown-4 ligands **1a**–**e**, **2a**–**e**, and **3a**–**e** on their metal ion complexation behavior were probed by extractions from aqueous solutions into chloroform. The structural variations included changing the conformation of the calix[4]arene scaffold (1,3-alternate, cone, and partial-cone) and varying the identity of the two pendant acidic groups (carboxylic acid and *N*-(X)sulfonyl carboxamides). Competitive solvent extractions of five alkali metal cation species and of four alkaline earth metal cation moieties were performed. Single species solvent extractions were conducted with Hg^{2+} and Pb^{2+}. (Calix[4]arenes with two *N*-(X)sulfonyl oxyacetamide groups on the lower rim and analogous calixcrown compounds are reported to efficiently extract Hg^{2+} and Pb^{2+} from acidic aqueous solutions into chloroform.[11,12,14,15]) The solvent extraction studies included hard[21] alkali and alkaline earth metal cations, intermediate Pb^{2+}, and soft Hg^{2+}.

Since polyether cavities in the calix[4]arene-1,3-crown-4 ligands are too small to accommodate even Li^+ in nesting complexes, coordination of the metal cation by the polyether portion of the ligand should involve perching on one or more of the alkyl aryl ether oxygens.

2.4.1. Competitive solvent extraction of alkali metal cations by di-ionizable calix[4]arene-1,3-crown-4 ligands. Competitive solvent extractions of aqueous alkali metal cation solutions (10.0 mM each in Li^+, Na^+, K^+, Rb^+, and Cs^+) by 1.0 mM solutions of di-ionizable calix[4]arene-1,3-crown-4 ligands **1a**–**e**, **2a**–**e**, and **3a**–**e** in chloroform were performed. The results are presented in Figs. 3–6, respectively, as plots of metal ion loadings of the organic phase versus the equilibrium pH of the aqueous phase. Since monovalent cations were being extracted by di-ionizable ligands, the maximum metal loading was 200%. In the literature, preferred complexation of Na^+ among the alkali metal cations by calix[4]arene ligands has often been reported.

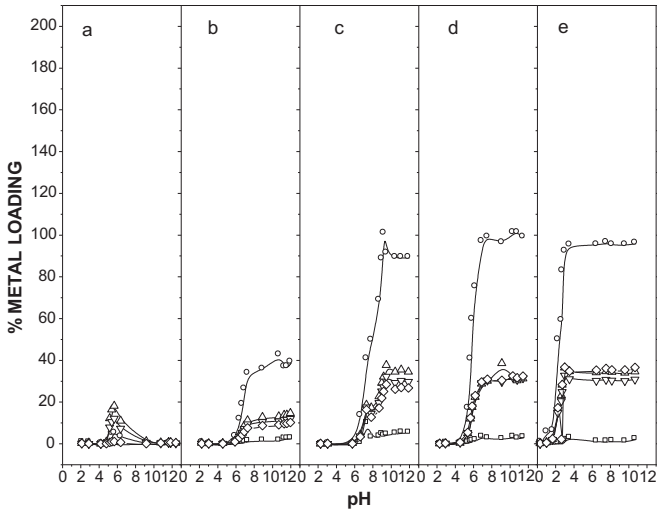


Fig. 3. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extractions of alkali metal cations into chloroform by 1,3-alternate di-ionizable calix[4]arene-1,3-crown-4 ligands (a) **1a**, (b) **1b**, (c) **1c**, (d) **1d**, and (e) **1e**. (□=Li^+, ○=Na^+, △=K^+, ▽=Rb^+, ◇=Cs^+).

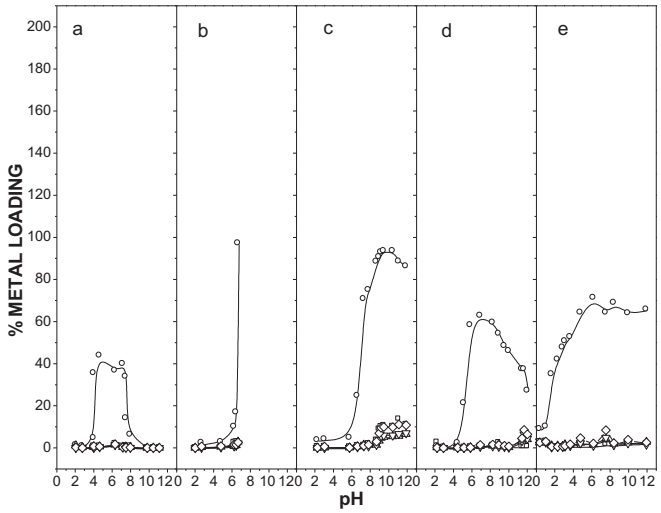


Fig. 4. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkali metal cations into chloroform by the cone di-ionizable calix[4]arene-1,3-crown-4 ligands (a) **2a**, (b) **2b**, (c) **2c**, (d) **2d**, and (e) **2e**. (□=Li^+, ○=Na^+, △=K^+, ▽=Rb^+, ◇=Cs^+).

Fig. 3 records results for competitive alkali metal cation extractions by alternate conformation ligands **1a**–**e**. In this conformation, the two ionizable side arms are directed away from the polyether binding site. Di(carboxylic acid) **1a** exhibited only very limited extraction with little selectivity among the alkali metal

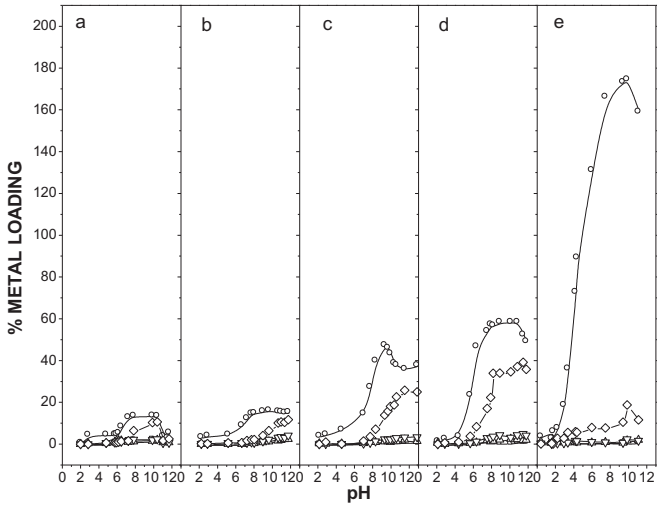


Fig. 5. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkali metal cations into chloroform by partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands (a) **3a**, (b) **3b**, (c) **3c**, (d) **3d**, and (e) **3e**. (□=Li^+, ○=Na^+, △=K^+, ▽=Rb^+, ◇=Cs^+).

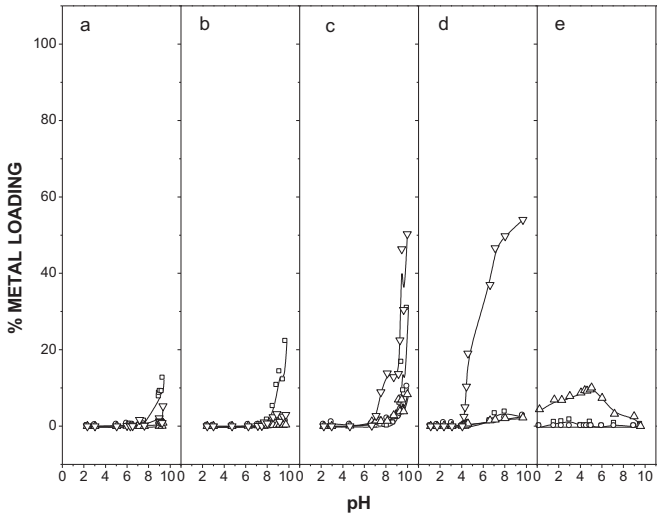


Fig. 6. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by 1,3-alternate di-ionizable calix[4]arene-1,3-crown-4 ligands **1a**–**e**, (a) **1a**, (b) **1b**, (c) **1c**, (d) **1d**, and (e) **1e**. (□=Mg^{2+}, ○=Ca^{2+}, △=Sr^{2+}, ▽=Ba^{2+}).

cations. On the other hand, the *N*-(X)sulfonyl carboxamide ligands **1b**–**e** all showed best extraction of Na^+, nearly negligible extraction of Li^+, and intermediate extractions of the other alkali metal cations with little differentiation among K^+, Rb^+, and Cs^+. For **1c**–**e**, the total metal ion loading approaches 200% with 100% loading of Na^+. This suggests preferred complexation of Na^+ at the polyether binding site followed by non-selective electrostatic binding of K^+, Rb^+, and Cs^+ by an ionized group of the 1:1 complex. This would minimize repulsion of the two positively charged metal ions.

