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Thiacalix[4]arene derivatives as radium ionophores: a study on the requirements for Ra^{2+} extraction†

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The synthesis and NOE-based structural characterization is described of thiacalix[4]arene tricarboxylic acid (**7**), thiacalix[4]crown-5 and -6 monocarboxylic acids (**2** and **5**), and the bis(*N*-methylsulfonyl)thiacalix[4]crowns-5 and -6 (**4a,b**). The $^{226}Ra^{2+}$ selectivity coefficients, $\log(K^{Ra}_{ex}/K^{M}_{ex})$, of the new thiacalix[4]arene derivatives are compared directly with those of thiacalix[4]crown-5 and -6 (**1a,b**), thiacalix[4]crown-5 and -6 dicarboxylic acids (**3a,b**), and thiacalix[4]arene di- and tetracarboxylic acids (**6** and **8**). Thiacalix[4]arene dicarboxylic acid (**6**) already exhibits a high $^{226}Ra^{2+}$ selectivity, but this is significantly improved in the case of **3b**, having an additional crown-(6-)ether bridge. The covalent combination of a crown ether and carboxylic acid substituents as in the thiacalix[4]arenes **2, 3a,b, 4a,b**, and **5** gives a better $^{226}Ra^{2+}$ selectivity in the presence of Sr^{2+} or Ba^{2+} than mixtures of dibenzo-21-crown-7 and thiacalix[4]arene dicarboxylic acid (**6**) or of pentadecanoic acid and thiacalix[4]crown-6 (**1b**).

Introduction

Radiotoxic Ra^{2+} nuclides, in particular $^{226}Ra^{2+}$, are found as traces of naturally occurring radioactive material (NORM) in aqueous waste streams of non-nuclear industries, *e.g.* coal mining.[1] To prevent public exposure, Ra^{2+} has to be selectively extracted from solutions containing also a significant excess of other alkaline earth cations such as Ca^{2+}, Sr^{2+}, and Ba^{2+}.[1,2] In addition, Ra^{2+} is the alkaline earth cation with the lowest tendency to form complexes,[3] making the effort substantial.

In order to transfer Ra^{2+} efficiently from an aqueous into an organic medium, the extractant needs to neutralize the divalent cation and to meet its coordination preference.[4] In a recent study by Hendriksen *et al.*[5] aminocarboxylic acids,[6] tetraazacyclododecane tetraacetic acid, and calix[4]arene tetracarboxylic acid have been used for $^{226}Ra^{2+}$ extraction. However, most work on Ra^{2+} extraction is focused on so-called synergistic extraction, using mixtures of crown ethers and an acid for neutralization.[4,7–12] Alternatively, Bartsch *et al.*[13] functionalized crown ethers with acidic groups.[14–16] Recently, we reported the excellent $^{226}Ra^{2+}$ complexation properties of the thiacalix[4]crown dicarboxylic acids (**3a,b**).[17]

Here we describe a systematic study of the influence of the different structural elements of thiacalix[4]crown dicarboxylic acids on the Ra^{2+} selectivity. The following structural variations were studied: the crown ether size, the number and type of acidic groups, and the covalent attachment of acidic groups *vs.* mixtures of ligands and acids (Chart 1). Finally, the synthesis of new trisubstituted thiacalix[4]arenes is described.

Results and discussion

Synthesis and characterization of ionophores 2–8

The thiacalix[4]crown monocarboxylic acids (**2** and **5**) were synthesized starting from dihydroxythiacalix[4]crowns **1a,b** (Scheme 1). Reaction of dihydroxythiacalix[4]crown-5 (**1a**)[18,19] with ethyl bromoacetate in the presence of Na_2CO_3 (0.5 equiv) in refluxing acetonitrile for 64 h gave a mixture of **1a** (~30%), cone thiacalix[4]crown-5 monoethyl ester (**9**), and cone thiacalix[4]crown-5 diethyl ester (**10a**) (~10%).[20] From this mixture **9** was isolated in 59% yield. The corresponding reaction of dihydroxythiacalix[4]crown-6 (**1b**)[19] using K_2CO_3 (2 equiv) as a base gave a mixture of cone thiacalix[4]crown-6 diethyl ester (**10b**),[17] partial cone thiacalix[4]crown-6 monoethyl ester **11**, and the 1,3-alternate thiacalix[4]crown-6 diethyl ester (**12**) (~10%),[19] from which **10b** and **11** were isolated in 38% and 19% yield, respectively.[21]

