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Rigid *versus* flexible: how important is ligand "preorganization" for metal ion recognition by lower rim-functionalized calix[4]arenes?

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For an assessment of the outcomes from use of an appropriately "preorganized" calixarene-based ionophore *versus* its conformationally mobile prototype, solvent extraction propensities of flexible calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] for alkali, alkaline earth metal cations, Pb^{2+}, Ag^{+} and Hg^{2+} are compared with those for seven new rigid analogs fixed in the *cone*, *partial cone* and *1,3-alternate* conformations. For each of the metal ions, the preferred calix[4]arene conformation was determined from the NMR spectra for the metal salt of the flexible ligand. Except for Ag^{+}, flexible calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] were found to provide greater metal ion extraction efficiency and better selectivity than the corresponding "preorganized" ionophores.

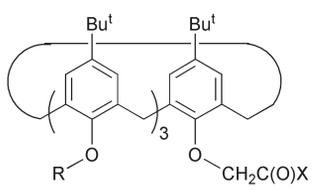
Introduction

During the last decades calixarenes have received the attention of many researchers due to their unique complexing abilities toward various metal cations.[1] The broad spectrum of selectivities exhibited by these ligands led to applications in metal ion recognition and separations.[2] It was found that the affinity of a calixarene toward a particular metal ion depends on the conformation of the metacyclophane moiety.[1,3] Variation of the calixarene geometry changes the spatial orientation of the pendant functional groups that are responsible for metal ion binding and, at the same time, modifies the shape of the π-electron-rich cavity of the ligand that is capable of cation–π interactions. Both of these factors may alter the efficiency and selectivity of the ionophore in metal ion complexation.

It was observed (both in crystal structures of the complexes and in solution by NMR spectroscopy) that during coordination with a metal cation, a flexible calixarene tends to adopt the conformation most appropriate for accommodating the "guest".[4,5] This finding provided an impetus for the preparation of calix[4]arenes locked in *cone*, *partial cone* (*paco*) and *1,3-alternate* conformations and study of their complexation properties toward various metal ion species. As was noted for a variety of calix[4]arene derivatives, different conformational isomers of the same ligand typically exhibit distinctive selectivity ratios and sometimes even contrasting selectivity patterns.[6] Hence, "preorganization" of a calixarene moiety in the appropriate conformation is generally believed to promote enhancement of the receptor selectivity for a particular metal cation relative to that of the flexible analog.

Following this idea, we proposed that an approach—*synthesis of a mobile functionalized calix[4]arene → determination of the preferred ligand conformation in the complex with the metal cation of interest by NMR spectroscopy → synthesis of the analogous ligand restricted to this particular conformation*—would provide a simple route to calixarene-based ionophores with improved efficiency and selectivity for desired metal ions. Herein, we describe the results obtained from the application of this methodology to calix[4]arenes containing proton-ionizable functional groups on the lower rim.

The approach was first probed for Li^{+}-selective mono-proton-ionizable calix[4]arenes **1**.[7] By NMR spectroscopy, flexible ligands **1a**^{flex}, which exhibited significant preference for Li^{+} over Na^{+} and other alkali metal cations (AMC) in solvent extraction, were found to adopt the *cone* conformation in their Li^{+} complexes. Therefore, the related rigid *cone* calixarenes **1b**^{cone} were synthesized and competitive AMC extractions studied. Surprisingly, the "preorganized" ionophores exhibited much lower Li^{+}/Na^{+}-selectivities than their flexible analogs.



1

X = OH, $NHSO_2Y$;
Y = CF_3, Me, Ph, 4-$NO_2C_6H_4$

1a^{flex}: R = Me
1b^{cone}: R = Bu

This unexpected observation motivated us to search the literature for evidence of improvements† to metal ion recognition due to the application of calixarene-based ionophores restricted to definite conformations *versus* the analogous mobile ligands. The search revealed that this topic has received much less attention from researchers than the comparative studies of complexing abilities for different conformational isomers of the same ligand. Surprisingly, only a limited number of reports provide direct comparison of complexation propensities for flexible calix[4]arenes and their conformationally fixed analogs.

The most substantial information on the topic is available for calix[4]arene-crown ethers (see ref. 8 for a review). It was shown unequivocally that K^{+}/Na^{+}-selectivity of calix[4]arene-crown-5 and Cs^{+}-selectivity of calix[4]arene-crown-6 ethers increased dramatically on going from flexible to the corresponding rigid ionophores immobilized in the *paco*- and *1,3-alternate*

† Among the positive effects that might arise with the use of a properly "preorganized" ionophore instead of the corresponding mobile one are modification of the selectivity profile in favor of the targeted metal ion or, if both flexible and rigid ligands are specific for the same cation, enhancement of the binding efficiency and selectivity toward that particular species on going from flexible ligand to its rigid analog.

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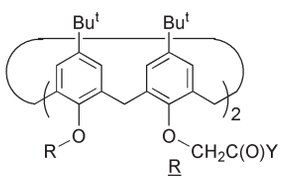
conformations, respectively, in accordance with the conformational preferences of the analogous mobile ligands in their K^+- and Cs^+-complexes. However, from the data available for comparison of rigid *versus* flexible lower rim-functionalized calix[4]arenes, an advantage of "preorganization" over flexibility for metal ion recognition is not evident. In some of the cases, the conformationally mobile receptors gave better results. The examples are complexation of AMC with tetraalkoxycalix[4]arenes,[9] solvent extraction of alkaline earth metal cations (AEMC) by calix[4]arene dicarboxylic acids,[10] optical sensing of Pb^{2+} by calix[4]arene amides,[11] and solvent extraction of trivalent lanthanides and actinides Am^{3+}, Cm^{3+}, and Th^{4+} by calix[4]arene carbamoylmethylphosphine oxides.[12]

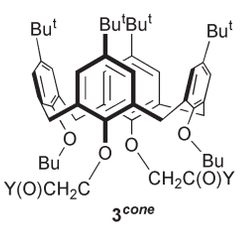
In order to provide greater insight into the problem, we have now conducted a systematic investigation of the effect of ionophore "preorganization" on the metal ion recognition characteristics of a series of lower rim-functionalized, di-ionizable calix[4]arenes. Flexible ligands **2**^{flex}[13] and related novel receptors locked in *cone* (**3**^{cone}), *paco* (**3**^{paco}) and *1*,*3-alternate* (**3**^{alt}) conformations were studied as extractants of various metal-ion species—AMC, AEMC, Pb^{2+}, Ag^+, and Hg^{2+}. For each metal cation, extraction by the mobile ligand was compared with that by the rigid analog restricted to the appropriate conformation determined from the NMR-spectra of the corresponding complex metal ion-flexible calixarene.