Fig. 4 presents results for competitive alkali metal cation extraction by cone conformation ligands **2a**–**e**, all of which exhibited high selectivity for Na^+. In the cone conformation, the two ionizable groups may be oriented over the polyether unit forming an electron-rich pocket for complexation of Na^+. Strong favoring for 1:1 complex formation with Na^+ is indicated by the total metal ion loadings below 100% (compared with a 200% maximum) for all members of this ligand series. Coordination of a second alkali metal cation by the 1:1 complex would require dislocation of one of the ionizable groups complexing the Na^+.

Fig. 5 presents the results from competitive solvent extraction of alkali metal cations by partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands **3a**–**e**. For all five ligands, the cation selectivity order was $Na^+ > Cs^+$ with negligible extraction of Li^+, K^+, and Rb^+. The total metal loading was very low for di(carboxylic acid) **3a**. When the acidic group was *N*-(X)sulfonyl acetamide, the extraction efficiency changed markedly as the X group was varied $-Me < -Ph < -C_6H_4\text{-}4\text{-}NO_2 < -CF_3$, the trend of side arm acidity for $-C(O)NHSO_2X$.[13] Partial-cone **3e** with X=$-CF_3$ provided the best combination of extraction selectivity and efficiency for Na^+ extraction among ligands **1**–**3**. This is somewhat surprising since in the partial-cone conformation one acidic side arm may be situated over the polyether ring, but the other side arm must point away from the polyether ring.

2.4.2. Competitive solvent extraction of alkaline earth metal cations by di-ionizable calix[4]arene-1,3-crown-4 ligands. For extraction of alkaline earth metal cations by di-ionizable calix[4]crown-4 ligands **1a**–**e**, **2a**–**e**, and **3a**–**e**, the two anionic centers formed upon ionization produce an electroneutral complex with a divalent cation so the maximum metal ion loading was 100%.

For competitive solvent extractions of aqueous alkaline earth metal ion (10.0 mM in each) solutions by 1.0 mM solutions of di-ionizable calix[4]arene-crown-4 ligands **1a**–**e**, **2a**–**e**, and **3a**–**e** in chloroform, plots of metal ion loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Figs. 6–8, respectively.

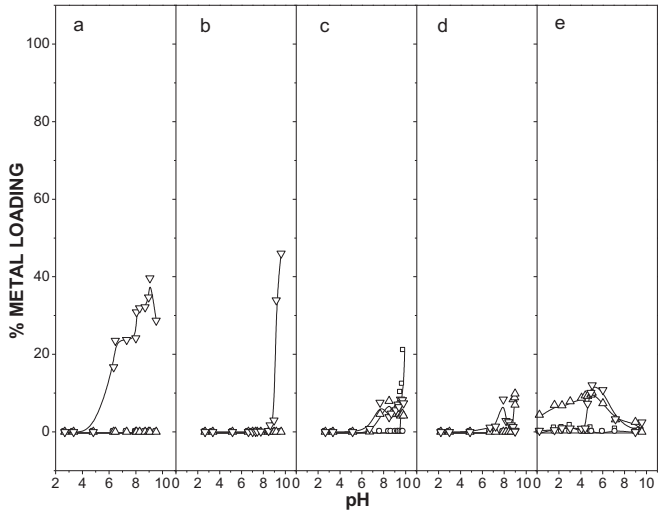


Fig. 7. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by cone di-ionizable calix[4]arene-1,3-crown-4 ligands (a) **2a**, (b) **2b**, (c) **2c**, (d) **2d**, and (e) **2e**. (□=Mg^{2+}, ○=Ca^{2+}, △=Sr^{2+}, ▽=Ba^{2+}).

Fig. 6 displays the results for di-ionizable calix[4]arene-1,3-crown-4 1,3-alternate conformers **1a**–**e**. The total metal ion loadings were low for ligands **1a**, **1b**, and **1e**. Ligands **1c** and **1d** with *N*-(X)sulfonyl carboxamide side arms and X=phenyl and *p*-nitrophenyl, respectively, gave appreciable extraction with selectivity for Ba^{2+}. Since the two ionizable groups are directed away from the polyether ring in the 1,3-alternate conformation, the results suggest coordination of Ba^{2+} between the two ionized side arms and possible interactions with the π-clouds of their aromatic rings.

Fig. 7 presents the alkaline earth metal cation extraction data for cone di-ionizable calix[4]crown-4 ligands **2a**–**e**. In sharp contrast with the results shown above for the 1,3-alternate isomers **1a**–**e**, highest extraction efficiency with very high Ba^{2+} selectivity was observed for the cone di(carboxylic acid) **2a** and the di(*N*-methylsulfonyl carboxamide) **2b**. The results obtained in the current study with the cone di-ionizable calix[4]arene-1,3-crown-4 series **2a**–**e** are also quite different than those reported earlier for cone *p*-(*tert*-butyl)calix[4]arene-1,3-crown-4 analogues for which increasing the side arm acidity enhanced the extraction efficiency and Ba^{2+} selectivity.[15]

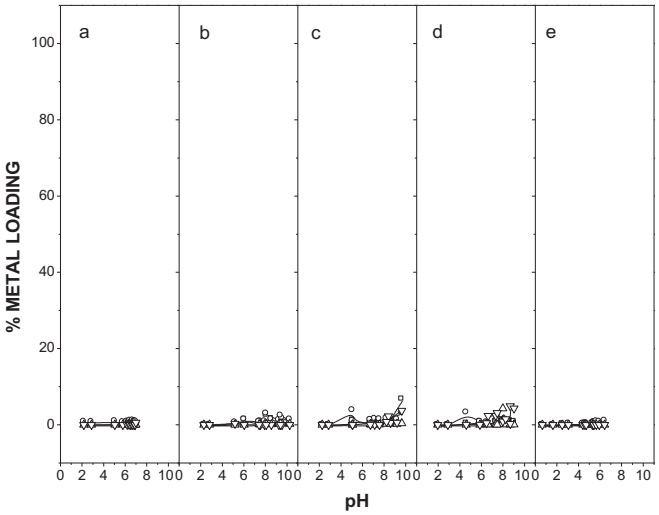


Fig. 8. Percent metal loading versus equilibrium pH of the aqueous phase for competitive solvent extraction of alkaline earth metal cations into chloroform by partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands (a) **3a**, (b) **3b**, (c) **3c**, (d) **3d**, and (e) **3e**. (□=Mg^{2+}, ○=Ca^{2+}, △=Sr^{2+}, ▽=Ba^{2+}).

In Fig. 8, results for competitive solvent extraction of alkaline earth metal cations by partial-cone di-ionizable calix[4]arene-1,3-crown-4 ligands **3a**–**e** are displayed. As can be seen, negligible extraction was observed. This reveals that in alkaline earth cation extraction by a di-ionizable calix[4]arene-1,3-crown-4 isomer both ionizable side arms must be available to participate in binding.

2.4.3. Competitive solvent extraction of Pb^{2+} by di-ionizable calix[4]arene-1,3-crown-4 ligands. In the study of Pb^{2+} extraction, an aqueous solution containing 1.00 mM Pb^{2+} was extracted by 0.50 mM solutions of di-ionizable ligands **1a**–**e**, **2a**–**e**, and **3a**–**e** in chloroform. Plots of Pb^{2+} loading of the organic phase versus the equilibrium pH of the aqueous phase are shown in Fig. 9a–c, respectively.

From the data presented in the panels, the relative extraction efficiencies may be compared in terms of Pb^{2+} loading of the organic phase as a function of the aqueous phase pH. Extraction from a more acidic aqueous solution shows stronger binding. As is readily evident, the Pb^{2+} extraction efficiency was highest for the 1,3-alternate series ligands **1a**–**e** as a group, intermediate for the cone series ligands **2a**–**e**, and lowest for the partial-cone series ligands **3a**–**e**. Thus, a conformation with the two ionized side arms oriented away from polyether region of the ligand is preferred. It seems reasonable that the divalent metal cation is sandwiched between the two anionic side arms.

For the 1,3-alternate ligands with *N*-(X)sulfonyl carboxamide side arms, the Pb^{2+} extraction efficiency increased as the electron-withdrawing propensity of X was enhanced $-Me$, $-Ph < -C_6H_4\text{-}4\text{-}NO_2 < -CF_3$ increasing the acidity to the two side arms. Ligands **1a**, **1d**, and **1e** gave quantitative extraction, whereas ligands **1b** and **1c** provided maximum extractions of about 70%.