Hydrolysis of the esters **9** and **11** with tetramethylammonium hydroxide afforded the thiacalix[4]crown monocarboxylic acids (**2** and **5**) in 81% and 85% yield, respectively. The conformations have unambiguously been determined *via* ROESY and NOESY NMR spectroscopy (Fig. 1).[22] In their ^1H NMR spectra, the thiacalix[4]crown monocarboxylic acids (**2** and **5**) show two singlets and two doublets for the ArH peaks of which the two singlets in **5** overlap (Fig. 1b). On the basis of symmetry, the doublets can be assigned to the ArH2a/ArH4a and ArH2b/ArH4b protons of the crown-ether bridge containing aryl groups, while the protons of the other two aryl groups (ArH1a,b and ArH3a,b) give singlets. A significant difference in the ^1H NMR spectra of **2** and **5** (the shift of the ArH2b/ArH4b resonances) points to a difference in conformation.

Most characteristic for thiacalix[4]crown-5 monocarboxylic acid (**2**) is the presence of NOE cross peaks between the OH resonance with both methylene resonances of the crown-ether bridge and that of the methylene group adjacent to the carboxylic acid moiety (see Fig. 1a). This indicates that thiacalix[4]crown-5 monocarboxylic acid (**2**) is in the cone conformation.

NOESY experiments performed on the thiacalix[4]crown-6 monocarboxylic acid (**5**) revealed strong couplings between the methylene protons next to the carboxylic acid moiety and the ArH2b/ArH4b protons (Fig. 1b).[22] The ArH3 peak[23] shows NOE interactions with the crown-ether bridge, while the ArH1, ArH2a, and ArH4a peaks interact with each other.[24] Furthermore, the OH resonance shows NOESY couplings with the protons of the crown-ether bridge, but not with the methylene protons adjacent to the carboxylic acid moiety (see Fig. 1b). All these NOE interactions indicate that compound **5** has the partial cone conformation, in which the carboxylic acid group

† Electronic supplementary information (ESI) available: full NOE/NOESY spectra of **2, 5, 7** and [Ba(**5**)Pic] together with stoichiometries/models used to obtain extraction constants and $^{226}Ra^{2+}$ selectivity coefficients for the various ionophores used. See http://www.rsc.org/suppdata/ob/b5/b501587a/

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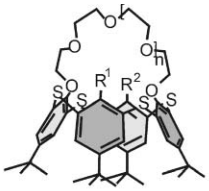
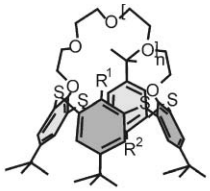


1a $R^1 = R^2 =$ OH (n= 1)
1b $R^1 = R^2 =$ OH (n= 2)

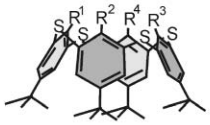
2 $R^1 =$ OH, $R^2 = OCH_2CO_2H$ (n= 1)

3a $R^1 = R^2 = OCH_2CO_2H$ (n= 1)
3b $R^1 = R^2 = OCH_2CO_2H$ (n= 2)

4a $R^1 = R^2 = OCH_2CONHSO_2CH_3$ (n= 1)
4b $R^1 = R^2 = OCH_2CONHSO_2CH_3$ (n= 2)



5 $R^1 =$ OH, $R^2 = OCH_2CO_2H$ (n= 2)

