

Novel caesium-selective, 1,3-alternate calix[4]arene-bis(crown-6-ethers) with proton-ionizable groups for enhanced extraction efficiency †

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Synthesis of a series of novel 1,3-alternate calix[4]arene-bis(crown-6-ethers) with a proton-ionizable group (PIG) located in front of one crown ether cavity is reported. Variation of the X group in the *N*-(X-sulfonyl)carbamoyl substituent on the calixbiscrowns provides variation of acidity of the PIG. NMR spectroscopic studies demonstrate that the position of the PIG within the molecule allows it to participate in cooperative metal ion coordination by the ligand. In solvent extraction of alkali metal cations from aqueous solutions of varying pH into chloroform, the novel ionophores possess enhanced efficiency relative to a non-ionizable analog, while retaining high Cs⁺ selectivity. The Cs⁺ extraction constants of the proton-ionizable calixbiscrowns are proportional to their acidities. Under the conditions employed, 1 : 1 complexes of the ionized calixbiscrowns with Cs⁺ are the dominant species extracted into the organic phase.

Introduction

Calixarene-crown ethers or calixcrowns, macrocyclic compounds that combine calixarene and polyether units, are being utilized as hosts for selective metal ion recognition.¹ In particular, 1,3-alternate calix[4]arene-crown-6-ethers have received considerable attention since they possess high Cs⁺ over Na⁺ selectivity in solvent extraction and liquid membrane transport.² Special interest in Cs⁺ selective ligands is based on the need for radioactive caesium separation from nuclear fuel reprocessing solutions containing much larger amounts of sodium.³ Despite the high Cs⁺ selectivity of the 1,3-alternate calix[4]arene-crown-6-ethers, implementation of such ligands in practical separation processes is hampered by low extraction efficiency of their caesium salt complexes into low polarity solvents.⁴

A few approaches to increase the efficiency of these ligands have been reported. A bifunctional receptor which combined an anion-binding site with a calixcrown unit was reported to enhance the transport of CsCl across a supported liquid membrane.⁵ In other work,^{4c} so-called 'modifiers' were employed to facilitate extraction efficiency by improving solvation of anions in the organic medium.

Recently we proposed an alternative approach for enhancing Cs⁺ extraction by incorporating a proton-ionizable (cation-exchange) group (PIG) into a 1,3-alternate calix[4]arene-crown-6-ether ligand.⁶ Proper location of the PIG in the ligand was considered to be a very important factor. To retain extraction selectivity, the PIG must be able to participate in metal ion complexation cooperatively with the crown ether unit and the aromatic rings of the calix[4]arene. Positioning of a PIG on a calix[4]arene unit in front of the polyether unit seemed to satisfy this requirement. The only previously reported calixcrown of this type was a 1,3-alternate calix[4]arene-bis(crown-6-ether) with two PIGs located in front of one crown ether

unit.⁷ Since such an arrangement was not expected to favor selective complexation of a monovalent cation, we explored an alternative. A synthesis of novel 1,3-alternate calix[4]arene-bis(crown-6-ethers) with one PIG located in the front of one crown ether unit was developed.⁶ In preliminary studies, the two new ligands **3** and **4** were found to exhibit enhanced Cs⁺ extraction efficiency compared to the non-ionizable analog **1** without a PIG, while retaining high Cs⁺ extraction selectivity. This encouraged us to study the properties of such new proton-ionizable calixbiscrowns in more detail, especially the role of the PIG in metal ion complexation and the effect of its acidity on the extraction abilities of the ligands.

Herein, we report the synthesis of a series of 1,3-alternate calix[4]arene-bis(crown-6-ethers) with a PIG of varying acidity located in front of one crown ether cavity and their behavior in solvent extraction of alkali metal cations (AMC). Also, we report results from probing of the PIG participation in metal ion complexation by these ligands by NMR spectroscopy.

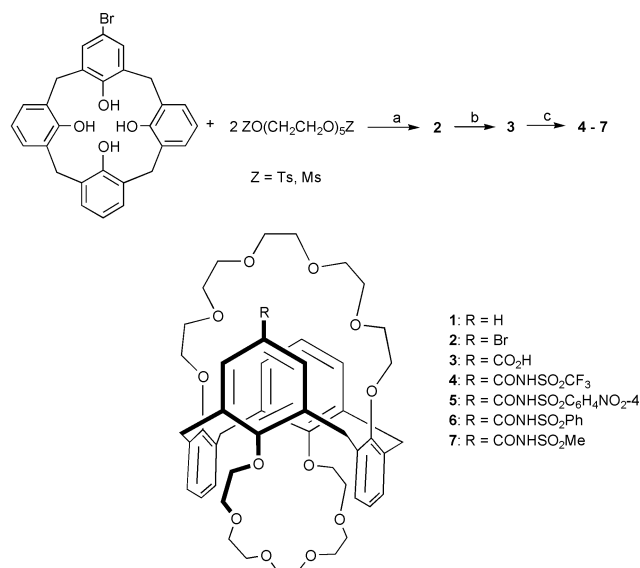
Results and discussion

Synthesis of proton-ionizable calixbiscrowns

The synthesis of the proton-ionizable calixbiscrowns **3–7** was performed according to Scheme 1. First, bromocalix[4]arene-bis(crown-6-ether) **2** was prepared from bromocalix[4]arene⁸ by reaction with pentaethylene glycol bis(toluenep-sulfonate) or bis(methanesulfonate) in the presence of Cs₂CO₃. A 1,3-alternate conformation of the calix[4]arene moiety in **2** was verified by NMR spectroscopy. Thus, a singlet at 3.84 ppm and two doublets at 3.75 and 3.79 ppm and two signals at 37.7 and 38.0 ppm were observed in the ¹H and ¹³C NMR spectra, respectively, for the Ar-CH₂-Ar methylene groups of **2**.