For the cone series, Pb^{2+} extraction was observed only with ligands **2a**–**c**. For the cone ligands with *N*-(X)sulfonyl carboxamide side arms, no significant Pb^{2+} extraction was noted with the stronger acidifying X groups in **2d** and **2e**. The reason for the opposite effects of X group variation on Pb^{2+} extraction efficiency for

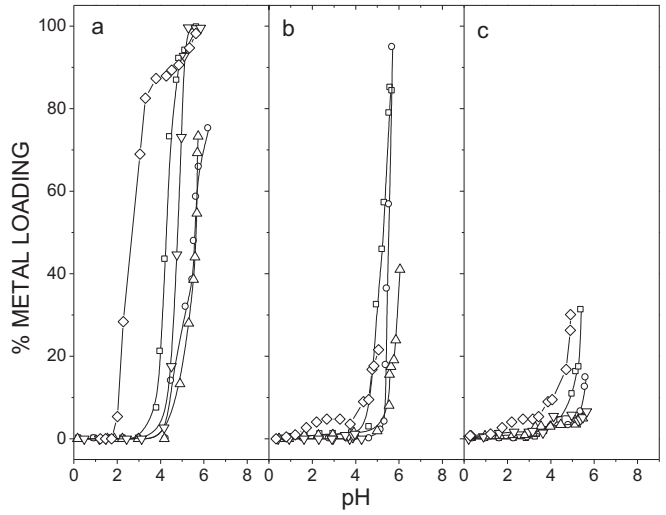


Fig. 9. Percent metal loading versus equilibrium pH of the aqueous phase for single species solvent extraction of Pb^{2+} into chloroform by di-ionizable calix[4]arene-1,3-crown-4 ligands in three conformations: (a) 1,3-alternate, **1a**–**e**, (b) cone, **2a**–**e**, and (c) partial-cone, **3a**–**e**. (□=–CO_2H, ○=–$C(O)NHSO_2CH_3$, △=–$C(O)NHSO_2C_6H_5$, ▽=–$C(O)NHSO_2C_6H_4$-4-NO_2, ◇=–$C(O)NHSO_2CF_3$).

the 1,3-alternate and cone conformation ligands is not obvious at this time.

With the partial-cone series of ligands having one ionizable group located near the polyether cavity and the other distant, only limited Pb^{2+} extraction efficiencies were found with the most effective ligands **3a** and **3e**. Thus, having the two acidic side arms in close proximity is judged to be a requirement for effective Pb^{2+} extraction by the di-ionizable calix[4]arene-1,3-crown-4 ligands.

2.4.4. Competitive solvent extraction of Hg^{2+} by di-ionizable calix[4]arene-1,3-crown-4 ligands. Aqueous nitrate solutions containing 0.25 mM Hg^{2+} were extracted with 0.25 mM solutions of di-ionizable calix[4]arene-1,3-crown-4 ligands **1a**–**e**, **2a**–**e**, and **3a**–**e** in chloroform. Plots of Hg^{2+} loading of the organic phase versus the equilibrium pH of the aqueous phase are presented in Fig. 10a–c, respectively.

For the di(carboxylic acid)s **1a**, **2a**, and **3a** (squares in Fig. 10a–c, respectively), Hg^{2+} extraction was low and the three profiles are very similar. In comparison, extraction levels for most of the *N*-(X) sulfonyl carboxamide-containing ligands substantially surpass those noted for the di(carboxylic acid) ligands. This demonstrates an important effect of ionizable group identity.

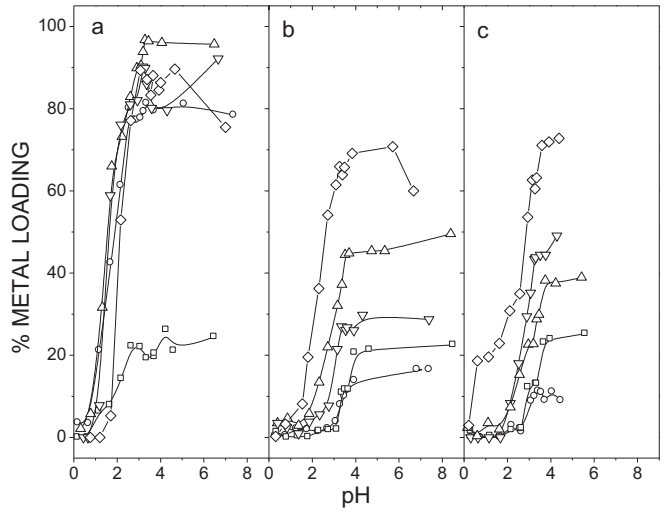


Fig. 10. Percent metal loading versus equilibrium pH of the aqueous phase for single species solvent extraction of Hg^{2+} into chloroform by di-ionizable calix[4]arene-1,3-crown-4 ligands in three conformations: (a) 1,3-alternate, **1a**–**e**, (b) cone, **2a**–**e**, and (c) partial-cone, **3a**–**e**. (□=–CO_2H, ○=–$C(O)NHSO_2CH_3$, △=–$C(O)NHSO_2C_6H_5$, ▽=–$C(O)NHSO_2C_6H_4$-4-NO_2, ◇=–$C(O)NHSO_2CF_3$).

The highest extraction efficiencies were found for ligands **1b**–**e** in the 1,3-alternate conformation. In this conformation, the two ionized *N*-(X)sulfonyl carboxamide side arms project away from the polyether cavity providing an electronegative pocket for complexation of the divalent cation. Noteworthy are the high levels of Hg^{2+} extraction obtained from quite acidic aqueous solutions.

The extraction profiles for cone ligands **2b**–**e** and partial-cone ligands **3b**–**e** Fig. 10b and c, respectively, are quite similar. Thus for Hg^{2+} extraction having the two ionized side arms on the same side of the polyether unit appears to be of much lesser importance than it was in extractions of Ba^{2+} and Pb^{2+}.

For the cone ligands **2b**–**e** (Fig. 10b), the Hg^{2+} extraction efficiency decreased as X was varied in the order –CF_3>–Ph>–C_6H_4-4-NO_2>–Me. Except for reversed positions for the two aryl groups, this trend follows the electron-withdrawing ability of X.

For the partial-cone ligands **3b**–**e** (Fig. 10c), the extraction efficiency diminished as X was changed in the order –CF_3>–C_6H_4-4-NO_2>–Ph>–Me. This ordering mirrors the change in the electron-withdrawing ability of X.

3. Conclusions

Synthetic routes are established for three series of di-ionizable calix[4]arene-1,3-crown-4 structural isomers in 1,3-alternate, cone, and partial-cone conformations, **1a**–**e**, **2a**–**e**, and **3a**–**e**, respectively. Side arm acidic groups include –CO_2H and –$C(O)NHSO_2X$ with variation in the inductive effects of X. In one synthetic sequence, a conformationally unrestricted intermediate is isolated in an unusual 1,2-alternate conformation as determined by X-ray diffraction.

To probe the effect of varying the calix[4]arene scaffold conformation on metal ion complexation, solvent extraction of metal cations from aqueous solutions into chloroform are conducted. This includes competitive extraction of hard alkali metal cations and alkaline earth metal cations, intermediate Pb^{2+}, and soft Hg^{2+}.

For ligands with significant extraction of alkali metal cations, Na^+ selectivity is noted. Propensities for extraction of the remaining alkali metal cation species are found to vary depending upon the calix[4]arene unit conformation in the ligand.

Modest extraction of alkaline earth metal cations is observed for some ligands in the 1,3-alternate and cone conformations. When effective, the ligands exhibit selectivity for Ba^{2+}. Isomers with partial-cone conformations give negligible extraction of alkaline earth metal cations.

For intermediate Pb^{2+}, ligands with the calix[4]arene unit in the 1,3-alternate conformation are strong extractants. High levels of Pb^{2+} extraction are also observed for some of the cone conformation ligands. The partial-cone isomers are weak extractants of Pb^{2+}.

For soft Hg^{2+}, the three di(carboxylic acid) ligands exhibit uniformly weak extraction behavior. With pendant –$C(O)NHSO_2X$ acidic functions, high extraction efficiency is obtained when the calix[4]arene unit is in a 1,3-alternate conformation. Lower, but still substantial Hg^{2+}, is produced by ligands with –$C(O)NHSO_2X$ ionizable groups and cone and partial-cone conformations.