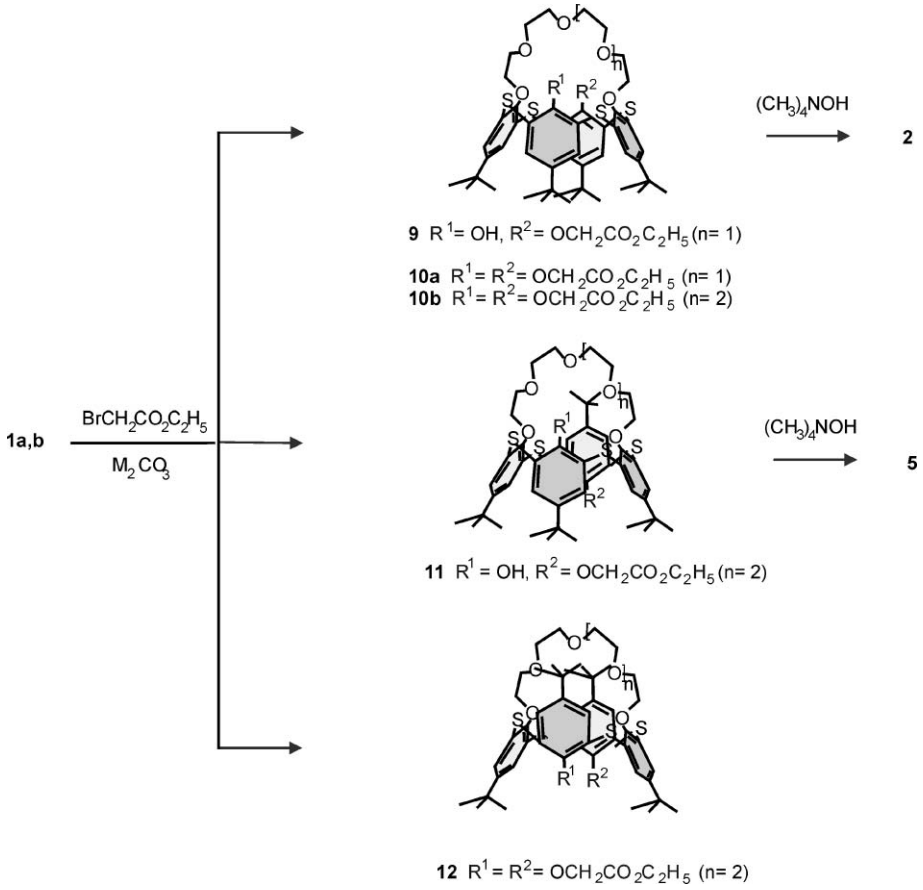


6 $R^1 = R^3 =$ OH, $R^2 = R^4 = OCH_2CO_2H$

7 $R^1 =$ OH, $R^2 = R^3 = R^4 = OCH_2CO_2H$

8 $R^1 = R^2 = R^3 = R^4 = OCH_2CO_2H$

Chart 1



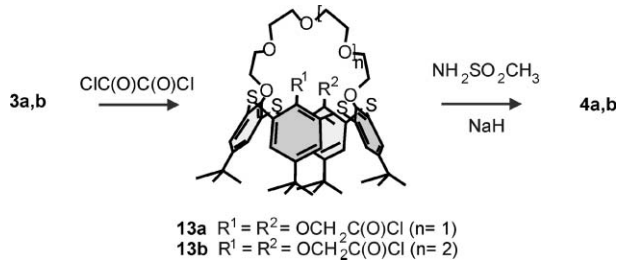
Scheme 1

is situated on the opposite side of both the crown-ether bridge and the OH group.

The thiacalix[4]crown dicarboxylic acids (**3a,b**) were prepared as described.[17]

The cone thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**) were prepared in 58% and 60% yield, respectively, by reaction of the corresponding cone crown dicarboxylic acids **3a,b** with 2.5 equiv of oxalyl chloride to give the acid chlorides **13a,b**, followed by reaction with 2.5 equiv of methanesulfonamide in the presence of 10 equiv of NaH in THF (Scheme 2). The formation of **4a,b** clearly followed from the presence of characteristic signals for the methylsulfonyl groups at δ 3.19 and 3.24 ppm, respectively, in the ^{1}H NMR spectra.