A carboxylic group was introduced into the calixbiscrown unit by treatment of **2** with BuLi and then with CO₂⁹ giving rise to the ligand **3** with the PIG located in front of one crown ether unit. The *N*-(X-sulfonyl)carbamoyl-substituted calixbiscrowns **4–7** with PIGs of the varying acidity were synthesized by conversion of calixbiscrown carboxylic acid **3** into the

† Electronic supplementary information (ESI) available: HSQC spectra for Na⁺ and Cs⁺ complexes of ionized **7**, and graphs for Cs⁺ extraction. See <http://www.rsc.org/suppdata/p2/b1/b109638a/>



Scheme 1 Synthesis of the proton-ionizable calixbiscrowns **3–7**. *Reagents and conditions:* a) Cs₂CO₃, MeCN, reflux; b) i) BuLi, THF, –75 °C; ii) CO₂, THF, –75 °C; c) i) (COCl)₂, C₆H₆, 70 °C; ii) XSO₂NH₂, NaH, THF, rt.

corresponding acid chloride followed by reaction with the appropriate sulfonamides in the presence of NaH.¹⁰

Probing PIG participation in metal ion coordination by NMR spectroscopy

New calixbiscrowns **3–7** with proton-ionizable groups exhibited significantly enhanced efficiency in solvent extraction of AMC compared to non-ionizable **1** (*vide infra*). Although enhanced extraction efficiency was anticipated, it was unclear what role the PIG played in this enhancement. Compounds **3–7** were designed in such a way that the PIG would be located in close proximity to the position occupied by Cs⁺ in complexes with 1,3-alternate calix[4]arene-bis(crown-6-ethers),^{2d} so the PIG could directly participate in the metal ion complexation. Alternatively, the group might act just as a cation-exchange unit, serving in its ionized form as the counterion for a complexed metal cation thereby enhancing the metal ion extraction efficiency by eliminating the need for co-extraction of an anion from an aqueous phase. In assessing the role of the PIG, NMR spectroscopy was employed to probe for PIG participation in metal ion coordination by calixbiscrowns **3–7**.

Recently we reported¹¹ probing the solution structures of dibenzo-14-crown-4 derivatives with pendent oxyacetate sidearms by NMR spectroscopy. Analysis of the changes in the chemical shift difference for diastereotopic protons (diastereotopic nonequivalence, $\Delta\delta$) in the crown ether portion of the molecules, especially for atoms remote from the sidearm attachment site, provided insight into the preferred orientation of the sidearm relative to the crown ether moiety. We have now applied a similar approach to study the preferred PIG orientation in solution in complexes of ionized calixbiscrown **7** with AMC in which changes for signals of protons in the crown ether portions of the molecule in the NMR spectra upon salt formation were analyzed. ‡

Signals for 51 protons including 40 from the crown ether portions of calix[4]arene-bis(crown-6-ether) **7** appear between 3.24 and 3.78 ppm in the ¹H NMR spectrum (Fig. 1a). In the ¹H NMR spectra of the Na⁺ and Cs⁺ complexes of ionized **7** (Fig. 1, b and c, respectively), some signals for the crown ether

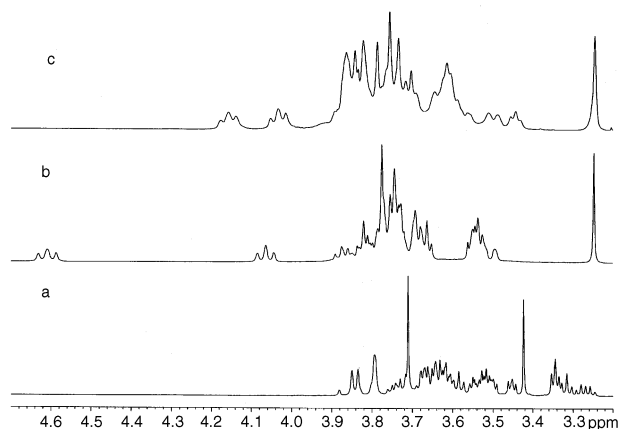


Fig. 1 Partial ¹H NMR spectra for (a) calixbiscrown **7**; (b) the Na⁺ complex of ionized **7**; (c) the Cs⁺ complex of ionized **7** (499.7 MHz, CDCl₃).

protons are shifted downfield substantially. Although the signals overlap severely in the ¹H NMR spectra, in the TOCSY spectra the shifted signals which integrate for two protons each are included in an array of four signals that are coupled with each other (Fig. 2). Two of these signals showed NOE con-

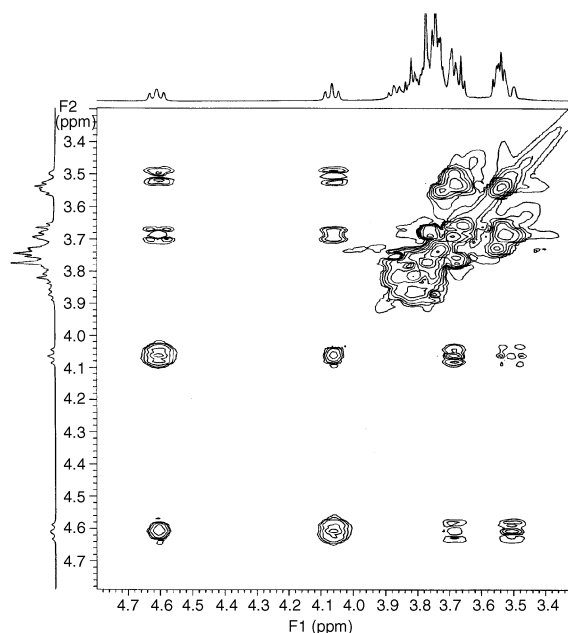


Fig. 2 TOCSY spectrum for the Na⁺ complex of ionized **7**.

nections with aromatic protons *ortho* to the PIG. Therefore, these four signals were assigned to the four diastereotopic protons of the ethylene bridges A and A' in the polyether unit (Fig. 3). In the HSQC spectra, signals for the geminal diastereotopic protons have connectivity to the same carbon signal. † Thus, $\Delta\delta$ values could be determined as the difference in chemical shifts for the two proton signals connected to the same carbon signal. Due to the large number of overlapped proton signals, we were unable to make unambiguous assignments for all of the signals in ionized **7**. We limited the analysis to signals with the largest $\Delta\delta$ values and obtained the data shown in Table 1. §

§ Since exact assignments have not been made for all of the proton signals, the geminal protons H₁ and H₂ having the largest difference in chemical shifts are assumed to be those drawn on Fig. 3. However, the analysis of $\Delta\delta$ values would not differ if another pair of the geminal protons of the same ethylene bridge gave rise to signals with the largest $\Delta\delta$ values in the complexes.

‡ Complexes of ionized **7** with AMC were prepared by a reaction of **7** with an excess of a corresponding AM carbonate in CDCl₃ (see Experimental). Complexes of Li⁺, K⁺ and Rb⁺ exhibited broad ¹H NMR spectra, so we were able to analyze only spectra for the Na⁺ and Cs⁺ complexes.