High levels of Pb^{2+} and Hg^{2+} extractions from acidic solutions by ligands with –$C(O)NHSO_2X$ acidic groups and a 1,3-alternate conformation are noteworthy.

Previously, we have published results for competitive solvent extraction of alkaline earth metal cations from aqueous solutions into chloroform by di-ionizable calix[4]arene-1,3-crown-5[27] (cone conformation) and di-ionizable calix[4]arene-1,3-crown-6[14] (cone, 1,3-alternate, and partial-conformation) ligands. When combined

with data obtained in the present study, the effects of some systematic structural variations emerge. Based upon the data obtained with di-ionizable calix[4]arene-crown-4 and -crown-6 ligands, the efficiency and selectivity of alkaline earth metal cation extraction diminish as the conformation of a di-ionizable calix[4]arene-crown ether is varied in the order of cone>1,3-alternate>partial-cone. For variation of the crown ring size with cone conformation ligands, the efficiency and selectivity of alkaline earth metal cation extraction decreases in the order of crown-6>crown-5>crown-4. Cone di-ionizable calix[4]arene-1,3-crown-6 compounds give efficient and selective extraction of Ba^{2+}. Models show the metal ion positioned within the polyether cavity with apical coordination by an ionized group above and below the crown ether ring.

4. Experimental

4.1. General

Melting points were determined with a Mel-Temp melting point apparatus. Infrared (IR) spectra were recorded with a Nicolet IR100 FT-IR spectrometer as deposits from CH_2Cl_2 solutions on NaCl plates unless otherwise noted. The catalytic hydrogenolysis reaction was carried out with a low pressure Parr reaction apparatus. The ^1H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA 500 MHz FT-NMR (^1H 500 MHz and ^{13}C 126 MHz) spectrometer in $CDCl_3$ with Me_4Si as internal standard unless mentioned otherwise. Chemical shifts (δ) are given in parts per million downfield from TMS and coupling constants values (J) are in hertz. Elemental analysis was performed by Desert Analytics Laboratory (now Columbia Analytical Services) of Tucson, Arizona.

Reagents were purchased from commercial suppliers and used directly unless otherwise noted. Acetonitrile (MeCN) was dried over CaH_2 and distilled immediately before use. Tetrahydrofuran (THF) was dried over sodium with benzophenone as an indicator and distilled just before use. Triethylene glycol ditosylate was prepared according to a published procedure.[22]

4.2. Ligand synthesis

*4.2.1. 25,27-Dihydroxycalix[4]arene-1,3-crown-4 (**5**).*[16] A slurry of calix[4]arene (**4**) (17.00 g, 0.040 mol) and Na_2CO_3 (42.40 g, 0.40 mol) in MeCN (2.0 L) was refluxed for 2 h under nitrogen. Triethylene glycol ditosylate (19.24 g, 0.042 mol) dissolved in MeCN (200 mL) was added dropwise during a 3-h period. The mixture was refluxed for 7 days. After evaporation of the MeCN in vacuo, CH_2Cl_2 (500 mL) and 10% aq HCl (500 mL) were added to the residue. The organic phase was separated, washed with brine (2×250 mL), and then water (2×250 mL), dried over $MgSO_4$, and evaporated in vacuo to give the crude product, which was purified by chromatography on silica gel with CH_2Cl_2/EtOAc (10:1 to 2:1) as eluent to give **5** (13.40 g, 69%) as a white solid with mp >400 °C, (lit.[16] mp >400 °C). IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3309 (OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 4.02 (s, 4H, OCH_2CH_2O), 4.18–4.25 (m, 8H, OCH_2CH_2O), 4.38 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 6.59 (t, J=7.5 Hz, 2H, ArH), 6.82 (t, J=7.5 Hz, 2H, ArH), 7.00–7.06 (m, 8H, ArH), 8.75 (s, 2H, OH). ^{13}C NMR ($CDCl_3$): δ 31.8, 69.2, 69.5, 74.6, 119.3, 125.7, 128.2, 128.7, 128.9, 134.5, 152.1, 152.9.

*4.2.2. 1,3-Alternate 25,27-bis(ethoxycarbonylmethoxy)calix[4]arene-1,3-crown-4 (**6**).* A mixture of **5** (1.00 g, 1.86 mmol) and KH (0.45 g, 11.20 mmol) in THF (50 mL) was stirred under nitrogen at room temperature for 30 min and $BrCH_2CO_2Et$ (1.86 g, 11.20 mmol) was added in one portion. The mixture was stirred at room temperature for another 24 h. After evaporating the THF in vacuo, the residue was allowed to cool to room temperature. Then CH_2Cl_2 (50 mL) and 10% aq HCl (25 mL) were added slowly. The organic layer was separated, washed with water (2×50 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by recrystallization from MeOH/CH_2Cl_2 to give **6** (0.86 g, 65%) as a white solid with mp 195 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1750 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (t, J=7.5 Hz, 6H, CH_2CH_3), 2.97 (t, J=5.0 Hz, 4H, OCH_2CH_2O), 3.18 (s, 4H, $OCH_2C(O)$), 3.36 (s, 4H, OCH_2CH_2O), 3.54 (t, J=5.0 Hz, 4H, OCH_2CH_2O), 3.86 (d, J=16.5 Hz, 4H, $ArCH_2Ar$), 4.01 (q, J=7.0 Hz, 4H, OCH_2CH_3), 4.20 (d, J=16.5 Hz, 4H, $ArCH_2Ar$), 6.87 (t, J=7.5 Hz, 2H, ArH), 6.94 (t, J=7.5 Hz, 2H, ArH), 7.13 (d, J=7.5 Hz, 8H, ArH). ^{13}C NMR ($CDCl_3$) δ: 14.0, 38.3, 60.2, 67.8, 68.5, 69.7, 70.0, 122.8, 123.4, 130.2, 133.6, 134.9, 155.8, 156.6, 170.4. Anal. Calcd for $C_{42}H_{46}O_{10}$: C, 70.98, H, 6.48%. Found: C, 70.74; H, 6.38%.

*4.2.3. 1,3-Alternate 25,27-Bis(carboxymethoxy)calix[4]arene-1,3-crown-4 (**1a**).* A mixture of diester **6** (5.00 g, 7.04 mmol), 10% aq Me_4NOH (TMAOH) (200 mL), and THF (200 mL) was refluxed for 24 h. After evaporating the THF in vacuo, 200 mL of 6 N aq HCl was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were washed with water (2×200 mL) and dried over $MgSO_4$. After evaporation of the THF in vacuo, di(carboxylic acid) **1a** (4.37 g, 95%) was obtained as a white solid that decomposed at 270 °C without melting. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3418 (OH), 1753 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.62 (s, 4H, OCH_2CH_2O), 3.43 (t, J=4.0 Hz, 4H, OCH_2CH_2O), 3.70 (t, J=4.0 Hz, 4H, OCH_2CH_2O), 3.93 (AB pattern, J=16.5 Hz, J'=12.0 Hz, 8H, $ArCH_2Ar$), 4.14 (s, 4H, $OCH_2C(O)$), 6.94 (t, J=7.5 Hz, 2H, ArH), 7.07 (m, 6H, ArH), 7.17 (d, J=7.5 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 37.8, 67.4, 69.0, 69.4, 70.8, 124.4, 124.56, 129.4, 130.2, 133.4, 133.5, 153.7, 156.0, 168.1. Anal. Calcd for $C_{38}H_{38}O_{10}\cdot 0.8CH_2Cl_2$: C, 70.75; H, 6.06%. Found: C, 70.82; H, 5.83%.

*4.2.4. General procedure for preparation of 1,3-alternate 25,27-bis[N-(X)sulfonyl carbamoylmethoxy]calix[4]arene-1,3-crown-4 compounds **1b–e**.* Di(carboxylic acid) **1a** (1.50 g, 2.30 mmol) was dried with a benzene azeotrope before addition of oxalyl chloride (2.92 g, 23.00 mmol) in benzene (100 mL). The solution was refluxed overnight. After conversion to the di(acid chloride) was confirmed by a shift of the C=O IR absorption, the benzene was evaporated in vacuo and the residue was dried under oil pump vacuum for 30 min. The residue was dissolved in freshly distilled THF (20 mL) and the solution was added to a mixture of the appropriate sulfonamide (5.10 mmol) and NaH (0.55 g, 23.00 mmol) in THF (40 mL) under nitrogen at room temperature. The reaction mixture was allowed to stir at room temperature for 24 h. The THF was removed in vacuo and CH_2Cl_2 (50 mL) and 10% aq HCl (50 mL) were added to the residue. The organic layer was separated, washed with brine (2×50 mL), and then water (2×50 mL), and dried over $MgSO_4$. Evaporation of the CH_2Cl_2 in vacuo gave the crude product, which was purified by either recrystallization or column chromatography on silica gel. For the latter, an extra acid wash process was necessary. The eluted product was dissolved in CH_2Cl_2 (50 mL) and washed with 6 N aq HCl (100 mL). The organic layer was separated, washed with water (2×100 mL), dried over $MgSO_4$, and evaporated in vacuo to give the final product.