For comparison, the thiacalix[4]arene di- (**6**),[25] tri- (**7**), and tetracarboxylic acids (**8**)[25] were synthesized. Reaction of thiacalix[4]arene (**14**) with 3 equiv of ethyl bromoacetate in the presence of 1.5 equiv of Na_2CO_3 in acetone gave a mixture of the esters **15–17** (Scheme 3), from which **16** was obtained



Scheme 2

in 7% yield. Subsequent hydrolysis of the ester groups in **16** with tetramethylammonium hydroxide gave thiacalix[4]arene tricarboxylic acid **7** in 92% yield.

Indicative of the cone conformation of **16** were the NOE couplings between the four ArH resonances and between the –OH resonance and all three of the $-OCH_2CO_2-$ methylene

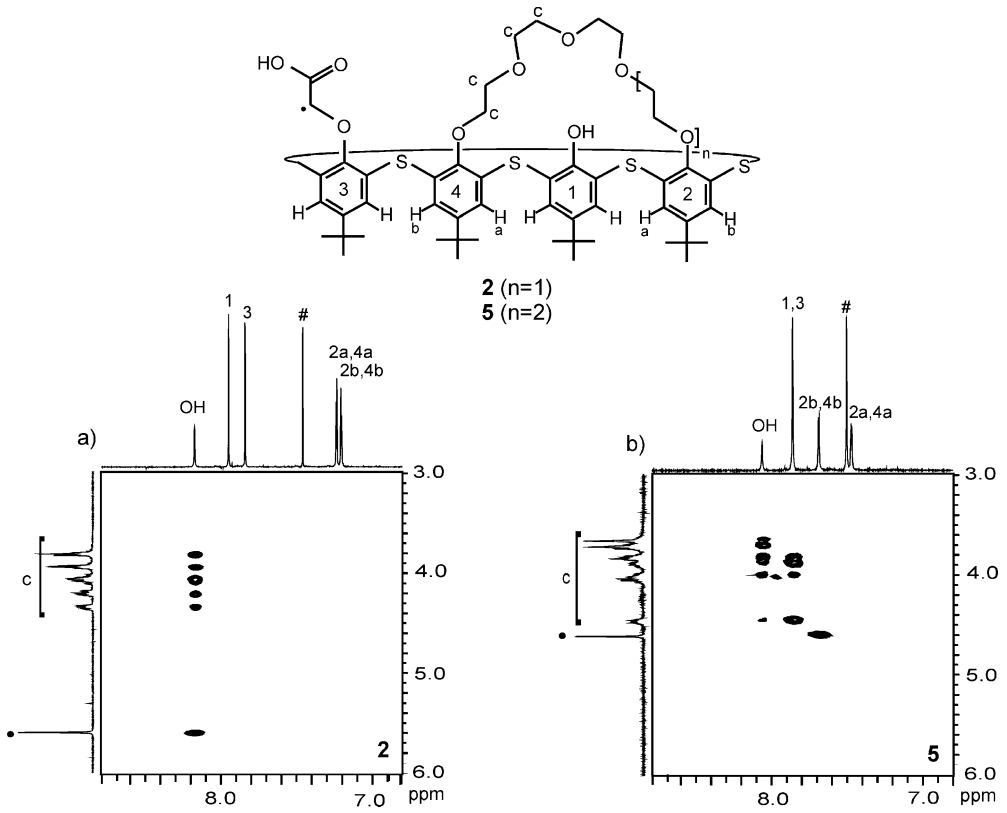
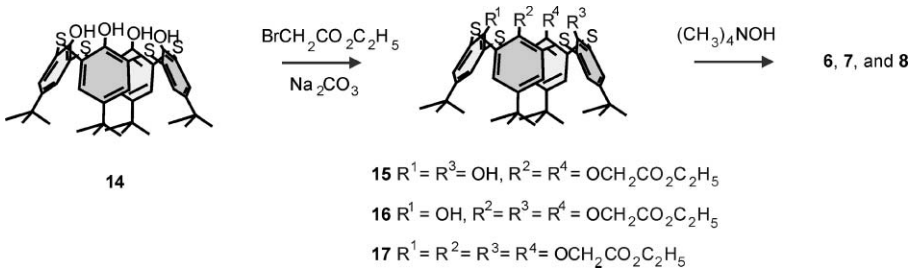


Fig. 1 ROESY (a) and NOESY (b) spectra of the thiacalix[4]crown monocarboxylic acids [**2** (cone) and **5** (partial cone)], respectively, in $CDCl_3$ at 25 °C. The resonances of $CHCl_3$ are indicated with #.