Table 1 ^1H NMR data for the diastereotopic geminal protons in the complexes of ionized calixbiscrown 7

	δ		$\Delta\delta_{1-2}^a$
	H ₁	H ₂	
7-Na	4.61	3.51	1.10
7-Cs	4.16	3.50	0.66

^a $\Delta\delta_{1-2} = \delta\text{H}_1 - \delta\text{H}_2$.

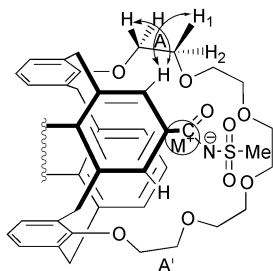


Fig. 3 Alkali metal complex of ionized 7, showing the four diastereotopic protons of the ethylene bridge A; arrows indicate NOE connections between two of these protons with an aromatic proton.

It should be noted that no separation for the proton signals of the polyether loop was observed in the complex of caesium picrate with the non-ionizable calixbiscrown **1**.¹² Apparently, the separation of the signals for the diastereotopic protons results from the presence of the PIG in **7**. Significant $\Delta\delta$ values for the geminal diastereotopic protons of the polyether loop in the complexes of ionized calixbiscrown **7** indicate that the ionized group is located in close proximity to the crown ether moiety. From the larger $\Delta\delta$ value for the complex with smaller Na^+ compared to Cs^+ , a closer position of the ionized group to the polyether bridge in the former is deduced. Consequently, participation of the ionized group in metal ion coordination in the new calixbiscrowns is demonstrated.

Complexation-based solvent extraction studies of proton-ionizable calixbiscrowns

Ligands **3–7** contain two crown ether cavities both of which are potential binding sites for alkali metal cations. However, in contrast with the related non-ionizable calixbiscrown **1** in which the two crown-6 moieties are equivalent, they are non-equivalent in the new proton-ionizable calixbiscrowns **3–7**. Interaction of a crown ether unit containing an adjacent proton-ionizable sidearm with the AMC M^+ in a two-phase solvent extraction system is described by eqn. (1), where HL is the mono-ionizable



ligand and subscripts org and aq denote the organic and aqueous phases, respectively. The equilibrium constant for this reaction, also called the extraction constant, is defined by eqn. (2).

$$K_{\text{ex}} = [\text{ML}_{\text{org}}][\text{H}^+_{\text{aq}}]/[\text{HL}_{\text{org}}][\text{M}^+_{\text{aq}}] \quad (2)$$

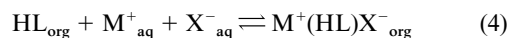
In the intra-complex compound ML, as shown by NMR spectroscopy (*vide supra*), the metal cation is coordinated cooperatively by the crown ether oxygens and the ionized sidearm which also serves as the counterion for M^+ .

By a simple transformation, eqn. (2) can be converted into eqn. (3), where K_s is the stability constant for the complex ML, K_a is the proton dissociation constant for ligand HL in aqueous solution, k_{HL} is the distribution constant for the ligand between

$$K_{\text{ex}} = K_s K_a k_{\text{HL}} k_{\text{ML}} \quad (3)$$

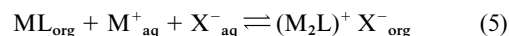
the aqueous and organic phases, and k_{ML} is the distribution constant for the complex between the organic and aqueous phases. Hence, the acidity of the PIG in the ligand is an important factor for an extraction that proceeds by the mechanism shown in eqn. (1).

The other crown ether moiety in ligands **3–7** does not have a PIG in close proximity. By a potential concurrent solvent extraction mechanism involving this crown ether unit, the calixbiscrown may coordinate the metal ion as a neutral ligand. Such a reaction requires participation of an aqueous phase anion X^- and yields the ion-pair complex $\text{M}^+(\text{HL})\text{X}^-$ [eqn. (4)].



In solvent extraction by a calixbiscrown with a very small K_a , especially under conditions of high aqueous phase acidity which suppresses proton dissociation of the ligand, both crown ether units could presumably interact with metal ions in a similar manner.

The extraction shown in eqn. (1) is more energetically favorable than that represented in eqn. (4) and is expected to be the primary step for metal ion extraction by the proton-ionizable calixbiscrowns. Conceivably, the second, “neutral” crown ether unit could be involved in a second complexation step [eqn. (5)].



In the literature,^{1b} interaction of non-ionizable 1,3-alternate calix[4]arene-bis(crown-6-ether) **1** with caesium salts (CsX) in organic solvents has been reported to result in formation of complexes with both 1 : 1 and 1 : 2 ligand-to-metal stoichiometries, *i.e.*, CsLX and Cs_2LX_2 , respectively. In the latter, a Cs^+ is bound in each crown ether cavity. Incorporation of a second Cs^+ into the complex CsLX is characterized by a much smaller equilibrium constant than for the formation of CsLX from free ligand L and CsX . Apparently due to this, binding of only one Cs^+ per molecule of **1** was observed in solvent extraction systems.^{2a,c} Nevertheless, based on a computational study of Cs^+ extraction into 1,2-dichloroethane by the derivative of calix[4]arene-bis(benzocrown-6-ether), formation of both CsLX and Cs_2LX_2 complexes was concluded.^{4b}

Investigation of proton dissociation propensities of 3–7. As follows from eqn. (3), the acidity of the PIG should be a very important characteristic of calixbiscrowns **3–7** as extractants for AMC. Since the K_a of water-insoluble **3–7** could not be determined in water, the acidities of these compounds were evaluated in methanol. Acid–base titration curves of 1.00 mM calixbiscrowns in methanol with 1.00 mM LiOH in methanol (ionic strength 1.00 mM, LiCl) are presented in Fig. 4. For these experiments, LiOH was chosen as the base since no Li^+ complexation with the calixcrowns was observed (*vide infra*).