*4.2.4.1. 1,3-Alternate 25,27-bis(N-methanesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**1b**).* The crude product was recrystallized from CH_2Cl_2/MeOH to give a 67% yield of pale yellow solid with mp 176–180 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3345 (NH), 1719 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.76 (s, 4H, OCH_2CH_2O), 3.32 (s, 6H, CH_3), 3.34 (t, J=5.0 Hz, 4H, OCH_2CH_2O), 3.64 (t, J=5.0 Hz, 4H, OCH_2CH_2O), 3.90 (s, 8H, $ArCH_2Ar$), 4.01 (s, 4H, $OCH_2C(O)$), 6.97 (t, J=7.5 Hz, 2H, ArH), 7.02 (t,

J=7.5 Hz, 2H, ArH), 7.17 (q, J=4.0 Hz, 8H, ArH), 8.14 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 38.0, 41.5, 69.1, 70.5, 70.6, 124.0, 124.1, 129.7, 130.8, 133.2, 134.2, 155.6, 156.2, 168.5. Anal. Calcd for $C_{40}H_{44}N_2O_{12}S_2$: C, 59.40; H, 5.44; N, 3.46%. Found: C, 59.37; H, 5.36; N, 3.11%.

*4.2.4.2. 1,3-Alternate 25,27-bis(N-benzenesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**1c**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to afford in 85% yield a white solid that decomposed at 265 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3337 (NH), 1721 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 4H, OCH_2CH_2O), 3.27 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.59 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.85 (s, 4H, $OCH_2C(O)$), 3.86 (s, 8H, $ArCH_2Ar$), 6.78 (t, J=8.0 Hz, 2H, ArH), 6.97–7.02 (m, 6H, ArH), 7.13 (d, J=7.5 Hz, 4H, ArH), 7.58–7.61 (m, 4H, ArH), 7.67–7.70 (m, 2H, ArH), 8.14–8.16 (m, 4H, ArH), 8.42 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 38.0, 69.0, 69.1, 70.5, 70.5, 123.8, 124.3, 128.8, 128.9, 129.5, 130.6, 133.3, 134.1, 134.2, 138.3, 155.4, 156.1, 167.3. Anal. Calcd for $C_{50}H_{48}N_2O_{12}S_2\cdot 0.1CH_2Cl_2$: C, 63.91; H, 5.16; N, 2.98%. Found: C, 63.90; H, 5.02; N, 3.06%.

*4.2.4.3. 1,3-Alternate 25,27-bis(N-4-nitrobenzenesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**1d**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to give in 66% yield a pale yellow solid that decomposed at 262 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3326 (NH), 1732 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 4H, OCH_2CH_2O), 3.24 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.59 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.81 (s, 4H, $OCH_2C(O)$), 3.88 (s, 8H, $ArCH_2Ar$), 6.80 (t, J=7.5 Hz, 2H, ArH), 7.00–7.05 (m, 6H, ArH), 7.16 (d, J=7.5 Hz, 4H, ArH), 8.32–8.35 (m, 4H, ArH), 8.41–8.43 (m, 4H, ArH), 8.60 (br s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 38.0, 68.9, 69.2, 70.5, 70.6, 124.1, 124.2, 129.6, 130.2, 130.8, 133.1, 134.3, 143.6, 150.9, 155.4, 156.2, 167.6. Anal. Calcd for $C_{50}H_{46}N_4O_{16}S_2$: C, 58.70; H, 4.53; N, 5.48%. Found: C, 59.08; H, 4.53; N, 5.11%.

*4.2.4.4. 1,3-Alternate 25,27-bis(N-trifluoromethanesulfonyl carbamoylmethoxy)calix[4]-arene-1,3-crown-4 (**1e**).* The crude product was recrystallized from CH_2Cl_2/MeOH in 82% yield as a white solid that decomposed at 225 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3311 (NH), 1756 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 4H, OCH_2CH_2O), 3.28 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.63 (t, J=4.5 Hz, 4H, OCH_2CH_2O), 3.94 (d, J=8.0 Hz, 12H, $ArCH_2Ar$, $OCH_2C(O)$), 6.96 (t, J=7.5 Hz, 2H, ArH), 7.04 (t, J=7.5 Hz, 2H, ArH), 7.13 (d, J=8.0 Hz, 4H, ArH), 7.18 (d, J=7.5 Hz, 4H, ArH) 8.50 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 38.0, 69.1, 68.9, 70.6, 124.3, 124.5, 129.7, 130.9, 133.2, 134.3, 155.2, 156.3, 166.8. Anal. Calcd for $C_{40}H_{38}N_2O_{12}S_2F_6$: C, 52.40; H, 4.15; N, 3.06%. Found: C, 52.31; H, 4.29; N, 3.42%.

*4.2.5. Cone 25,27-Bis(ethoxycarbonylmethoxy)calix[4]arene-1,3-crown-4 (**7**).* A mixture of **5** (1.00 g, 1.86 mmol) and NaH (0.27 g, 11.20 mmol) in THF (50 mL) was stirred under nitrogen at room temperature for 30 min and then $BrCH_2CO_2Et$ (1.86 g, 11.20 mmol) was added. The mixture was stirred at room temperature for 24 h. After evaporating the THF in vacuo, CH_2Cl_2 (50 mL) and 10% aq HCl (25 mL) were added slowly to the residue. The organic layer was separated, washed with water (2×50 mL), dried over $MgSO_4$, and evaporated in vacuo. MeOH was added into the oily residue producing a precipitate, which was filtered. The crude product was recrystallized from hexane/EtOAc to give **7** (0.66 g, 50%) as a white solid with mp 148–150 °C. IR (deposit from CH_2Cl_2 solution on NaCl plate): 1754 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J=7.0 Hz, 6H, CH_2CH_3), 3.21 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 3.83 (s, 4H, OCH_2CH_2O), 4.13–4.20 (m, 8H, OCH_2CH_2O), 4.25 (q, J=7.5 Hz, 4H, OCH_2CH_3), 4.45 (s, 4H, $OCH_2C(O)$), 4.51 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 6.15 (d, J=7.5 Hz, 4H, ArH), 6.23–6.26 (AB pattern, J=7.0 Hz, J'=1.0 Hz, 2H, ArH), 6.96 (t, J=7.5 Hz, 2H, ArH), 7.15 (d, J=7.5 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 14.2, 30.7, 60.8, 70.2, 71.7, 71.82, 73.8, 122.3, 122.6, 127.7, 129.2, 132.7, 136.6, 154.4, 158.0, 169.43. Anal. Calcd for $C_{42}H_{46}O_{10}$: C, 70.98; H, 6.48%. Found: C, 70.90; H, 6.15%.

*4.2.6. Cone 25,27-bis(carboxymethoxy)calix[4]arene-1,3-crown-4 (**2a**).* The procedure was the same as that employed for preparation of **1a** from **7**. After the reaction, **2a** (4.45 g, 97%) was collected as a white solid with mp 260–262 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3426 (OH), 1745 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.22 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 3.90 (s, 4H, OCH_2CH_2O), 4.07 (t, J=5.5 Hz, 4H, OCH_2CH_2O), 4.273 (t, J=5.5 Hz, 4H, OCH_2CH_2O), 4.32 (d, J=13.5 Hz, 4H, $ArCH_2Ar$), 4.37 (s, 4H, $OCH_2C(O)$), 6.13 (d, J=8.0 Hz, 4H, ArH), 6.28 (t, J=7.5 Hz, 2H, ArH), 7.00 (t, J=7.5 Hz, 2H, ArH), 7.17 (d, J=7.5 Hz, 4H, ArH). ^{13}C NMR: ($CDCl_3$): δ 30.4, 70.6, 70.8, 71.5, 74.0, 122.8, 123.4, 128.1, 129.4, 132.4, 136.2, 152.7, 158.1, 170.6. Anal. Calcd for $C_{38}H_{38}O_{10}$: C, 69.72; H, 5.81%. Found: C, 69.42; H, 5.76%.