Scheme 3

resonances, which were similar to those observed for the cone thiacalix[4]crown-5 monocarboxylic acid (**2**) (see Fig. 1a).[26]

The role of covalently attached carboxylic acid groups

It is not *a priori* obvious that the covalent combination of carboxylic acids and the thiacalix[4]crown-6 platform (**3b**) binds $^{226}Ra^{2+}$ better than a mixture of the thiacalix[4]crown-6 (**1b**) with pentadecanoic acid or of thiacalix[4]arene dicarboxylic acid (**6**) with dibenzo-21-crown-7. Therefore, the $^{226}Ra^{2+}$ extraction behavior of the different systems was studied in standard competition experiments in the presence of an excess of Ca^{2+}, Sr^{2+}, or Ba^{2+} (10^{-4} – 1 M; Fig. 2).[27] The experiments were performed with equal volumes of the organic and aqueous phases.

Fig. 2 shows that dibenzo-21-crown-7, a crown ether known for its optimal crown-cavity[4] to Ra^{2+} radius[28] fit, only improves the $^{226}Ra^{2+}$ selectivity of the thiacalix[4]arene dicarboxylic acid (**6**) in the presence of Ca^{2+} cations. For Ca^{2+}, the $^{226}Ra^{2+}$ extraction curve of this mixture is identical to that of thiacalix[4]crown-6 dicarboxylic acid (**3b**).[17] (Dibenzo-)21-crown-7-ethers clearly favor binding of $^{226}Ra^{2+}$ over Ca^{2+}, a result that agrees with data published by Chiarizia *et al.*[10] In the presence of Sr^{2+} and Ba^{2+}, dibenzo-21-crown-7 does not influence $^{226}Ra^{2+}$ extraction by **6** (Figs. 2b and c). These data support the literature results,[7,10] where it is illustrated that when the radius of the competing cations[28] increases, the influence of a 21-crown-7 ether on the $^{226}Ra^{2+}$ selectivity diminishes in a synergistic mixture with acids ($Ca^{2+} \gg Sr^{2+} > Ba^{2+}$). Nevertheless, thiacalix[4]crown-6 dicarboxylic acid (**3b**)[17] still allows for separation of Ra^{2+} from Sr^{2+} and Ba^{2+}. These results clearly show the improved $^{226}Ra^{2+}$ selectivity of thiacalix[4]crown-6 dicarboxylic acid (**3b**) over a mixture of thiacalix[4]arene dicarboxylic acid (**6**) and dibenzo-21-crown-7.

The other combination, thiacalix[4]crown-6 (**1b**) and two equiv of pentadecanoic acid,[29] did not extract the $^{226}Ra^{2+}$ ion in competition with Ca^{2+}, Sr^{2+}, and Ba^{2+}.[30] So it can be concluded that the mixture of thiacalix[4]arene dicarboxylic acid (**6**) and dibenzo-21-crown-7 is far more $^{226}Ra^{2+}$ selective than the mixture of thiacalix[4]crown-6 (**1b**) and pentadecanoic acid.