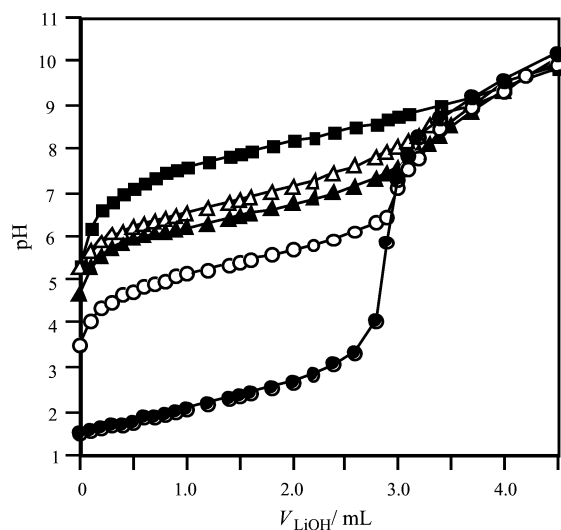
As is evident from the plots of pH vs. volume of LiOH, the acidities of the calixbiscrowns decrease in the order **4** \gg **5** $>$ **6** $>$ **7** $>$ **3**. The proton dissociation constants of the ligands in methanol (K_a') were determined from the titration curves shown in Fig. 4 as indicated in the Experimental section. As judged from the $\text{p}K_a'$ values listed in Table 2, *N*-(X-sulfonyl)-carbamoyl-substituted calixcrowns **4–7** possess greater acidities than the related carboxylic acid **3**.

Within the series **4–7**, the capability for NH-group proton dissociation decreases as the substituent X in the PIG is varied from CF_3 to $4\text{-NO}_2\text{C}_6\text{H}_4$, to Ph, to Me. Such a tendency is consistent with the order of decreasing electron-withdrawing abilities of these substituents.¹³

Investigation of Cs^+ extraction by 3–7. With solvent extraction proceeding *via* an $\text{H}^+ - \text{Cs}^+$ exchange reaction [eqn. (1)],

Table 2 Proton dissociation constants (pK_a') in methanol and Cs^+ extraction constants (K_{ex}) for calixbiscrowns 3–7

	Calixbiscrown				
	3	4	5	6	7
pK_a' (MeOH)	7.9	2.3	5.4	6.5	6.8
K_{ex} (CHCl ₃)	7.10×10^{-5}	42.7	7.02×10^{-2}	3.18×10^{-3}	9.63×10^{-4}

**Fig. 4** Acid–base titration curves of 1.00 mM calixbiscrowns 3 (■), 4 (●), 5 (○), 6 (▲) and 7 (△) with 1.00 mM LiOH in methanol ($\mu = 1.00$ mM, LiCl).

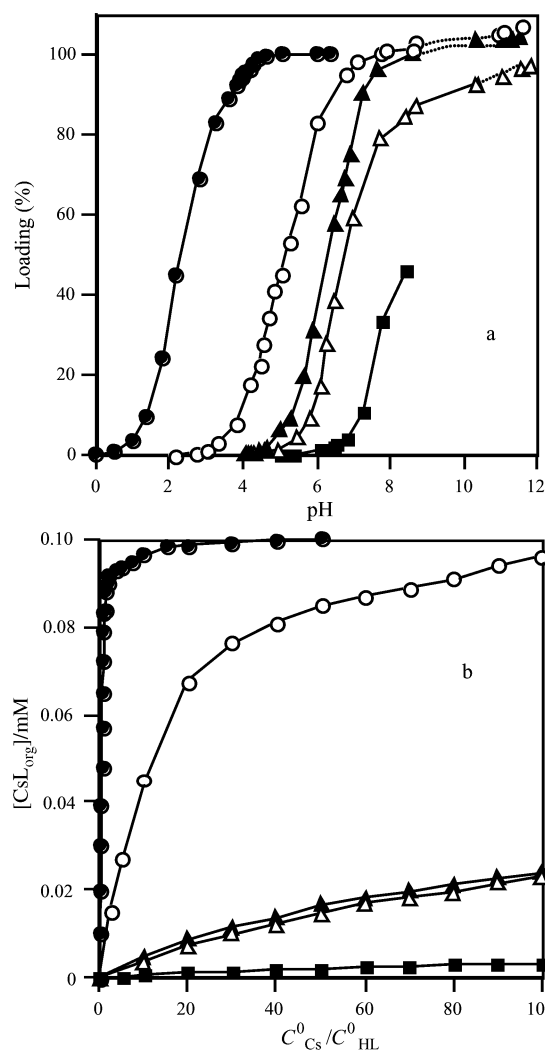
metal ion uptake by calixcrowns 3–7 is controlled by the acidity of the aqueous phase. To validate an ion-exchange mechanism, extraction of Cs^+ from 0.20 mM aqueous nitrate solutions into chloroform by 0.10 mM 3–7 was studied at varying aqueous phase pH. The ligand loadings plotted against pH of the aqueous phase at equilibrium are presented in Fig. 5a. As is evident from the graph, Cs^+ transfer into the organic phase by 4–7 increases dramatically when the basicity of the aqueous solution is enhanced.

Determination of the Cs^+ extraction profile for calixbiscrown carboxylic acid 3 was hampered by substantial precipitation in the organic phase at $pH > 8$. This phenomenon is believed to originate from the limited solubility of the extraction complex in chloroform. With *N*-(*X*-sulfonyl)carbamoyl-substituted calixbiscrowns 5–7, only slight precipitation (which was more pronounced for 5 and 7 than for 6) was observed in extraction from alkaline aqueous solutions. Nevertheless, the appropriate sections of the extraction pH profiles for 5–7 in Fig. 5a are shown as dotted lines to indicate that the Cs^+ loadings of the ligands in these pH regions might be less accurate.

Even though the Cs^+ concentration in the organic phase determined after extraction from strongly basic solutions by 5–7 is expected to be somewhat lower than the actual metal ion uptake by these ligands due to some precipitation of the extraction complex, Cs^+ loading of the more acidic 5 and 6 slightly exceeded 100% (see Fig. 5a). This suggests that with an excess of $CsNO_3$ in the aqueous phase over ligand concentration in the organic phase, extraction by the proton-ionizable calixbiscrown may involve incorporation of a second Cs^+ into the originally formed complex CsL to give a small amount of Cs_2LNO_3 .

For determination of the Cs^+ extraction constants, K_{ex} , eqn. (2) may be converted into eqn. (6), where $D = [CsL_{org}]/[Cs^+_{aq}]$ is the distribution ratio of Cs^+ between the organic and aqueous phases.¹⁴ From eqn. (6), $\log K_{ex}$ is equal to the y -axis intercept of a plot $\log D$ vs. $(\log [HL_{org}] + pH)$.

$$\log D = \log K_{ex} + \log [HL_{org}] + pH \quad (6)$$

**Fig. 5** Extraction of Cs^+ into chloroform by 0.10 mM calixbiscrowns 3 (■), 4 (●), 5 (○), 6 (▲) and 7 (△): plots of (a) metal loading vs. the aqueous phase pH for extraction from 0.20 mM aqueous $CsNO_3$ solutions with varying pH and (b) $[CsL_{org}]$ vs. C^0_{Cs}/C^0_{HL} for extraction from aqueous solutions with varying $CsNO_3$ concentrations and pH 5.0.