2 (flexible): Me
3 (rigid) : Bu

2(a-c)^{flex}: Y=NHSO$_2$X
X
2a^{flex}: CF_3
2b^{flex}: Ph
2c^{flex}: Me

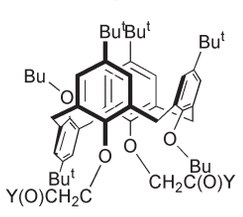
2d^{flex}: Y=OH



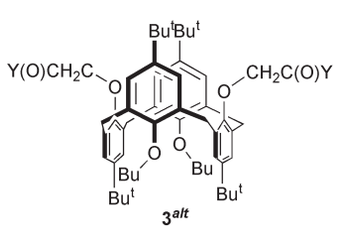
3^{cone}

3(a-c)^{cone,paco,alt} : Y=NHSO$_2$X
X
3a^{cone,paco,alt} : CF_3
3b^{cone,paco,alt} : Ph
3c^{paco,alt} : Me

3d^{cone,paco,alt} : Y=OH



3^{paco}



3^{alt}

Results and discussion

NMR investigation of flexible calix[4]arene ligand conformations in metal ion complexes

Structural studies to determine the preferred conformation(s) of the calix[4]arene moiety in the presence of different metal ions, *i.e.*, alkali metal cations (AMC), alkaline earth metal cations (AEMC), Pb^{2+}, Ag^+, and Hg^{2+}, were performed with flexible calix[4]arene di-[*N*-(X-sulfonyl)carboxamide] **2a**^{flex}.‡ NMR spectra of the corresponding metal salts of **2a**^{flex} in $CDCl_3$ solution were investigated. The complexes were typically prepared by interaction of the ligand with an excess of the appropriate metal carbonates. To obtain the Ag^+-and Hg^{2+}-complexes, metal oxides were used instead of carbonates. The spectral data obtained for most of the metal ion-ionized ligand complexes are presented in Table 1; those for the AMC-salts of **2a**^{flex} were published earlier.[5]

Complexes of **2a**^{flex} with each of the five AMC (Li^+, Na^+, K^+, Rb^+, and Cs^+) had distinctive spectral patterns, which indicated that the flexible calixarene moiety in these compounds adopted different conformations. In the complexes with Li^+, K^+ and Cs^+ ions, pronounced dominance of one particular ligand conformation (*cone*, *paco*, and *1*,*3-alternate*, respectively) was observed. In the Na^+-salt of **2a**^{flex}, both *cone*- and *paco*-shaped calixarenes were present; while Rb^+ favored concurrently the *paco* and *1*,*3-alternate* structures of the ligand.

In contrast with the salts of alkali metals, NMR spectra of all of the alkaline earth metal complexes of **2a**^{flex} were similar (Table 1). Such a resemblance is indicative of common conformational preference of Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} on coordination with the ligand. The spectra contained three signals in the *tert*-butyl region with an intensity ratio of 2 : 1 : 1, the signals for two non-equivalent methoxy groups, two pairs of doublets for the ArCH_2Ar protons, a pair of doublets for the diastereotopic protons in the equivalent OCH_2C(O) groups, and a pair of doublets and two singlets in the aromatic region. This pattern is consistent with *paco* as the dominant conformation of the calix[4]arene unit. As estimated from the spectral data, at least 90% of all **2a**^{flex} molecules adopted this conformation in the complexes with each of the AEMC in $CDCl_3$ solution.

The ^{1}H NMR spectrum for the Pb^{2+}-salt of **2a**^{flex} (Table 1) was similar to those of the AEMC. Thus *paco* is the preferred conformation of the calix[4]arene moiety in the lead complex as well, with over 95% of the ligand molecules adopting a *paco* shape when bound with Pb^{2+} ion in $CDCl_3$.

In the ^{1}H NMR spectrum of the Ag^+ complex with **2a**^{flex}, two sets of signals were observed, indicating the presence of two significantly populated conformations of the calix[4]arene in solution. Detailed analysis of the spectrum was hampered by broadening of some of the signals. Nevertheless, distinctive patterns characteristic of the *paco* and *1*,*3-alternate* conformations of the calix[4]arene skeleton were evident (see Table 1). The distribution of these two ligand structures in the Ag^+-complex is estimated as 60% *paco* and 40% *1*,*3-alternate*.

The Hg^{2+}-salt of **2a**^{flex} in $CDCl_3$ exhibited a complicated ^{1}H NMR spectrum with more than three sets of signals (for three possible limited calix[4]arene conformations) and multiple signal overlapping. Such a large number of signals could originate from several stable rotamers for the three main conformations. Another possible explanation is the formation of stable complexes of different composition. Thus, the conformational preference for the calix[4]arene moiety in **2a**^{flex} in the presence of Hg^{2+} could not be determined.

Synthesis of di-ionizable calix[4]arenes immobilized in *cone*, *paco* and *1*,*3-alternate* conformations

Synthesis of the conformational isomers (*cone*, *paco* and *1*,*3-alternate*) of calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] **3(a–c)** was performed according to Scheme 1. The corresponding isomeric calix[4]arene diacids **3d**[14a,15] were converted into the calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] *via* the appropriate di(acid chlorides) (see Experimental for details).

Solvent extraction of metal ions by rigid *versus* flexible di-ionizable calix[4]arenes

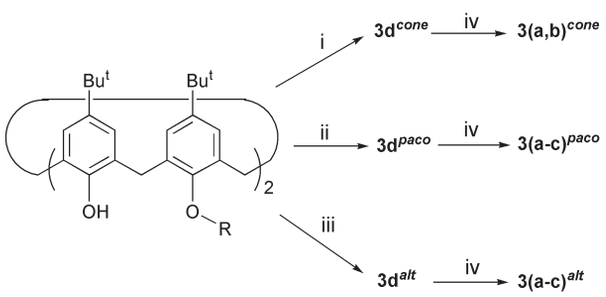
Our previous studies[13,14,16] showed that in solvent extractions of alkali metal cations (AMC), alkaline earth metal cations (AEMC), Pb^{2+}, Ag^+, and Hg^{2+}, the most NH-acidic flexible ligand **2a**^{flex} with X = CF_3 was the most potent ionophore in the series of ligands **2**^{flex}. For all of the above-mentioned metal cations except Hg^{2+}, the difference in the binding ability of **2a**^{flex} and the analogs with other, less electron-withdrawing substituents X was quite significant. In contrast, the efficiency

‡ As was observed in our earlier NMR studies,[5] conformational preferences of flexible calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] in their AMC-complexes are unaffected by the substituent X identity.