*4.2.7. General procedure for the preparation of cone 25,27-bis[N-(X)-sulfonyl carbamoylmethoxy]calix[4]arene-1,3-crown-4 compounds **2b**–**e**.* The procedure was the same as that employed for synthesizing compounds **1b**–**e** but starting from **2a**.

*4.2.7.1. Cone 25,27-bis(N-methanesulfonyl carbamoylmethoxy) calix[4]arene-1,3-crown-4 (**2b**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to produce a 40% yield of white solid with mp 225–227 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3289 (NH), 1716 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.24 (d, J=13.0 Hz, 4H, $ArCH_2Ar$), 3.41 (s, 6H, CH_3), 3.89 (s, 4H, OCH_2CH_2O), 3.91 (t, J=5.5 Hz, 4H, OCH_2CH_2O), 4.27–4.30 (m, 8H, $ArCH_2Ar$, OCH_2CH_2O), 4.33 (s, 4H, $OCH_2C(O)$), 6.03 (d, J=8.0 Hz, 4H, ArH), 6.25 (t, J=8.0 Hz, 2H, ArH), 7.01 (t, J=8.0 Hz, 2H, ArH), 7.18 (d, J=8.0 Hz, 4H, ArH), 10.88 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 30.6, 42.0, 69.4, 70.1, 73.8, 74.8, 122.7, 123.7, 128.2, 129.6, 132.1, 136.0, 153.3, 158.4, 169.0. Anal. Calcd for $C_{40}H_{44}N_2O_{12}S_2$: C, 59.40; H, 5.44; N, 3.46%. Found: C, 59.76; H, 5.50; N, 3.73%.

*4.2.7.2. Cone 25,27-bis(N-benzenesulfonyl carbamoylmethoxy) calix[4]arene-1,3-crown-4 (**2c**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to afford a 70% yield of white solid with mp 178–180 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3306 (NH), 1719 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.15 (d, J=13.0 Hz, 4H, $ArCH_2Ar$), 4.00–4.02 (m, 8H, OCH_2CH_2O), 4.22–4.23 (m, 8H, $ArCH_2Ar$, $OCH_2C(O)$), 4.32 (t, J=5.5 Hz, 4H, OCH_2CH_2O), 6.00 (d, J=8.0 Hz, 4H, ArH), 6.22 (t, J=8.0 Hz, 2H, ArH), 7.00 (t, J=8.0 Hz, 2H, ArH), 7.16 (d, J=8.0 Hz, 4H, ArH), 7.59 (t, J=8.0 Hz, 4H, ArH), 7.67–7.71 (m, 2H, ArH), 8.14–8.16 (m, 4H, ArH), 10.87 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ: 30.6, 70.0, 70.4, 73.9, 74.6, 122.7, 123.6, 128.1, 128.5, 129.0, 129.6, 132.1, 134.1, 136.2, 138.8, 153.458, 158.228, 167.5. Anal. Calcd for $C_{50}H_{48}N_2O_{12}S_2$: C, 64.36; H, 5.19; N, 3.00%. Found: C, 64.40; H, 5.37; N, 3.11%.

*4.2.7.3. Cone 25,27-Bis(N-4-nitrobenzenesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**2d**).* The crude product was chromatographed on silica with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to give a 61% yield of pale yellow solid with mp 198–201 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3320 (NH), 1719 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.18 (d, J=13.0 Hz, 4H, $ArCH_2Ar$), 4.04 (t, J=5.0 Hz, 4H, OCH_2CH_2O), 4.06 (s, 4H, OCH_2-CH_2O), 4.22–4.24 (m, 8H, $ArCH_2Ar$, $OCH_2C(O)$), 4.36 (t, J=5.0 Hz, 4H, OCH_2CO), 6.01 (d, J=8.0 Hz, 4H, ArH), 6.24 (t, J=8.0 Hz, 2H, ArH), 7.02 (t, J=8.0 Hz, 2H, ArH), 7.18 (d, J=8.0 Hz, 4H, ArH), 8.35–8.37 (m, 4H, ArH), 8.42–8.44 (m, 4H, ArH), 11.20 (s, 2H, NH). ^{13}C NMR

($CDCl_3$): δ 30.6, 69.6, 70.4, 73.8, 74.8, 122.8, 123.8, 124.2, 128.2, 129.7, 130.1, 132.0, 135.9, 144.1, 150.9, 153.3, 158.4, 167.8. Anal. Calcd for $C_{50}H_{46}N_4O_{16}S_2$: C, 58.70; H, 4.53; N, 5.48%. Found: C, 58.75; H, 4.90; N, 5.09%.

*4.2.7.4. Cone 25,27-bis(N-trifluoromethanesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**2e**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to give a 67% yield of a pale yellow solid with mp 170–174 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3053 (NH), 1753 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.26 (d, *J*=13.0 Hz, 4H, $ArCH_2Ar$), 3.88–3.92 (m, 8H, OCH_2CH_2O), 4.26 (d, *J*=13.0 Hz, 4H, $ArCH_2Ar$), 4.34 (t, *J*=3.0 Hz, 4H, OCH_2CH_2O), 4.40 (s, 4H, $OCH_2C(O)$), 6.04 (d, *J*=8.0 Hz, 4H, ArH), 6.27 (t, *J*=8.0 Hz, 2H, ArH), 7.02 (t, *J*=8.0 Hz, 2H, ArH), 7.20 (d, *J*=8.0 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 30.6, 68.3, 70.1, 74.0, 75.1, 120.6, 122.7, 123.9, 128.3, 129.6, 132.0 135.8, 153.5, 158.7, 167.1. Anal. Calcd for $C_{40}H_{38}N_2O_{12}S_2F_6$: C, 52.40; H, 4.15; N, 3.06%. Found: C, 52.83; H, 3.82; N, 3.06%.

*4.2.8. 25,27-Bis(benzyloxy)-26,28-bis(hydroxy)calix[4]arene (**9**).* A mixture of calix[4]arene (**4**) (10.00 g, 23.60 mmol) and K_2CO_3 (3.90 g, 28.30 mmol) in MeCN (350 mL) was refluxed for 1 h under nitrogen. Benzyl bromide (8.90 g, 51.90 mmol) was injected all in once by syringe. The mixture was refluxed for 1 h and poured into ice water. The precipitate was filtered and recrystallized from CH_2Cl_2/MeOH to give **9** (13.80 g, 90%) as white crystals with mp 224–225 °C (lit.[23] mp 219–222 °C); ^1H NMR ($CDCl_3$): δ 3.34 (d, *J*=13.0 Hz, 4H, $ArCH_2Ar$), 4.31 (d, *J*=13.0 Hz, 4H, $ArCH_2Ar$), 5.06 (s, 4H, OCH_2Ar), 6.65 (t, *J*=8.0 Hz, 2H, ArH), 6.75 (t, *J*=8.0 Hz, 2H, ArH), 6.89 (d, *J*=8.0 Hz, 4H, ArH), 7.05 (d, *J*=8.0 Hz, 4H, ArH), 7.34–7.40 (m, 6H, ArH), 7.64–7.66 (m, 4H, ArH), 7.81 (s, 2H, OH). ^{13}C NMR ($CDCl_3$): δ 31.4, 78.4, 118.9, 125.4, 127.4, 127.9, 128.0, 128.4, 128.7, 129.0, 133.2, 136.8, 151.9, 153.3.