Such plots for Cs^+ extraction profiles of 3–7 were linear with correlation coefficients r^2 of no less than 0.985 and slopes of about 1.[†] Therefore, under the experimental conditions, the complex CsL was the dominant species extracted. Extraction constants determined from the plots[†] are listed in Table 2. The Cs^+ extraction propensities of the calixbiscrowns decrease in the order $4 \gg 5 > 6 > 7 > 3$.

To probe for the involvement of other extraction mechanisms [e.g., formation of ion-pairs $Cs^+(HL)NO_3^+$, eqn. (4), and complexes Cs_2LNO_3 , eqn. (5)], the experimental conditions for Cs^+ extraction by 3–7 were modified. Aqueous solutions with varying $CsNO_3$ concentrations and a constant initial pH of 5.0 were extracted with 0.10 mM solutions of the calixbiscrowns in chloroform. The data obtained are presented in Fig. 5b as plots of $[CsL_{org}]$ vs. C^0_{Cs}/C^0_{HL} where $[CsL_{org}]$ is concentration of Cs^+ detected in the organic phase after extraction and C^0_{Cs} and C^0_{HL} are the initial concentrations of $CsNO_3$

in the aqueous phase and ligand in the organic phase, respectively.

In these experiments, the more acidic calixbiscrowns **4** and **5** exhibited the most efficient Cs⁺ extraction and a tendency for gradual lowering of the aqueous phase pH up to 3.5–3.8 as the metal loading of the ligands increased. With **6** and **7**, pH changes of only 0.6–0.8 units were observed after extraction together with lower levels of Cs⁺ extraction by these calixbiscrowns. With **3**, the weakest acid in the series, there was almost no variation of the aqueous phase pH with a Cs⁺ loading of less than 5%.

Calculations showed that with none of the ligands **3–7** did the extraction data satisfy eqn. (4) or (5). In agreement with an ion-exchange mechanism, graphs log *D* vs. (log [HL_{org}] + pH) for **4** and **5** were linear† with correlation coefficients *r*² of 0.998 and 0.987, respectively, and slopes of about 1 over nearly all of the ranges of C⁰_{Cs}/C⁰_{HL} studied. The values *K*_{ex} determined for **4** and **5** from the graphs are 46.0 and 7.69 × 10⁻², respectively, which is consistent with the values found by the other procedure (Table 2). The low levels of Cs⁺ extraction by calixbiscrowns **3**, **6** and **7** accompanied by small pH changes did not allow accurate *K*_{ex} calculations to be made. However, the estimated *K*_{ex} values obtained for these three ligands (6 × 10⁻⁵, 2 × 10⁻³ and 1 × 10⁻³, respectively) are in accord with the data listed in Table 2.

Competitive alkali metal extractions by calixbiscrowns 3–7.

To evaluate the selectivity of the five proton-ionizable calixbiscrowns for Cs⁺ over other AMC, competitive extraction from the aqueous solutions of 0.10 mM Li, Na, K, Rb and Cs nitrates/hydroxides at pH 9.8 by 0.10 mM solutions of the ligands in chloroform was performed. As is evident from Fig. 6 where the metal loadings of the ligands are presented,

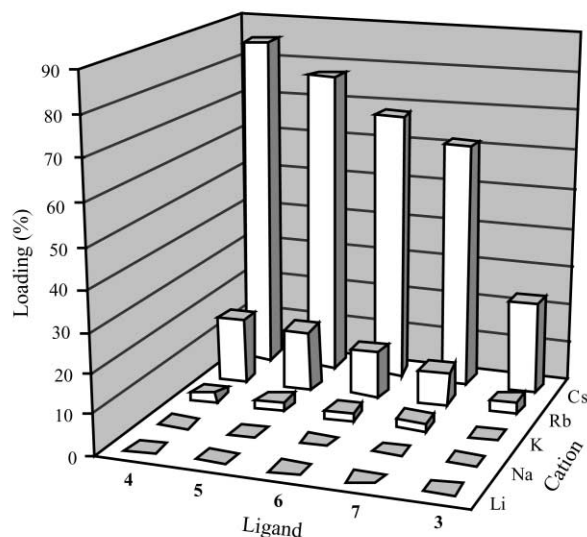


Fig. 6 Competitive extraction of 0.10 mM alkali metal cations from aqueous nitrate solution (pH 9.8) into chloroform by 0.10 mM calixbiscrowns **3–7**.

the calixbiscrowns exhibited preferential binding of Cs⁺ with significantly lower loadings of Rb⁺ (the ratio of Rb⁺ and Cs⁺ loadings ranging from 5.7 for **4** to 8.0 for **3**) and very small (less than 2%) loadings of K⁺. Extraction of Li⁺ and Na⁺ by **3–7** was undetectable.

In accord with their greater acidity, the *N*-(*X*-sulfonyl)-carbamoyl-substituted calixbiscrowns **4–7** exhibited much more efficient extraction of Cs⁺ and Rb⁺ than the related carboxylic acid **3**. Within the series, metal ion uptake decreased in the order **4** > **5** > **6** > **7**.