Table 1 Selected ^{1}H NMR data for metal salts of flexible calixarene **2a**^{flex} in $CDCl_3$

Metal ion	Preferred conformation	*tert*-Butyl protons[a]	ArCH_2Ar	Lower rim substituents	Aromatic protons
Mg^{2+}	*paco*	1.14 s (2) 1.22 s (1) 1.31 s (1)	3.61 d (J 12.6) 3.98 d (J 12.6) 3.57 d (J 15.7) 4.62 d (J 15.7)	0.42 s (*endo* CH_3O) 3.93 s (*exo* CH_3O) 4.62 d (J 16.7) 5.23 d (J 16.7) (OCH_2CO)	7.10 d (J 2.0) 7.14 s 7.22 d (J 2.0) 7.27 s
Ca^{2+}	*paco*	1.12 s (2) 1.24 s (1) 1.33 s (1)	3.62 d (J 12.6) 4.05 d (J 12.6) 3.61 d (J 15.7) 4.71 d (J 15.7)	0.32 s (*endo* CH_3O) 3.88 s (*exo* CH_3O) 4.57 d (J 16.2) 5.17 d (J 16.2) (OCH_2CO)	7.09 d (J 2.2) 7.17 s 7.23 d (J 2.2) 7.31 s
Sr^{2+}	*paco*	1.10 s (2) 1.25 s (1) 1.34 s (1)	3.58 d (J 12.8) 4.07 d (J 12.8) 3.62 d (J 15.7) 4.68 d (J 15.7)	0.26 s (*endo* CH_3O) 3.79 s (*exo* CH_3O) 4.43 d (J 16.3) 5.28 d (J 16.3) (OCH_2CO)	7.04 br d 7.17 s 7.22 br d 7.29 s
Ba^{2+}	*paco*	1.07 s (2) 1.28 s (1) 1.34 s (1)	3.59 d (J 12.6) 4.12 d (J 12.6) 3.68 d (J 16.2) 4.75 d (J 16.2)	0.22 s (*endo* CH_3O) 3.80 s (*exo* CH_3O) 4.25 d (J 15.1) 5.15 d (J 15.1) (OCH_2CO)	7.01 d (J 2.3) 7.16 s 7.20 d (J 2.3) 7.29 s
Pb^{2+}	*paco*	1.11 s (2) 1.28 s (1) 1.34 s (1)	3.57 d (J 12.4) 4.08 d (J 12.4) 3.66 d (J 15.9) 4.56 d (J 15.9)	0.32 s (*endo* CH_3O) 3.15 s (*exo* CH_3O) 4.75 d (J 16.3) 5.19 d (J 16.3) (OCH_2CO)	7.06 d (J 2.3) 7.16 s 7.24 d (J 2.3) 7.29 s
Ag^{+}	*paco*	1.15 s (2) 1.25 s (1) 1.42 s (1)	3.36 d (J 12.3) 4.00 d (J 12.3) 3.70 br d 3.83 br d	2.18 br s (*endo* CH_3O) 3.79 s (*exo* CH_3O) 4.74 br d 4.99 br d (OCH_2CO)	6.99 s 7.02 br d 7.11 br d 7.29 s
1,3-alt		1.28 s (2) 1.29 s (2)	3.86 br s	3.69 s (CH_3O) 4.77 s (OCH_2CO)	7.13 s 7.22 s

[a] Number of *tert*-butyl groups in parentheses.



i: R=Bu; 1) $BrCH_2CO_2Me$, NaH, DMF; 2) OH^-, H_2O/THF
ii: R=CH_2CO_2Me; 1) BuBr, KH, THF; 2) OH^-, H_2O/THF
iii: R=Bu; 1) $BrCH_2CO_2Me$, KH, THF; 2) OH^-, H_2O/THF
iv: 1) $(COCl)_2$, C_6H_6; 2) XSO_2NH_2, NaH or KH, THF
X = CF_3, Ph, Me

Scheme 1

of Hg^{2+} extraction by the flexible calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] **2**^{flex} varied only slightly and seemed to be affected by the size of the substituent X rather than its electron-withdrawing ability. Taking into account these earlier findings, for comparison of the metal ion-recognition propensities of conformationally immobile (**3**) *versus* flexible (**2**) calixarenes, solvent extractions of AMC, AEMC, Pb^{2+} and Ag^+ herein were performed with CF_3-substituted ligands **2a** and **3a** only; while for Hg^{2+}, ligands with X = CF_3, Ph and Me, **2(a–c)** and **3(a–c)** were employed, as well as the corresponding flexible (**2d**) and "preorganized" (**3d**) calix[4]arene diacids.

Metal loadings of the calixarenes in solvent extraction were calculated as %Loading = $[M_{org}]/C_L \times 100$, where $[M_{org}]$ is metal concentration in the organic phase after extraction and C_L is the total ligand concentration in the organic phase. Since for all of the metal cations, except for AMC, observed loadings of the calixarenes approached 100% (see *vide infra*), complexes with 1:1 metal-to-ligand stoichiometry were assumed to be a principal species extracted under the given experimental conditions.

Competitive extraction of alkali metal cations (AMC)

As was found earlier, flexible calixarene **2a**^{flex} provided very efficient binding of AMC.[16] In competitive extraction of equimolar (10.0 mM) Li^+, Na^+, K^+, Rb^+, and Cs^+ from aqueous chloride solutions with varying pH into chloroform containing 1.0 mM ionophore, **2a**^{flex} exhibited a pronounced preference for Na^+ (Fig. 1a), with total AMC loading approaching 200%.§ Restriction of the calixarene moiety to the *cone*, *paco* and *1,3-alternate* conformations was anticipated to change the AMC-extraction selectivities of the corresponding rigid ligands **3a** relative to their flexible analog **2a**^{flex}. Based upon the conformational preferences determined for each of the AMC with **2a**^{flex},[5] **3a**^{cone} was expected to favor Li^+, while **3a**^{paco} and **3a**^{alt} should exhibit selectivities for K^+ and Cs^+, respectively.

However, competitive AMC extraction experiments performed for **3a**^{cone}, **3a**^{paco} and **3a**^{alt} showed that these three rigid ligands, analogously to the flexible **2a**^{flex}, were appreciably selective for Na^+. All of the calixarenes **2a** and **3a** had similar extraction pH-profiles (for example, see Figs. 1a and 1b for **2a**^{flex} and **3a**^{paco}, respectively). The pH of half-extraction (evaluated from Na^+-loadings of the ligands) varied from 1.9–2.0 with **2a**^{flex} and **3a**^{cone} to 1.4 with **3a**^{alt} to 0.90 with **3a**^{paco}.

Hence, the calixarene "preorganization" did not produce the anticipated effect on the selectivity of AMC recognition; although some minor changes in the desired direction should be pointed out. Thus, on going from flexible calixarene **2a**^{flex} to the rigid analogs **3a**, a general modest decrease in the extraction selectivity for Na^+ over other AMC was observed (see Fig. 2). This trend was the most pronounced for **3a**^{cone}.

§ Calixarenes **2** and **3** contain two proton-ionizable groups, which allows binding of two univalent cations per ligand molecule.