*4.2.9. Partial-cone 25,27-bis(benzyloxy)-26,28-bis(tert-butoxycarbonylmethoxy)calix[4]arene (**10**).* A mixture of **9** (1.30 g, 2.00 mmol) and KH (0.20 g, 4.40 mmol) in freshly distilled THF (50 mL) was stirred under nitrogen for 2 h at room temperature and *tert*-butyl bromoacetate (0.97 g, 5.00 mmol) was added. The mixture was stirred at room temperature for 24 h. After removing the THF in vacuo, 1 N aq HCl (100 mL) and CH_2Cl_2 (100 mL) were added to the residue. The organic layer was separated, washed with water (2×100 mL), and dried over $MgSO_4$. After removing the solvent in vacuo, the residue was chromatographed on silica gel with hexanes/EtOAc (5:1) as eluent to give diester **10** (0.88 g, 55%) as a white solid with mp 62 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1754 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (s, 9H, $OC(CH_3)_3$), 1.59 (s, 9H, $OC(CH_3)_3$), 3.12 (d, *J*=13.5 Hz, 2H, $ArCH_2Ar$), 3.51 (d, *J*=13.5 Hz, 2H, $ArCH_2Ar$), 3.67 (d, *J*=13.5 Hz, 2H, $ArCH_2Ar$), 3.98 (s, 2H, $OCH_2C(O)$), 4.27 (s, 2H, $OCH_2C(O)$), 4.40 (d, *J*=13.5 Hz, 2H, $ArCH_2Ar$), 4.74 (d, *J*=12.0 Hz, 2H, OCH_2Ar), 4.85 (d, *J*=12.0 Hz, 2H, OCH_2Ar), 6.25 (d, *J*=8.0 Hz, 2H, ArH), 6.50 (t, *J*=7.5 Hz, 2H, ArH), 6.74 (t, *J*=7.5 Hz, 1H, ArH), 6.85 (t, *J*=7.5 Hz, 1H, ArH), 7.02–7.04 (AB pattern, *J*=7.5 Hz, *J′*=1.5 Hz, 4H, ArH), 7.01–7.12 (AB pattern, *J*=7.5 Hz, *J′*=1.5 Hz, 2H), 7.33–7.36 (m, 2H, ArH), 7.38–7.41 (m, 4H, ArH), 7.46–7.47 (d, *J*=7.5 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 27.9, 28.2, 31.7, 34.8, 68.4, 71.4, 76.4, 80.2, 81.8, 121.9, 122.0, 122.4, 127.7, 127.9, 128.4, 128.5, 129.0, 129.1, 130.5, 132.2, 133.4, 133.8, 134.6. Anal. Calcd for $C_{54}H_{56}O_6 \cdot 0.3CH_2Cl_2$: C, 78.91, H, 6.90%. Found: C, 78.95; H, 6.93%.

*4.2.10. Partial-cone 25,27-bis(hydroxy)-26,28-bis(tert-butoxycarbonylmethoxy)calix[4]arene (**11**).* Diester **10** (5.00 g, 6.20 mmol) was dissolved in freshly distilled THF (50 mL). To the solution, EtOH (50 mL) and 10% Pd/C were added. Hydrogenolysis was conducted under H_2 (50 psi) for 24 h. After the catalyst was filtered, the solvent was removed in vacuo. Diester **11** (3.90 g, quantitative yield) was obtained as a white solid with mp 195–197 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3407 (OH), 1734 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (s, 18H, $OC(CH_3)_3$), 3.76–3.79 (d, *J*=15.5 Hz, 4H, $ArCH_2Ar$), 3.98 (s, 4H. $OCH_2C(O)$), 4.10–4.13 (d, *J*=15.5 Hz, 4H, $ArCH_2Ar$), 6.70–6.73 (t, *J*=7.5 Hz, 2H, ArH), 6.89 (s, 2H, OH), 6.98–7.01 (t, *J*=7.5 Hz, 2H, ArH), 7.07–7.08 (d, *J*=7.5 Hz, 4H, ArH), 7.17–7.18 (d, *J*=7.5 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 27.9, 34.5, 70.8, 82.4, 119.6, 125.1, 127.1, 128.4, 129.0, 133.6, 153.2, 153.3, 167.6. Anal. Calcd for $C_{40}H_{44}O_{10} \cdot 0.3CH_2Cl_2$: C, 74.11; H, 6.90%. Found: C, 74.02; H, 7.13%.

*4.2.11. Partial-cone 26,28-bis(tert-butoxycarbonylmethoxy)calix[4]arene-1,3-crown-4 (**12**).* A mixture of diester **11** (0.50 g, 0.80 mmol) and K_2CO_3 (1.12 g, 8.00 mmol) in MeCN (100 mL) was refluxed for 2 h. To the refluxing mixture, triethylene glycol ditosylate (0.37 g, 0.88 mmol) in MeCN (50 mL) was added dropwise during a 2-h period. The mixture was refluxed for another 5 days. After evaporation of the MeCN in vacuo, CH_2Cl_2 (50 mL), and 1 N aq HCl (50 mL) were added to the residue. The organic layer was separated, washed with water (2×100 mL), and dried over $MgSO_4$. A viscous oily product was obtained after the solvent was removed in vacuo. The residue was crystallized from hexanes/EtOAc to give **12** (0.28 g, 45%) as colorless crystals with mp 200–202 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 1743 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.16 (s, 9H, $OC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.76 (s, 2H, $OCH_2C(O)$), 3.23–3.27 (m, 2H, OCH_2CH_2O), 3.35 (d, *J*=13.5 Hz, 2H, $ArCH_2Ar$), 3.56–3.60 (m, 2H, OCH_2CH_2O), 3.73 (s, 4H, OCH_2CH_2O), 3.80–3.86 (m, 4H, OCH_2CH_2O, $ArCH_2Ar$), 4.00–4.05 (m, 4H, OCH_2-CH_2O, $ArCH_2Ar$), 4.52 (s, 2H, $OCH_2C(O)$), 4.60–4.62 (d, *J*=13.0 Hz, 2H, $ArCH_2Ar$), 6.61–6.64 (t, *J*=7.5 Hz, 1H, ArH), 6.84–6.93 (m, 4H, ArH), 7.01–7.06 (m, 3H, ArH), 7.18–7.23 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 28.0, 28.1, 30.3, 36.7, 68.8, 69.0, 70.2, 72.7, 73.0, 80.1, 81.5, 122.8, 123.7, 123.8, 128.2, 128.7, 130.2, 132.8, 134.0, 134.6, 137.5, 1545.0, 155.8, 155.8, 169.0, 169.3. Anal. Calcd for $C_{46}H_{54}O_{10} \cdot 0.6CH_2Cl_2$: C, 68.43; H, 6.80%. Found: C, 68.54; H, 6.53%.

*4.2.12. Partial-cone 26,28-bis(carboxymethoxy)calix[4]arene-1,3-crown-4 (**3a**).* A solution of diester **12** (1.00 g, 1.33 mmol) in THF (25 mL) mixed with NaOH (0.50 g, 12.50 mmol) in water (25 mL) was refluxed for 24 h. The THF was removed in vacuo. The residue was acidified with 1 N aq HCl (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was separated, washed with water (2×100 mL), and dried over $MgSO_4$. After removing the solvent in vacuo, diacid **3a** (0.86 g, quantitative yield) was collected as a white solid with mp 246 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3066 (OH), 1748 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.16 (s, 2H, $OCH_2C(O)$), 3.35–3.40 (m, 4H, OCH_2CH_2O, $ArCH_2Ar$), 3.53–3.57 (m, 2H, OCH_2CH_2O), 3.65–3.77 (m, 6H, OCH_2CH_2O), 3.87–4.01 (AB pattern, *J*=33.0 Hz, *J′*=18.0 Hz, 4H, OCH_2CH_2O), 4.03–4.08 (m, 2H, OCH_2CH_2O), 4.42 (d, *J*=13.0 Hz, 2H, $ArCH_2Ar$), 4.64 (s, 2H, $OCH_2C(O)$), 6.82 (t, *J*=7.5 Hz, 1H, ArH), 6.87–6.93 (m, 4H, ArH), 7.03 (d, *J*=7.5 Hz, 2H, ArH), 7.10–7.13 (m, 1H, ArH), 7.18 (d, *J*=7.5 Hz, 2H, ArH), 7.23–7.25 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 30.2, 30.3, 37.8, 65.7, 68.5, 69.5, 71.7, 74.3, 124.3, 124.5, 124.7, 128.7, 128.8, 129.5, 132.2, 133.2, 133.8, 136.4, 153.9, 154.4, 155.1, 168.3, 170.8. Anal. Calcd for $C_{38}H_{38}O_{10}$: C, 69.72; H, 5.81%. Found: C, 69.46; H, 6.21%.

*4.2.13. General procedure for the preparation of partial-cone 26,28-bis[N-(X)-sulfonyl carbamoylmethoxy]calix[4]arene-1,3-crown-4 compounds **3b**–**e**.* The procedure was the same as that employed for the preparation of compounds **1b**–**e** and **2b**–**e** but starting from **3a**.