For potential applicability of the ligands as caesium

separation agents, their high extraction selectivities for Cs⁺ over Na⁺ and K⁺ are crucial. Since extraction of AMC into an organic phase by a proton-ionizable ligand is increased by raising the aqueous phase alkalinity, it seemed important to determine if the Cs⁺/Na⁺ and Cs⁺/K⁺ extraction selectivities of the calixbiscrowns is influenced by pH. So the pH dependence of competitive extractions of 0.10 mM aqueous Na, K and Cs nitrates (pH adjusted with dilute HNO₃ or LiOH) by 0.10 mM calixbiscrowns **4–7** in chloroform was investigated. All of the calixbiscrowns were found to exhibit similar behavior: a dramatic increase of Cs⁺ uptake and only a slight variation of Na⁺ and K⁺ loadings with enhanced alkalinity of the aqueous solution. (The results are illustrated in Fig. 7 by the extraction

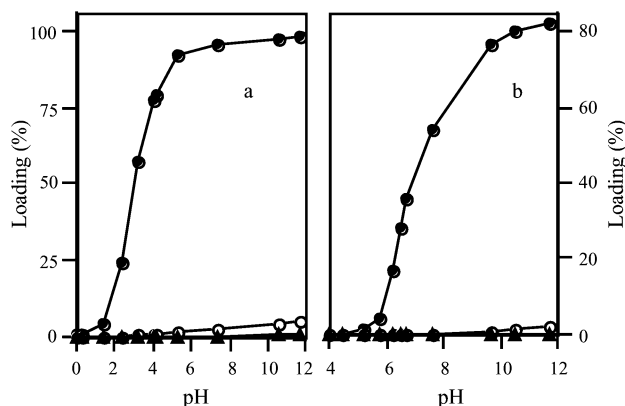


Fig. 7 pH profiles for competitive extraction of Na⁺ (▲), K⁺ (○) and Cs⁺ (●) from 0.10 mM (in each) aqueous nitrate solutions into chloroform by 0.10 mM (a) **4** and (b) **7**.

profiles for ligands **4** and **7**, which have very different acidities.) Therefore, the proton-ionizable calixbiscrowns retain high Cs⁺/Na⁺ and Cs⁺/K⁺ extraction selectivities over a broad pH range.

To probe the effect of Na⁺ and K⁺ concentrations on the Cs⁺ selectivity of calixbiscrown **4**, competitive extractions were performed for these three AMC from aqueous nitrate solutions containing a low, constant concentration of Cs⁺ and varying concentrations of Na⁺ and K⁺. The data presented in Table 3 demonstrate that the distribution coefficient for Cs⁺ (*D*_{Cs}) decreases as the excess of competing metal ions in the aqueous solution becomes larger. However, the Cs⁺/K⁺ and the estimated Cs⁺/Na⁺ selectivities, as reflected by the ratio of distribution coefficients *D*_{Cs}/*D*_K and *D*_{Cs}/*D*_{Na}, increase somewhat. The Cs⁺/Na⁺ selectivities found for the proton-ionizable calixbiscrown **4** are of the same level as the value of 1500 reported for non-ionizable calixbiscrown **1** under different experimental conditions.^{2c}

Concluding remarks

NMR studies of the complexes of the ionized ligand **7** demonstrate that the PIG in the new calixbiscrowns participates in cooperative metal ion coordination. The extraction efficiency of the new ligands is controlled by their acidity, increasing with higher acidity. The high selectivity for Cs⁺ among AMC, which is characteristic for the core [4]arene-crown-6-ethers, was unaffected by the introduction of PIGs of varying acidities. These findings provide valuable information toward further development of calixcrown ligands.

Experimental

NMR spectra were measured with a Varian Unity INOVA spectrometer (499.7 MHz for ¹H, 125.7 MHz for ¹³C) at 296 K. Chemical shifts (δ) are expressed in ppm downfield from TMS and coupling constants (*J*) values are given in Hz.

Table 3 Competitive extraction of 0.10 mM CsNO₃ from aqueous solutions (pH 6.0) containing varying concentrations of NaNO₃ and KNO₃ into 0.10 mM solutions of calixbiscrown **4** in CHCl₃

$C_{\text{Cs}}^0 : C_{\text{Na}}^0 : C_{\text{K}}^0$ ^a	D_{Cs}	D_{Na} ^b	D_{K}	$D_{\text{Cs}}/D_{\text{Na}}$ ^b	$D_{\text{Cs}}/D_{\text{K}}$
1 : 1 : 1	3.86	5×10^{-3}	7.0×10^{-2}	8×10^2	55
1 : 10 : 10	1.10	1×10^{-3}	6.5×10^{-3}	1×10^3	170
1 : 10 ² : 10 ²	0.550	3×10^{-4}	2.9×10^{-3}	2×10^3	190
1 : 10 ³ : 10 ³	0.134	6×10^{-5}	6.3×10^{-4}	2×10^3	210
1 : 10 ⁴ : 10 ³	0.104	2×10^{-5}	5.2×10^{-4}	5×10^3	200

^a Ratio of the initial concentrations of Cs⁺, Na⁺ and K⁺ in the aqueous solution. ^b Due to the very low ligand propensity for Na⁺ extraction, the values are estimates.

TOCSY, ROESY and HSQC spectra were obtained using standard procedures. pH was measured with a Fisher Scientific Accumet® 50 pH/ion/conductivity meter. Concentrations of alkali metal cations in aqueous solutions were determined with Dionex DX-120 Ion Chromatograph. Samples for solvent extraction were shaken with a Glas-Col® Multi-Pulse Vortexer.

Anhydrous alkali metal nitrates and LiCl (99%, Alfa Aesar®) and LiOH (purified, Fisher Scientific) were used as received from chemical suppliers.

Bromocalix[4]arene,⁸ pentaethylene glycol bis(toluene-*p*-sulfonate)¹⁵ and **1**^{2c} were prepared by reported procedures.

Preparation of **2** and **3**

1,3-Alternate 5-bromocalix[4]arene-bis(crown-6-ether) **2**.

*With pentaethylene glycol bis(toluene-*p*-sulfonate).* A mixture of 5-bromocalix[4]arene (2.13 g, 4.23 mmol), Cs₂CO₃ (3.45 g, 10.6 mmol), pentaethylene glycol bis(toluene-*p*-sulfonate) (2.31 g, 4.23 mmol) and acetonitrile (300 mL) was refluxed under nitrogen for 3 d. The same quantities of Cs₂CO₃ and the bis(toluene-*p*-sulfonate) were added and refluxing was continued for another 3 d. The solvent was evaporated *in vacuo* and CH₂Cl₂ and 10% aqueous HCl (to pH < 1) were added to the residue. The organic layer was washed with water, dried (Na₂SO₄) and evaporated *in vacuo*. Chromatography of the residue on silica gel with ethyl acetate as the eluent gave **2** as a white solid. Yield 2.50 g (65%), mp 115–116 °C, δ_{H} 3.22–3.75 (m, 40 H), 3.75 (d, *J* 16.1, 2 H, ArCH₂Ar), 3.79 (d, *J* 16.1, 2 H; ArCH₂Ar), 3.84 (s, 4 H, ArCH₂Ar), 6.87 (t, *J* 7.6, 2 H), 6.91 (t, *J* 7.6, 1 H), 7.05–7.15 (m, 6 H), 7.21 (s, 2 H); δ_{C} 37.7 (ArCH₂Ar), 38.0 (ArCH₂Ar), 69.4, 69.45, 69.52, 69.54, 69.60, 69.9, 70.87, 70.89, 70.93, 71.12, 71.16, 71.18, 71.21, 71.23, 114.9 (ArC-Br), 122.75, 122.80, 129.6, 130.0, 132.1, 133.2, 133.7, 134.0, 136.4, 155.8, 156.4, 156.5. Anal. Calcd for C₄₈H₅₀BrO₁₂: C 63.50, H 6.55, Br 8.80. Found: C 63.09, H 6.35, Br 8.78%.