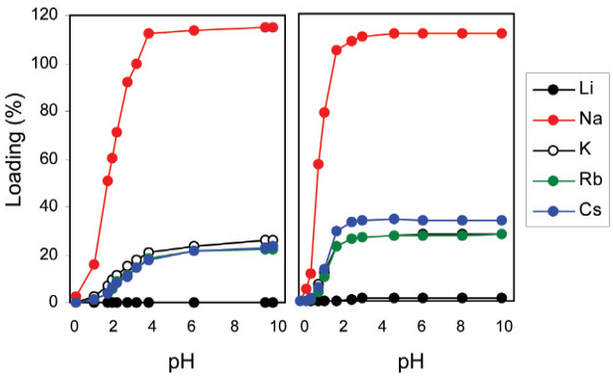


Fig. 1 pH-profiles for competitive AMC extraction from 10.0 mM (in each of Li^+, Na^+, K^+, Rb^+ and Cs^+) aqueous chloride/hydroxide solutions into chloroform by 1.0 mM calixarenes (a) **2a**^{flex} and (b) **3a**^{paco}.

Thus, a commonly very low Li^+-loading of the ionophores measured at pH 10 increased by a factor of 35 from 0.1% with **2a**^{flex} to 3.5% with **3a**^{cone}. Levels of Cs^+ extraction (measured at pH 10) were enhanced from 23% to 41% when flexible ligand **2a**^{flex} was replaced with its *1,3-alternate* analog **3a**^{alt}. However, these deviations in the extraction behavior of the flexible and rigid calixarenes were quite insignificant overall.

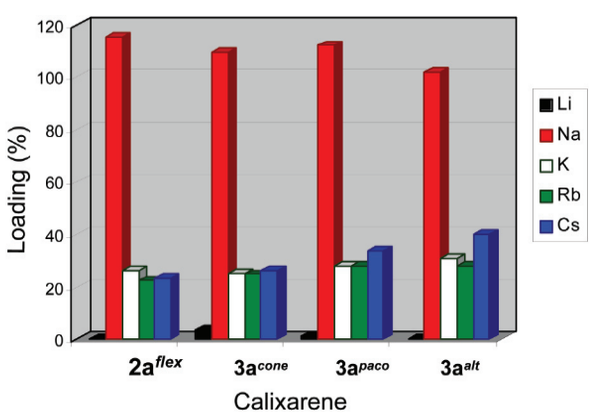


Fig. 2 Competitive AMC extraction from 10.0 mM (in each of Li^+, Na^+, K^+, Rb^+ and Cs^+) aqueous chloride/hydroxide solutions at pH 10 into chloroform by 1.0 mM calixarenes **2a**^{flex}, **3a**^{cone}, **3a**^{paco} and **3a**^{alt}.

Competitive extraction of alkaline earth metal cations (AEMC)

As was determined by solution NMR spectroscopy (*vide supra*), *paco* is the dominant conformation adopted by flexible ligand **2a**^{flex} in its complexes with all four of the AEMC—Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}. In competitive AEMC extraction from basic aqueous solutions into chloroform, **2a**^{flex} demonstrated a preference for Ba^{2+} (Fig. 3).[16] To find out whether "preorganization" of the ionophore in the *paco* conformation will further increase the Ba^{2+}-selectivity, ligand **3a**^{paco} was utilized in competitive AEMC extraction under conditions otherwise identical to those applied to **2a**^{flex}. Surprisingly, for this conformationally immobile calixarene, favoring of Ca^{2+} rather than Ba^{2+} extraction was observed (Fig. 3).

In contrast, two other isomers of **3a** (**3a**^{cone} and **3a**^{alt}) were selective toward Ba^{2+}. The AEMC-extraction profile of **3a**^{cone} generally resembled that of the flexible analog **2a**^{flex}; however, the *cone* ligand was the only one of calixarenes **2a** and **3a** to provide an appreciable (about 10%) uptake of Mg^{2+}. The *1,3-alternate* ionophore **3a**^{alt} provided the most efficient and selective separation of Ba^{2+} from the AEMC mixture (Fig. 3). Thus, Ba^{2+}/Ca^{2+}- and Ba^{2+}/Sr^{2+}-selectivities of **2a**^{flex} estimated as a ratio of the corresponding metal ion-distribution coefficients D_{Ba}/D_M were 13 and 2, respectively; while for **3a**^{alt}, these values were 58 and 202, respectively.

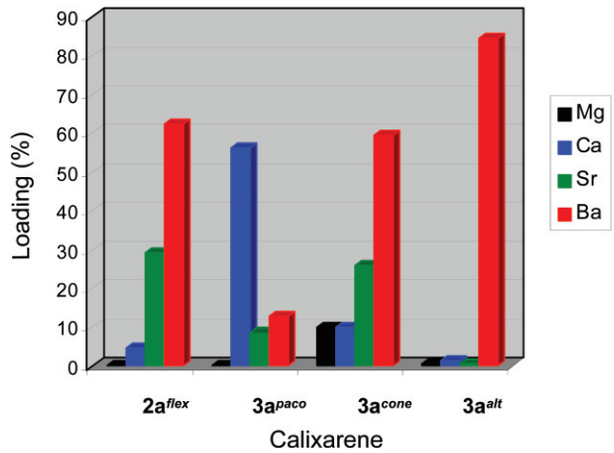


Fig. 3 Competitive AEMC extraction from 10.0 mM (in each of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+}) aqueous chloride/hydroxide solutions at pH 9.8 into chloroform by 1.0 mM calixarenes **2a**^{flex}, **3a**^{paco}, **3a**^{cone} and **3a**^{alt}.

Extraction of Pb^{2+}

Flexible calixarene **2a**^{flex} is an efficient extractant of Pb^{2+} from acidic aqueous solutions into chloroform.[13] As shown by NMR spectroscopy (*vide supra*), the ligand adopts predominantly the *paco* conformation in its complex with lead ion. Hence, to probe for an effect of proper ligand "preorganization" on its Pb^{2+}-recognition propensity, **3a**^{paco} was utilized in the extraction of $Pb(NO_3)_2$ at varying pH. For comparison, two other conformational isomers of **3a** (**3a**^{cone} and **3a**^{alt}) were studied as Pb^{2+}-extractants under otherwise identical conditions. The results of this study are presented in Fig. 4. As is evident from the plot, rigid **3a**^{paco} was somewhat weaker extractant of Pb^{2+} than the flexible analog **2a**^{flex}, although more effective than **3a**^{cone} and **3a**^{alt}. The pH of lead ion half-extraction varied with the ligand as **2a**^{flex} (1.9) < **3a**^{paco} (2.3) < **3a**^{alt} (2.5) < **3a**^{cone} (3.5).