*4.2.13.1. Partial-cone 26,28-bis(N-methanesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**3b**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to

25:1 gradient) as eluent to give in 26% yield a white solid with mp 144–146 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3357 (NH), 3296 (NH), 1716 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.46 (s, 2H, $OCH_2C(O)$), 2.92 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.35–3.39 (m, 2H, OCH_2CH_2O), 3.42 (d, J=13.0 Hz, 2H, $ArCH_2Ar$), 3.62–3.70 (m, 4H, OCH_2CH_2O), 3.78–3.86 (m, 4H, OCH_2CH_2O), 3.92 (AB patterns, J=17.0 Hz, J'=5.5 Hz, 4H, $ArCH_2Ar$), 4.03–4.07 (m, 2H, OCH_2CH_2O), 4.39 (d, J=12.0 Hz, 2H, $ArCH_2Ar$), 4.63 (s, 2H, $OCH_2C(O)$), 6.26 (s, 1H, NH), 6.86–7.25 (m, 12H, ArH), 11.48 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 30.21 37.4, 41.4, 41.6, 67.5, 68.1, 69.3, 71.8, 76.80, 124.0, 124.7, 124.8, 129.0, 129.3, 129.6, 129.8, 133.2, 133.3, 134.5, 136.8, 155.1, 166.8, 169.8. Anal. Calcd for $C_{40}H_{44}N_2O_{10}S_2 \cdot 0.1CH_2Cl_2$: C, 58.92; H, 5.45; N, 3.43%. Found: C, 58.84; H, 5.27; N, 3.09%.

*4.2.13.2. Partial-cone 26,28-bis(N-benzenesulfonyl carbamoylmethoxy)calix[4]arene-1,3-crown-4 (**3c**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to afford in 43% yield a pale yellow solid with mp 148–150 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3345 (NH), 3294 (NH), 1719 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.28 (s, 2H, $OCH_2C(O)$), 3.14 (d, J=12.5 Hz, 2H, $ArCH_2Ar$), 3.34–3.37 (m, 2H, OCH_2CH_2O), 3.59–3.76 (m, 6H, OCH_2CH_2O), 3.83–3.87 (m, 6H, OCH_2CH_2O, $ArCH_2Ar$), 4.00–4.04 (m, 2H, OCH_2CH_2O), 4.21 (d, J=12.5 Hz, 2H, $ArCH_2Ar$), 4.50 (s, 2H, $OCH_2C(O)$), 6.41 (s, 1H, NH), 6.56 (t, J=8.0 Hz, 2H, ArH), 6.80–6.83 (m, 2H, ArH), 6.89–6.92 (m, 2H, ArH), 6.99 (d, J=8.0 Hz, 2H, ArH), 7.06–7.12 (m, 2H, ArH), 7.16 (d, J=7.5 Hz, 2H, ArH), 7.50–7.69 (m, 6H, ArH), 7.85–7.87 (m, 2H, ArH), 8.07–8.09 (m, 2H, ArH), 11.53 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 30.0, 37.2, 67.4, 68.2, 69.4, 71.9, 77.0, 123.9, 124.7, 128.3, 128.4, 128.6, 128.8, 128.8, 129.1, 129.5, 129.7, 133.1, 133.3, 133.7, 133.8, 134.6, 136.6, 138.7, 139.1, 154.6, 154.9, 153.3, 165.4, 168.2. Anal. Calcd for $C_{50}H_{48}N_2O_{12}S_2$: C, 64.36; H, 5.19, N, 3.00%. Found: C, 64.30; H, 5.25; N, 2.73%.

*4.2.13.3. Partial-cone 26,28-bis(N-4-nitrobenzenesulfonyl carbamoylmethoxy)calix[4]-arene-1,3-crown-4 (**3d**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to provide a 15% yield of a pale yellow solid with mp 171–173 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3335 (NH), 1736 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.60 (s, 2H, $OCH_2C(O)$), 3.24 (d, J=13.0 Hz, 2H, $ArCH_2Ar$), 3.41–3.44 (m, 2H, OCH_2CH_2O), 3.60–3.90 (m, 12H, $ArCH_2Ar$, OCH_2CH_2O), 4.04–4.08 (m, 2H, OCH_2CH_2O), 4.27 (d, J=13.0 Hz, 2H, $ArCH_2Ar$), 4.55 (s, 2H, $OCH_2C(O)$), 6.36 (s, 1H, NH), 6.62 (t, J=8.0 Hz, 2H, ArH), 6.84–6.85 (m, 2H, ArH), 6.92 (t, J=8.0 Hz, 1H, ArH), 7.07–7.21 (m, 7H, ArH), 7.98–8.01 (m, 2H, ArH), 8.27–8.29 (m, 2H, ArH), 8.35–8.38 (m, 4H, ArH), 11.82 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 30.2, 37.4, 67.3, 68.0, 69.5, 71.6, 76.8, 123.8, 124.0, 124.1, 124.7, 124.8, 128.8, 129.3, 129.8, 129.8, 130.0, 133.0, 133.4, 134.4, 136.5, 143.9, 144.5, 150.7, 150.7, 154.5, 154.9, 155.2, 165.7, 168.6. Anal. Calcd for $C_{50}H_{46}N_4O_{16}S_2$: C, 58.70; H, 4.53, N, 5.47%. Found: C, 58.85; H, 4.23; N, 5.53%.

*4.2.13.4. Partial-cone 26,28-bis(N-trifluoromethanesulfonyl carbamoylmethoxy)calix-[4]arene-1,3-crown-4 (**3e**).* The crude product was chromatographed on silica gel with CH_2Cl_2/MeOH (250:1 to 25:1 gradient) as eluent to give a 38% yield of white solid that decomposed at 235 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): 3324 (NH), 3258 (NH), 1755 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.35 (s, 2H, $OCH_2C(O)$), 3.40–3.46 (m, 4H, OCH_2CH_2O, $ArCH_2Ar$), 3.63–3.67 (m, 2H, OCH_2CH_2O), 3.72–3.83 (m, 6H, OCH_2CH_2O, $ArCH_2Ar$), 3.92 (s, 4H, OCH_2CH_2O), 4.03–4.07 (m, 2H, OCH_2CH_2O), 4.36 (d, J=13.0 Hz, 2H, $ArCH_2Ar$), 4.71 (s, 2H, $OCH_2C(O)$), 6.38 (s, 1H, NH), 6.85 (t, J=8.0 Hz, 1H, ArH), 6.96 (t, J=8.0 Hz, 2H, ArH), 7.02–7.13 (m, 5H, ArH), 7.21 (d, J=8.0 Hz, 2H, ArH), 7.26–7.29 (m, 2H, ArH), 12.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 30.0, 37.4, 67.6, 67.7, 69.5, 71.6, 77.1, 124.2, 124.8, 125.1, 129.1, 129.4, 129.7, 129.9, 133.2, 133.3, 134.7, 136.7, 154.5, 154.9, 155.2, 164.3, 167.6. Anal. Calcd for $C_{40}H_{38}N_2O_{12}S_2F_6$: C, 52.40; H, 4.15; N, 3.06%. Found: C, 52.46; H, 4.38; N, 2.80%.

4.3. Solid-state structure determination of intermediate 11

Crystals suitable for structure determination of **11** were grown from deuteriochloroform/hexane. Crystal and intensity data for the structural study were obtained with a Nicolet R3m/V automated diffractometer with Mo Kα radiation (λ=0.71073 Å). The structure was solved and initially refined using programs contained in the SHELXTL PLUS® program package.[24] Final refinement and the structure display were accomplished using the SHELXTL PC® program package.[25] The crystal data and experimental details are listed in Table 5.

Table 5
Crystallographic data for intermediate **11**

Formula	$C_{40}H_{44}O_8$
FW (g mol^{-1})	652.75
Temperature (K)	296(2)
Crystal system	Monoclinic
Space group	$P2(1)/c$
a (Å)	12.257(3)
b (Å)	8.9690(18)
c (Å)	16.161(3)
α (°)	90
b (°)	105.29(3)
c (°)	90
Volume (Å)^3	1713.8(6)
Z	2
μ (mm^{-1})	0.087
F(000)	696
Crystal size (mm)	0.34×0.35×0.09
θ (°)	2.61–25.38
Reflections collected	18,310
Reflections observed	3149
Number of parameters	221
Goodness-of-fit on F^2	1.033
R ($I>2\sigma(I)$)	0.0423
Largest difference peak and hole (e Å^3)	0.390, −0.342

Crystallographic data for compound **11** have been deposited with CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and are identified by deposition number CCDC 853897. A copy of this information can be obtained free of charge on request by e-mail at deposit@ccdc.cam.ac.uk or at http://www.ccdc.cam.ac.uk.

4.4. Procedures for metal ion extraction

Procedures for competitive alkali metal cation extraction, competitive alkaline earth metal cation extraction, single species extraction of Hg^{2+}, and single species extraction of Pb^{2+} from aqueous solutions into chloroform have been reported previously.[26]

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