$^{226}Ra^{2+}$ extraction by thiacalix[4]arene derivatives 2, 3a,b, 4a,b, 5, 6, 7 and 8

The influence of the different structural elements of thiacalix[4]crown dicarboxylic acids on the $^{226}Ra^{2+}$ selectivity was determined based on the extraction behavior of thiacalix[4]crown monocarboxylic acids (**2** and **5**), thiacalix[4]crown dicarboxylic acids (**3a,b**), thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**), thiacalix[4]arene dicarboxylic acids (**6**), thiacalix[4]arene tricarboxylic acid (**7**), and thiacalix[4]arene tetracarboxylic acid

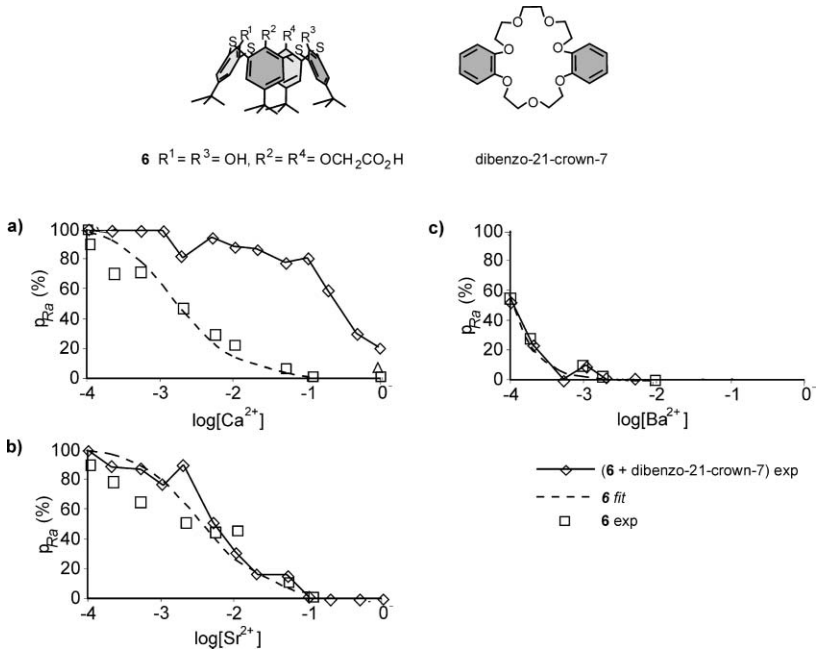


Fig. 2 $^{226}Ra^{2+}$ extraction percentages ($p_{Ra} = [^{226}Ra^{2+}]_{org}/[^{226}Ra^{2+}]_{tot}$ (%)) for different ratios of ionophore [L = **6** and **6** + dibenzo-21-crown-7] to $M(NO_3)_2$ [$M^{2+} = Ca^{2+}$ (a), Sr^{2+} (b), or Ba^{2+}(c)], and fixed ionophore ([**6**]$_{tot}$ = [dibenzo-21-crown-7]$_{tot}$ = 10^{-4} M; 1 ml of CH_2Cl_2), and $[^{226}Ra^{2+}]_{tot}$ (2.9×10^{-8} M; pH 8.9 tris-HCl) concentrations.

(**8**). First, the extraction strengths of the alkaline earth cations Ca^{2+}, Sr^{2+}, and Ba^{2+} by these ionophores were determined using both inductively coupled plasma-mass spectrometry (ICP-MS) and radiotracers.

The extraction constants (K^{M}_{ex}) of the competing cations Ca^{2+}, Sr^{2+}, and Ba^{2+} were obtained by a non-linear least squares fitting procedure with five experimental points in the range of (0.2–5) $\times 10^{-4}$ M of M^{2+} cations (Table 1). The complete models and extraction curves are given in the electronic supplementary information.†

For the thiacalix[4]crown monocarboxylic acids **2** and **5** the extraction curves obtained for Ca^{2+}, Sr^{2+}, and Ba^{2+} suggest a 1 : 1 complex stoichiometry. Consequently, the extraction constant of M^{2+} (Ca^{2+}, Sr^{2+}, and Ba^{2+}) can be expressed as in eqn. (1).

$$K^{M}_{ex} = [MLX]_{org}[Htris^{+}]_{aq}/[M^{2+}]_{aq}[HtrisL]_{org}[X^{-}]_{aq} \quad (1)$$

For the ionophores with two or three carboxylic acids **3a,b**,[17] **4a,b, 6**, and **7**, the 1 : 1 complex stoichiometry was determined in the same way. The extraction constant of M^{2+} can be expressed as in eqn. (2).[17]

$$K^{M}_{ex} = [ML]_{org}[Htris^{+}]_{aq}{}^{2}/[M^{2+}]_{aq}[(Htris)_2L]_{org} \quad (2)$$