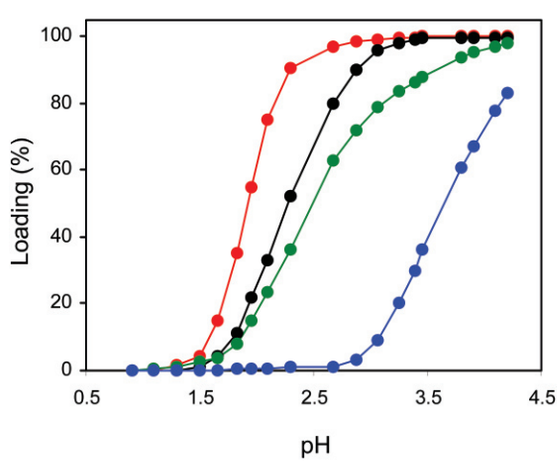


Fig. 4 pH-profiles for Pb^{2+} extraction from 1.0 mM aqueous nitrate solution into chloroform with 1.0 mM calixarenes **2a**^{flex} (red), **3a**^{paco} (black), **3a**^{alt} (green) and **3a**^{cone} (blue).

Extraction of Pb^{2+} with ligand **2a**^{flex} was unaffected by the presence in the aqueous phase of many alkali, alkaline earth and transition metal ions, except for Na^+, Ca^{2+} and the soft ions Ag^+, Pd^{2+} and especially Hg^{2+}.[13] To determine whether restriction of the calixarene moiety to the *paco* conformation would further improve the selectivity of Pb^{2+} separation, competitive extractions of $Pb(NO_3)_2$ from aqueous equimolar binary mixtures with Na^+, Ca^{2+}, Ag^+, Pd^{2+}, and Hg^{2+} nitrates at pH 4.3 with **3a**^{paco} as ionophore were performed. The results are presented in Fig. 5 in comparison with corresponding data for the flexible analog **2a**^{flex}. As is obvious from the graph, ligand "preorganization" in **3a**^{paco} improved to some extent the selectivity for Pb^{2+} over Na^+, Ca^{2+}, Pd^{2+}, and Hg^{2+} relative to

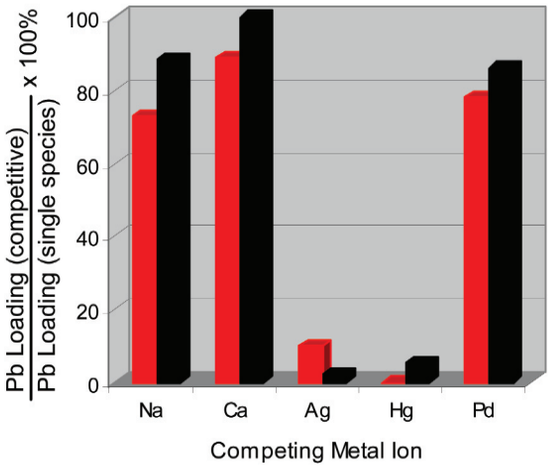


Fig. 5 Competitive extraction of aqueous 0.50 mM $Pb(NO_3)_2$ (pH 4.3) from equimolar binary mixtures with other metal cations into chloroform with 0.50 mM calixarenes **2a**^{flex} (red) and **3a**^{paco} (black).

those of **2a**^{flex}. However, Pb^{2+} extraction by **3a**^{paco} suffered greater interference from Ag^+ than that with the flexible analog.

Extraction of Ag^+

Previously we reported[14] that flexible calixarene **2a**^{flex} not only provides high levels of extraction of hard (AMC and AEMC) and softer (Pb^{2+}) metal ions, but is also an efficient extractant of soft Ag^+ ions from acidic aqueous solutions. Structural studies of the **2a**^{flex}-Ag^+ complex in $CDCl_3$ performed by NMR spectroscopy revealed two dominant conformations of the ligand—*paco* (~60%) and *1,3-alternate* (~40%). Accordingly, two rigid calixarenes **3a**^{paco} and **3a**^{alt} might be expected to extract silver ion more efficiently from aqueous solutions into chloroform. As shown in Fig. 6, both of these "preorganized" ligands possessed higher capabilities for binding Ag^+ than their flexible prototype and provided appreciable metal loadings at more acidic pH. Thus, the half-extraction pH for the three calixarenes varied from 0.70 with **3a**^{alt} to 0.93 with **3a**^{paco} to 1.7 with **2a**^{flex}. In contrast, the *cone* isomer **3a**^{cone} utilized in extraction of Ag^+ under otherwise identical conditions demonstrated the weakest propensity for this metal ion with the pH of half-extraction 2.7 (Fig. 6).

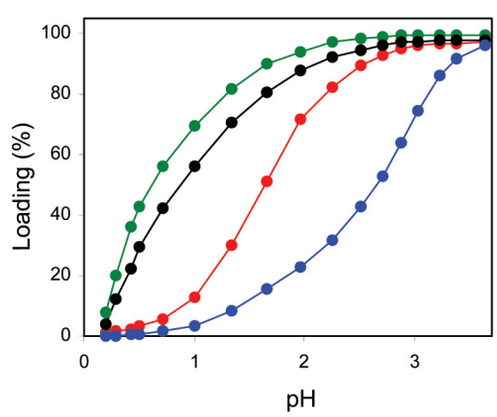


Fig. 6 pH-profiles for Ag^+ extraction from 1.0 mM aqueous nitrate solution into chloroform with 1.0 mM calixarenes **2a**^{flex} (red), **3a**^{alt} (green), **3a**^{paco} (black) and **3a**^{cone} (blue).

Hence, "preorganization" of the calixarene moiety in the appropriate conformations is generally favorable for recognition of Ag^+. At the same time, it should be pointed out that the *1,3-alternate* isomer behaved as a slightly more efficient Ag^+-extractant than the *paco* compound, in contrast to what would be predicted based on the estimated percent distribution of these two calixarene conformations in the Ag^+-complex with the flexible analog (*vide supra*).

Extraction of Hg^{2+}

As we reported earlier,[14] conformationally mobile calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] **2** provide high levels of Hg^{2+} extraction from acidic aqueous solutions into chloroform. In contrast with separations of AMC, AEMC, Pb^{2+} and Ag^+ with these flexible ligands, the efficiency of Hg^{2+} binding (measured in terms of half-extraction pH) decreased only slightly in the order CF_3 > Me > Ph > 4-$NO_2C_6H_4$, as the size of substituent X increased. For this reason, the ionophores employed in the comparative studies of rigid *versus* flexible ligands in recognition of Hg^{2+} were not limited to the most NH-acidic, CF_3-containing compounds only. Three mobile (**2a**^{flex}, **2b**^{flex} and **2c**^{flex} with X = CF_3, Ph and Me, respectively) and the analogous "preorganized" calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] **3** were utilized in these experiments.

Based on changes in the UV- and IR-spectra of the calixarenes on Hg^{2+} coordination, cation-π interaction between Hg^{2+} ion and the π-electron-rich aromatic cavity of the ligand is believed to be involved in the complex formation.[14] However, due to complexity of the ^{1}H NMR spectrum of the Hg^{2+} salt of **2a**^{flex} in $CDCl_3$ solution (*vide supra*), the preferred ligand conformation(s) in this complex could not be identified. Accordingly, rigid isomeric calix[4]arenes **3** in the three limiting conformations of *cone*, *paco and 1,3-alternate*, were studied as Hg^{2+}-extractants from aqueous solutions into chloroform.