With pentaethylene glycol bis(methanesulfonate). A mixture of 5-bromocalix[4]arene (3.00 g, 5.96 mmol), Cs₂CO₃ (9.72 g, 29.9 mmol), pentaethylene glycol bis(methanesulfonate) (4.70 g, 11.9 mmol) and acetonitrile was refluxed under nitrogen for 4 d. The solvent was evaporated *in vacuo* and CH₂Cl₂ and 1 M aqueous HCl were added to the residue. The organic layer was washed with water, dried (MgSO₄) and evaporated *in vacuo*. To the residue Et₂O (15 mL) was added, the organic solution was decanted and the product was dried *in vacuo*. Yield 4.02 g (74%); the spectral data are identical to those given above.

1,3-Alternate 5-carboxycalix[4]arene-bis(crown-6-ether) **3**.

To a solution of **2** (1.34 g, 1.48 mmol) in THF (40 mL) BuLi (4.43 mmol) in hexanes was added at –75 °C with stirring under nitrogen. After 10 min at –75 °C, CO₂ was bubbled through the solution for 10 min. After another 15 min at –75 °C, the mixture was allowed to warm to ambient temperature. The solvents were evaporated *in vacuo* and CH₂Cl₂ and 1 M aqueous HCl were added to the residue. The organic layer was washed with aqueous Na₂CO₃, dried (Na₂SO₄), and evaporated. The residue was washed with Et₂O and the resulting solid was dissolved in CH₂Cl₂. The solution was washed with 10% aqueous HCl and water and dried (MgSO₄).

Evaporation of the solvent *in vacuo* yielded **3** as a white solid (1.04 g, 81%), mp 89–90 °C. IR (deposit from CH₂Cl₂ solution on a NaCl plate) $\nu_{\text{max}}/\text{cm}^{-1}$ 1712 (C=O); δ_{H} 3.20–3.37 (m, 6 H), 3.37–3.47 (m, 4 H), 3.47–3.54 (m, 6 H), 3.54–3.77 (m, 24 H), 3.83 (s) + 3.84 (d, *J* 16.0) (6 H, ArCH₂Ar), 3.90 (d, *J* 16.0, 2 H, ArCH₂Ar), 6.87 (t, *J* 7.3, 1 H), 6.89 (t, *J* 7.3, 2 H), 7.12 (d, *J* 7.3, 6 H), 7.87 (s, 2 H); δ_{C} 37.9 (ArCH₂Ar), 69.4, 69.50, 69.54, 69.7, 70.1, 70.6, 70.77, 70.88, 70.93, 71.07, 71.14, 122.7, 123.1, 129.7, 130.01, 132.06, 133.13, 133.5, 134.0, 134.5, 156.40, 156.46, 161.5, 171.1 (CO₂H). Anal. Calcd for C₄₉H₆₀O₁₄: C 67.41, H 6.93. Found: C 67.21, H 6.93%.

General procedure for the preparation of 1,3-alternate 5-*N*-(*X*-sulfonyl)carbamoylcalix[4]arene-bis(crown-6-ethers) **4**–**7**

A solution of **3** (0.98 g, 1.11 mmol) and oxalyl chloride (0.28 g, 2.22 mmol) in C₆H₆ (25 mL) was stirred under nitrogen at 70 °C for 5 h and the solvent was removed *in vacuo*. A solution of the residue in THF (15 mL) was added to a mixture of a corresponding sulfonamide (1.66 mmol) and NaH (0.11 g, 4.42 mmol) in THF (20 mL). The mixture was stirred under nitrogen at room temperature for 12 h. Then 1 mL of H₂O was added and the THF was evaporated *in vacuo*. The residue was dissolved in CH₂Cl₂ and the resulting solution was washed with aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was chromatographed on silica gel and the product was dissolved in CH₂Cl₂. The solution was washed with 10% aqueous HCl, evaporated and dried *in vacuo*.

Compound 4. Eluent for chromatography: CH₂Cl₂–MeOH (92 : 8), yield 89%, off-white solid, mp 160–161 °C. IR (deposit from CH₂Cl₂ solution on a NaCl plate) $\nu_{\text{max}}/\text{cm}^{-1}$ 1720 (C=O); δ_{H} 3.24–3.38 (m, 8 H), 3.43–3.56 (m, 8 H), 3.56–3.77 (m, 24 H), 3.79 (s) + 3.80 (d, *J* 15.6) (6 H, ArCH₂Ar), 3.87 (d, *J* 15.6, 2 H, ArCH₂Ar), 6.85 (t, *J* 7.5, 1 H), 6.89 (t, *J* 7.5, 2 H), 7.09 (d, *J* 7.5, 2 H), 7.13 (d, *J* 7.5, 4 H), 7.56 (s, 2 H); δ_{C} 37.5 (ArCH₂Ar), 37.8 (ArCH₂Ar), 69.3, 69.5, 69.6, 69.9, 70.4, 70.56, 70.60, 70.7, 70.8, 70.9, 71.00, 71.09, 71.15, 71.3, 122.7, 122.8, 126.6, 129.8, 130.1, 130.4, 130.6, 132.8, 133.8, 134.0, 134.9, 156.2, 156.5, 161.5, 166.1 (CONH). Anal. Calcd for C₅₀H₆₀F₃NO₁₅S: C 59.81, H 6.02, N 1.39. Found: C 59.95, H 6.27, N 1.39%.