To evaluate the effect of calixarene conformation on Hg^{2+} recognition and, at the same time, to probe for the role of the substituent, X, CF_3- and Ph-containing ligands were initially employed in $Hg(NO_3)_2$ extraction under otherwise identical conditions. It was observed that, regardless of the X identity, Hg^{2+}-loading of the rigid conformers and their flexible analogs varied in the same order: flexible ≥ *1,3-alternate* > *cone* > *paco*, as shown in Fig. 7 for the ligands with X = Ph (**2b**^{flex}, **3b**^{alt}, **3b**^{cone} and **3b**^{paco}). Interestingly, when the corresponding flexible and rigid calix[4]arene carboxylic diacids **2d**^{flex}, **3d**^{alt}, **3d**^{cone} and **3d**^{paco} were utilized for Hg^{2+} extraction under otherwise identical conditions, the observed Hg^{2+}-loading decreased in a somewhat different sequence, with the *paco* conformer being a more potent mercuric ion extractant than the *cone* (Fig. 7).

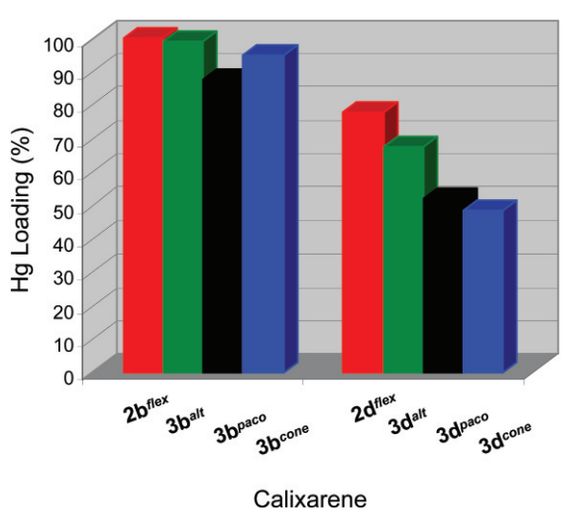


Fig. 7 Hg^{2+} extraction from 0.25 mM aqueous nitrate solution (pH 2.5) into chloroform by 0.25 mM calix[4]arene di-[*N*-(phenylsulfonyl)-carboxamides] and corresponding diacids.

The reason for this deviation remains unclear at this time. Apparently calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] in the *cone* conformation provide a better environment for involvement of Hg^{2+} in the cation-π interactions than the corresponding *paco* isomers; while for the carboxylic diacids **3d**^{cone} and **3d**^{paco} the trend may be the opposite. However, for both calix[4]arene carboxylic diacids and di-[*N*-(X-sulfonyl)-carboxamides], the same principal mode is observed: the

flexible ligand shows the most efficient Hg^{2+} binding, with the analogous ionophore immobilized in the *1,3-alternate* conformation being the second best, only slightly weaker Hg^{2+}-extractant.

To provide a more detailed comparison of the extraction behaviors of flexible calixarenes and their *1,3-alternate* analogs, pH-profiles of $Hg(NO_3)_2$ extraction from aqueous solutions into chloroform were performed with three pairs of ionophores: **2a**^{flex} and **3a**^{alt} (X = CF_3), **2b**^{flex} and **3b**^{alt} (X = Ph), and **2c**^{flex} and **3c**^{alt} (X = Me). In general, the Hg^{2+}-extraction profiles for the flexible and the corresponding rigid ligands were quite similar in the entire pH interval. With the smaller CF_3- and Me-substituents, no essential difference in Hg-loadings of the *1,3-alternate* and flexible ligands was observed (see Fig. 8 for **2c**^{flex} and **3c**^{alt}); while with the Ph-containing calixarenes, **2b**^{flex} was a somewhat more efficient extractant of Hg^{2+} than **3b**^{alt}. Therefore, "preorganization" of the di-ionizable calix[4]arenes did not provide any obvious improvement in the affinity for Hg^{2+} over the conformationally mobile analogs.

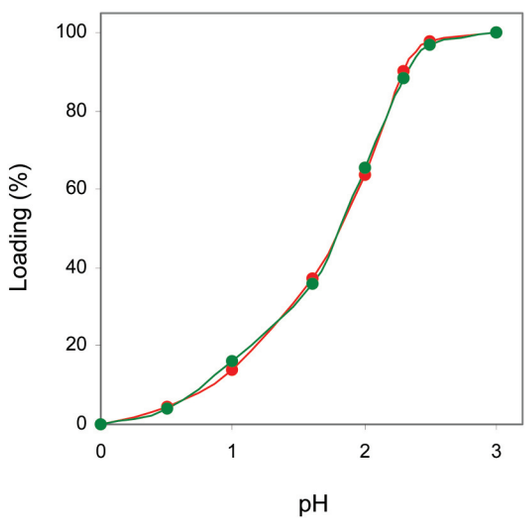


Fig. 8 pH-profiles for Hg^{2+} extraction from 0.25 mM aqueous nitrate solution into chloroform with 0.25 mM calixarenes **2c**^{flex}(red) and **3c**^{alt} (green).

Conclusions

The results obtained from the comparative study of the efficiency and selectivity of AMC, AEMC, Pb^{2+}, Ag^{+}, and Hg^{2+} extraction by flexible and corresponding conformationally fixed di-ionizable calix[4]arenes—di-[*N*-(X-sulfonyl)carboxamides] and carboxylic diacids—showed that in most cases, ligand "preorganization" in the appropriate conformation does not provide the anticipated improvement in metal ion recognition. Utilization of the proposed strategy for the design of ionophores with enhanced selectivity toward particular cations, *i.e.*, *synthesis of mobile functionalized calix[4]arene → determination of preferred conformation of this ligand in the complex with targeted metal cation by NMR spectroscopy → restriction of the calixarene to this specific conformation via synthesis* was successful only for Ag^{+}. For other metal ions studied in this work, flexible ligands demonstrated better complexation propensities than the related compounds immobilized in *1,3-alternate*, *cone* or *paco* conformation.

Experimental

General

^{1}H NMR spectra were measured with Varian Unity INOVA (499.7 MHz), Varian Mercury (299.9 MHz) and IBM AF-300 (300.1 MHz) spectrometers. Chemical shifts (δ) are expressed in ppm downfield from TMS and coupling constant (J) values are given in Hz. pH was measured with a Fisher Scientific Accumet® 50 pH/ion/conductivity meter. Concentrations of AMC and AEMC in aqueous solutions were determined with a Dionex DX-120 Ion Chromatograph; the concentrations of Pb^{2+} and Ag^{+} were measured with a Perkin Elmer 5000 atomic absorption spectrophotometer; the concentration of Hg^{2+} as a complex with dithizone in $CHCl_3$ was determined with a Shimadzu UV-260 UV-Vis spectrophotometer. Samples for solvent extraction were shaken with a Glas-Col® Multi-Pulse Vortexer.

Syntheses of the calixarenes

Flexible calixarenes **2** were prepared by the published procedures.[13] Conformationally immobile calix[4]arene di-[*N*-(X-sulfonyl)carboxamides] **3(a–c)** were obtained as shown in Scheme 1. A general procedure is given below. The synthesis of compound **3b**^{cone} was described earlier.[14a] Syntheses of the corresponding calix[4]arene diacids were performed as reported elsewhere: **3d**^{cone},[14a] **3d**^{alt} and **3d**^{paco}.[15]

General procedure for the preparation of 26,28-dibutoxy-25,27-bis[*N*-(X-sulfonyl)-carbamoylmethoxy]-5,11,17,23-tetrakis(1,1-dimethylethyl)-calix[4]arenes 3(a–c) fixed in the *1,3-alternate*, *cone* and *paco* conformations. A solution of acid **3d**^{cone}, **3d**^{paco} or **3d**^{alt} (1.40 g, 1.60 mmol) and oxalyl chloride (0.61 g, 4.80 mmol) in C_6H_6 (30 cm^3) was stirred under nitrogen at 70 °C for 4 h and the solvent was removed *in vacuo* to provide the corresponding di(acid chloride). A solution of the di(acid chloride) in THF (25 cm^3) was added to a mixture of the appropriate sulfonamide (4.0 mmol) and NaH or KH (16.0 mmol) in THF (20 cm^3), and the mixture was stirred under nitrogen at room temperature for 12 h. Then water (2 cm^3) was added (CAUTION!). The THF was evaporated *in vacuo*, and CH_2Cl_2 and water were added to the residue. The organic layer was washed with saturated aqueous Na_2CO_3 (or K_2CO_3) and then with water, dried ($MgSO_4$) and evaporated *in vacuo* to give the corresponding isomeric calix[4]arene dicarboxamide as the Na- or K-salt, respectively. After purification (see below for individual compounds), the salt was dissolved in CH_2Cl_2, washed with 10% aqueous HCl and then with water, dried ($MgSO_4$) and evaporated *in vacuo*.

3a^{cone} ***(X = CF$_3$).*** The Na-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (49 : 1) as eluent. Colorless solid, yield 1.45 g (80%), mp 122–123 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1745 (C=O); δ_H 0.82 (s, 18H), 0.97 (t, J = 7.4, 6H), 1.33 (s) + 1.34 (s) + 1.30–1.40 (m) (22H), 1.81–1.90 (m, 4H), 3.25 (d, J = 12.6) + 3.28 (d, J = 12.8) (4H), 3.74–3.82 (m, 2H), 3.86–3.97 (m, 2H), 4.10 (d, J = 12.6, 2H), 4.65 (d, J = 12.8) + 4.68 (s) (4H), 4.93 (s, 2H), 6.48 (d J = 2.0, 2H), 6.60 (d, J = 2.0, 2H), 7.15 (s, 2H), 7.18 (s, 2H), 9.33 (s, 1H), 13.59 (s, 1H); δ_C 13.67, 18.93, 25.60, 30.97, 31.01, 31.12, 31.22, 31.48, 31.55, 31.64, 33.70, 34.14, 34.45, 70.49, 73.93, 77.28, 118.69 (q, J = 318.5, CF_3SO_2), 119.22 (q, J = 321.8, CF_3SO_2), 124.89, 125.65, 125.99, 131.49, 132.50, 134.42, 135.17, 145.72, 146.57, 148.42, 150.22, 150.36, 153.97, 168.11, 173.40. Anal.Calcd for $C_{58}H_{76}F_6N_2O_{10}S_2$: C 61.14, H 6.72, N 2.46. Found: C 61.44, H 6.94, N 2.48%.

3a^{paco} ***(X = CF$_3$).*** The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (97.5 : 2.5) as eluent. Colorless solid, yield 1.18 g (65%), mp 125–126 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1747 (C=O); δ_H −0.02–+0.15 (m, 2H), 0.32–0.55 (m, 4H), 0.82–0.92 (m, 6H), 1.05–1.36 (m, 36H), 1.42–1.75 (m, 2H), 2.01–2.42 (m, 2H), 3.28–3.45 (m, 2H), 3.68–4.68 (m, 12H), 5.30 (br s, 1H), 6.90–7.25 (m, 8H), 10.30 (br s, 1H). Anal.Calcd for $C_{58}H_{76}F_6N_2O_{10}S_2$: C 61.14, H 6.72, N 2.46. Found: C 61.40, H 6.49, N 2.57%.

3b^{paco} ***(X = Ph).*** The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (19 : 1) as eluent.

Colorless solid, yield 1.25 g (68%), mp 123 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1721 (C=O); δ_H 0.0–0.12 (m, 2H), 0.47 (m, 3H), 0.51–0.65 (m, 2H), 0.90 (t, J = 7.3, 3H), 1.13 (s, 9H), 1.20 (m, 2H), 1.25 (s, 18H), 1.30 (s, 9H), 1.59 (m, 2H), 1.97 (m, 2H), 3.28 (d, J = 12.5, 2H), 3.77–4.02 (m, 8H), 4.32–4.42 (m, 4H), 6.94 (d, J = 2.3, 2H), 6.98 (s, 2H), 7.12 (s, 2H), 7.17 (d, J = 2.3, 2H), 7.50 (m, 4H), 7.62 (m, 2H), 8.14 (m, 4H), 10.21 (s 2H). Anal.Calcd for $C_{68}H_{86}N_2O_{10}S_2$: C 70.68, H 7.50, N 2.42. Found: C 70.93, H 7.64, N 2.43%.

3c*^{paco} *(X = Me). ¶ The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (97.5 : 2.5, then 19 : 1) as eluents. Slightly yellowish solid, yield 0.77 g, 47%, mp 132–133 °C. IR (deposit from $CHCl_3$ solution on a NaCl plate) ν_{max}/cm^{-1} 1719 (C=O); δ_H −0.10–+0.02 (m, 2H), 0.40–0.61 (m, 5H), 0.87 (t, J = 7.3, 3H), 1.12 (s, 9H), 1.17 (m, 2H), 1.27 (s, 18H), 1.34 (s, 9H), 1.59 (m, 2H), 2.01 (m, 2H), 3.34 (s, 4H), 3.38 (d, J = 12.4, 2H), 3.86–4.00 (m, 6H), 4.17 (d, J = 15.2, 2H), 4.40 (d + d, 4H), 6.96 (d, J = 2.3, 2H), 7.00 (s, 2H), 7.16 (s, 2H), 7.24 (d, J = 2.3, 2H), 9.90 (s, 2H). Anal.Calcd for $C_{58}H_{82}N_2O_{10}S_2$: C 67.54, H 8.01, N 2.72. Found: C 67.24, H 7.87, N 2.68%.