Compound 5. Eluent for chromatography: CH₂Cl₂–MeOH (95 : 5), yield 67%, light-yellow solid, mp 84–86 °C. IR (deposit from CH₂Cl₂ solution on a NaCl plate) $\nu_{\text{max}}/\text{cm}^{-1}$ 1700 (C=O); δ_{H} 3.03–3.11 (m, 2 H), 3.27–3.39 (m, 4 H), 3.40–3.72 (m, 34 H), 3.77–3.86 (m, 8 H, ArCH₂Ar), 6.78–6.91 (m, 3 H), 7.07–7.14 (m, 6 H), 7.46 (s, 2 H), 8.39 (d, *J* 9.3) + 8.42 (d, *J* 9.3) (4 H), 10.9 (s, 1 H, NH); δ_{C} 37.5 (ArCH₂Ar), 37.6 (ArCH₂Ar), 68.96, 69.7, 69.9, 70.0, 70.1, 70.2, 70.3, 70.5, 70.6, 71.0, 71.05, 71.07, 71.1, 71.2, 122.6, 122.8, 124.0, 127.0, 129.8, 130.0, 130.2, 130.4, 132.7, 133.8, 133.8, 134.7, 145.4, 150.3, 156.1, 156.5, 161.2, 167.5 (CONH). Anal. Calcd. for C₅₅H₆₄N₂O₁₇S: C 62.49, H 6.10, N 2.65. Found: C 62.10, H 5.99, N 2.48%.

Compound 6. Eluent for chromatography: CH₂Cl₂–MeOH (95 : 5), yield 65%, off-white solid, mp 96–98 °C. IR (deposit from CH₂Cl₂ solution on a NaCl plate) $\nu_{\text{max}}/\text{cm}^{-1}$ 1695 (C=O);

δ_{H} 3.11–3.19 (m, 2 H), 3.30–3.39 (m, 4 H), 3.41–3.52 (m, 10 H), 3.53–3.73 (m, 24 H), 3.75–3.84 (m, 8 H, ArCH₂Ar), 6.83–6.91 (m, 3 H), 7.06–7.15 (m, 6 H), 7.46 (s, 2 H), 7.55 (m, 2 H), 7.61 (m, 1 H), 8.20 (m, 2 H), 10.7 (s, 1 H, NH); δ_{C} 37.6 (ArCH₂Ar), 37.7 (ArCH₂Ar), 69.2, 69.8, 69.9, 70.0, 70.2, 70.4, 70.5, 70.6, 70.8, 71.07, 71.16, 71.21, 71.25, 122.8, 127.5, 128.6, 128.7, 129.7, 130.0, 130.1, 130.3, 132.9, 133.3, 133.8, 133.9, 134.6, 139.7, 156.3, 156.5, 160.9, 167.1 (CONH). Anal. Calcd for C₅₅H₆₅NO₁₅S: C 65.26, H 6.47, N 1.38. Found: C 65.30, H 6.50, N 1.55%.

Compound 7. Eluent for chromatography: CH₂Cl₂–MeOH (92 : 8), yield 67%, off-white solid, mp 77–78 °C. IR (deposit from CH₂Cl₂ solution on an NaCl plate) ν_{max} /cm⁻¹ 1690 (C=O); δ_{H} 3.23–3.37 (m, 8 H), 3.42 (s, 3 H, CH₃SO₂), 3.44–3.77 (m, 32 H), 3.79 (s, 4 H, ArCH₂Ar), 3.83 (d, *J* 15.8, 2 H, ArCH₂Ar), 3.86 (d, *J* 15.8, 2 H, ArCH₂Ar), 6.84 (t, *J* 7.5, 1 H), 6.89 (t, *J* 7.5, 2 H), 7.08 (d, *J* 7.5, 2 H), 7.13 (d, *J* 7.5, 4 H), 7.59 (s, 2 H), 10.4 (br s, 1 H, NH); δ_{C} 37.6 (ArCH₂Ar), 37.8 (ArCH₂Ar), 41.0 (CH₃SO₂), 69.1, 69.5, 69.62, 69.64, 69.8, 70.0, 70.4, 70.50, 70.54, 70.6, 70.7, 70.9, 71.04, 71.08, 71.12, 71.18, 71.21, 71.30, 122.55, 122.60, 122.8, 127.0, 129.7, 129.8, 130.2, 130.3, 132.9, 133.86, 133.89, 134.1, 134.7, 156.3, 156.58, 156.60, 161.1, 168.1 (CONH). Anal. Calcd for C₅₀H₆₃NO₁₅S·1.5H₂O: C 61.46, H 6.80, N 1.43. Found: C 61.45, H 6.67, N 1.35%.

Preparation of complexes of ionized 7 with AMC for NMR studies

To a 1.0 mL sample of a 20 mM stock solution of 7 in CDCl₃, the appropriate alkali metal carbonate (5–7 fold excess) was added. After magnetic stirring for 10 h at room temperature, the mixture was filtered and the solution was used for NMR spectral measurements.

Proton dissociation constant determination

Acid–base titration of a 3.0 mL sample of 1.00 mM calixbiscrown in methanol with 1.00 mM LiOH in methanol (ionic strength $\mu = 1.00$ mM, LiCl) was carried out by the standard procedure. Titration end points were determined from graphs of $\Delta\text{pH}/\Delta V_{\text{LiOH}}$ vs. V_{LiOH} . Proton dissociation constants ($\text{p}K_{\text{a}}$) were determined as the pH half way to the equivalence point.

Solvent extraction studies

Cs⁺ extraction. Extraction with varying aqueous phase pH. The 0.20 mM aqueous solutions of CsNO₃ with varying pH (dil. HNO₃ or LiOH) were extracted by 0.10 mM calixbiscrown in CHCl₃. After extraction, the pH of the aqueous phase was measured. The organic phase was stripped by shaking with aqueous 0.10 M HCl and the Cs⁺ concentration was determined by ion chromatography. To ensure the completeness of Cs⁺ back-extraction from the organic phase for ligands 4 and 5, the stripping step was performed three times and the concentration of Cs⁺ was measured in the combined aqueous solutions.

Extraction with varying aqueous phase Cs⁺ concentration. Aqueous CsNO₃ (concentration varied from 10.0 μM to 10.0 mM) with a constant initial pH 5.0 was extracted by 0.10 mM calixbiscrown in CHCl₃. After extraction, the pH of the aqueous phase was measured and the Cs⁺ concentration in the organic phase was determined as described above.

Competitive alkali metal cation extraction. An aqueous solution (0.10 mM in each) of alkali metal nitrates with the

pH adjusted with dilute HNO₃ or LiOH was extracted by 0.10 mM calixbiscrown in CHCl₃. After extraction, the pH of the aqueous phase was measured and the AMC concentrations in the organic phase were determined by ion chromatography as described above.

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