3a*^{alt} *(X = CF$_3$). The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (9 : 1) as eluent. Colorless solid, yield 1.02 g (56%), mp 257–258 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1765 and 1735 (C=O); δ_H 0.83 (t, J = 7.4, 6H), 0.91–0.97 (m, 4H), 1.08–1.17 (m, 4H), 1.25 (s, 18H), 1.30 (s, 18H), 3.32–3.36 (s + m, 8H), 3.92 (d, J = 18, 4H), 3.95 (d, J = 18, 4H), 7.07 (s, 4H), 7.08 (s, 4H), 9.10 (s, 2H); δ_C 13.78, 18.76, 30.40, 31.04, 31.41, 34.03, 39.03, 70.81, 71.32, 126.58, 127.06, 132.82, 133.68, 145.91, 146.98, 152.31, 154.71, 167.63. Anal.Calcd for $C_{58}H_{76}F_6N_2O_{10}S_2$: C 61.14, H 6.72, N 2.46. Found: C 61.16, H 6.80, N 2.32%.

3b*^{alt} *(X = Ph). The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (97.5 : 2.5, then 19 : 1) as eluents. Colorless solid, yield 1.18 g (64%), mp 259–260 °C (dec.). IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1720 (C=O); δ_H 0.82 (t, J = 7.2, 6H), 0.90–1.16 (m, 8H), 1.10 (s, 18H), 1.28 (s, 18H), 3.06 (s, 4H), 3.32 (m, 4H), 3.87 (s, 8H), 7.01s + 7.03s (8H), 7.47–7.55 (m, 4H), 7.57–7.65 (m, 2H), 8.03–8.09 (m, 4H), 9.26 (s, 2H). Anal. Calcd for $C_{68}H_{86}N_2O_{10}S_2$: C 70.68, H 7.50, N 2.42. Found: C 70.29, H 7.42, N 2.22%.

3c*^{alt} *(X = Me). The K-salt was purified by column chromatography on silica gel with CH_2Cl_2–MeOH (19 : 1, then 9 : 1) as eluents. Colorless solid, yield 1.04 g (63%), mp 279–281 °C (dec.). IR (deposit from CH_2Cl_2 solution on a NaCl plate) ν_{max}/cm^{-1} 1705 (C=O); δ_H 0.83 (t, J = 7.1, 6H), 0.93–1.18 (m, 8H), 1.25 (s, 18H), 1.27 (s, 18H), 3.17 (s, 6H), 3.28–3.37 (m) + 3.33 (s) (8H), 3.86 (d, J = 17.4, 4H), 3.89 (d, J = 17.4, 4H), 7.04 (s, 4H), 7.06 (s, 4H), 8.90 (s, 2H); δ_C 13.79, 18.82, 30.56, 31.27, 31.44, 33.99, 34.18, 39.01, 41.39, 70.82, 71.42, 126.47, 127.26, 132.79, 133.75, 145.46, 146.65, 152.60, 154.91, 169.72. Anal. Calcd for $C_{58}H_{82}N_2O_{10}S_2$: C 67.54, H 8.01, N 2.72. Found: C 67.67, H 7.91, N 2.58%.

General procedure for preparation of metal salts of flexible ligand 2a^{flex}

A 20 mM stock solution of **2a**^{flex} in $CDCl_3$ was prepared. A 1.0 mL sample of the stock solution and a 5–7-fold excess of the appropriate powdered metal carbonate (for AMC, AEMC and Pb^{2+}) or oxide (for Ag^+ and Hg^{2+}) in a vial was stirred magnetically for 12 h at room temperature. The mixture was filtered and the filtrate was used for the NMR spectral measurements.

Metal ion extraction studies

It should be mentioned that conformational restriction of the calixarenes **3**^{alt}, **3**^{cone} and **3**^{paco}, achieved due to introduction on the lower rim of bulky butyl groups, resulted in the general deceleration of complexation reactions of these ligands with metal ions relative to complexation with the flexible analogs. Due to this, to reach extraction equilibrium, 20–30 min vortexing of the aqueous and organic phases was needed with the rigid ligands, while a 5 min reaction time was sufficient for the flexible ones.

Competitive extraction of AMC. An aqueous solution 10.0 mM of each of the Li^+, Na^+, K^+, Rb^+ and Cs^+ chlorides with pH adjusted with dilute HNO_3 or LiOH was extracted by 1.0 mM ligand in $CHCl_3$. After extraction, the pH of the aqueous phase was measured, the organic phase was stripped with aqueous 0.10 M HCl, and the AMC concentrations in the stripping solution were determined by ion chromatography.

Competitive extraction of AEMC. An aqueous solution of 10.0 mM of each of the Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} chlorides/hydroxides at pH 9.8 was extracted by 1.0 mM ligand in $CHCl_3$. After extraction, the organic phase was stripped with aqueous 0.10 M HCl, and AEMC concentrations in the stripping solution were determined by ion chromatography.

Extraction of Pb^{2+}. A 1.0 mM aqueous $Pb(NO_3)_2$ solution (pH adjusted with HNO_3) was extracted into $CHCl_3$ with 1.0 mM ligand. After extraction, the pH of the aqueous phase was measured and the residual concentration of Pb^{2+} was determined by atomic absorption spectrophotometry.

Competitive extraction of Pb^{2+} from binary mixtures with other metal ions. An aqueous solution containing 0.50 mM $Pb(NO_3)_2$ and 0.50 mM competing metal nitrate at pH 4.3 was extracted with a 0.50 mM solution of ligand in $CHCl_3$. The residual concentration of Pb^{2+} in the aqueous phase after extraction was determined by atomic absorption spectrophotometry. The result was compared with that obtained from the extraction of "pure" $Pb(NO_3)_2$ under otherwise identical conditions.

Extraction of Ag^+. A 1.0 mM aqueous $AgNO_3$ solution (pH adjusted with HNO_3) was extracted by 1.0 mM ligand in $CHCl_3$. After extraction, the pH of the aqueous phase was measured and the residual concentration of Ag^+ was determined by atomic absorption spectrophotometry.

Extraction of Hg^{2+}. A 0.25 mM aqueous $Hg(NO_3)_2$ solution (pH adjusted with HNO_3) was extracted by 0.25 mM ligand in $CHCl_3$. The residual concentration of Hg^{2+} in the aqueous phase was determined spectrophotometrically after extraction into $CHCl_3$ containing 14 ppm dithizone (λ_{max} 495 nm).

Acknowledgements

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¶ *This compound was synthesized originally to complete the series of* ***3***^{paco} *calixarenes. However,* ***3c***^{paco} *was not employed in the metal ion extraction studies described herein and, therefore, its complexation properties will be reported elsewhere.*

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