Table 1 Extraction constants[a] of ionophores **2, 3a,b, 4a,b, 5, 6, 7** and **8**[31,32]

Ionophore	K^{Ca}_{ex}	K^{Sr}_{ex}	K^{Ba}_{ex}
2	3.8×10^4 M^{-1}	3.2×10^4 M^{-1}	3.7×10^4 M^{-1}
5	1.2×10^4 M^{-1}	$< 6.5 \times 10^2$ M^{-1}[b]	$< 1.0 \times 10^3$ M^{-1}[b]
3a	1.2 M	3.7 M	23 M
3b	$< 9.5 \times 10^{-1}$ M[b]	1.9×10^{-1} M	> 50 M[c]
4a	1.2 M	$< 3.2 \times 10^{-1}$ M[b]	2.0 M
4b	1.0 M	$< 6.5 \times 10^{-2}$ M[b]	$< 5.7 \times 10^{-1}$ M[b]
6	21 M	7.2×10^1 M	23 M
7	54 M	5.8 M	6.0 M
8	7.6×10^3	1.6×10^7	2.1×10^6

[a] Liquid–liquid extractions with ionophore (10^{-4} M; 1 ml of CH_2Cl_2) and $M(NO_3)_2$ salts ($M^{2+} = Ca^{2+}$, Sr^{2+}, and Ba^{2+}; (0.2–5) $\times 10^{-4}$ M; 1 ml of pH 8.9 tris-HCl buffer). [b] Due to the very low extraction percentages obtained, this value indicates an upper limit. [c] Due to the very high extraction percentages obtained, this value indicates a lower limit.

The Ca^{2+}, Sr^{2+}, and Ba^{2+} extraction by thiacalix[4]arene tetracarboxylic acid (**8**) suggests a 1 : 2 (ML_2) complex stoichiometry. Consequently, the extraction constant of M^{2+} is expressed as in eqn. (3).

$$K^{M}_{ex} = [M((Htris)_3L)_2]_{org}[Htris^{+}]_{aq}{}^{2}/[M^{2+}]_{aq}[(Htris)_4L]_{org}{}^{2} \quad (3)$$

Since the extraction constants (K^{M}_{ex}) reported in Table 1 do not have the same dimensions, a direct comparison between the K^{M}_{ex} values of the different ionophores is not possible.

With the stoichiometries and K^{M}_{ex} values of the different ionophores, the $^{226}Ra^{2+}$ selectivity coefficients were determined from competition experiments performed under standard conditions (see above). Representative $^{226}Ra^{2+}$ extraction curves are depicted in Fig. 2 (**6**) and Fig. 3 (**2, 3a,b**, and **5**).

If the extraction percentages of the competing cations, calculated with K^{M}_{ex}, are incorporated in eqns. (1–3) as $p_M = [M^{2+}]_{org}/[M^{2+}]_{tot}$ and the experimentally determined $^{226}Ra^{2+}$ extraction percentages as $p_{Ra} = [^{226}Ra^{2+}]_{org}/[^{226}Ra^{2+}]_{tot}$, the K^{Ra}_{ex}/K^{M}_{ex} values can be determined using a fitting procedure of the extraction curves of $^{226}Ra^{2+}$ (see eqn. (4)).[17]

$$K^{Ra}_{ex}/K^{M}_{ex} = p_{Ra}(1 - p_M)/(1 - p_{Ra})p_M \quad (4)$$

The K^{Ra}_{ex}/K^{M}_{ex} values allow for a direct comparison of the Ra^{2+} selectivity coefficients of the different ionophores used (Table 2).

Table 2 Selectivity coefficients ($\log(K^{Ra}_{ex}/K^{M}_{ex})$), obtained under standard conditions, of ionophores **2, 3a,b, 4a,b, 5, 6, 7**, and **8**[33]

Compound	$\log(K^{Ra}_{ex}/K^{Ca}_{ex})$	$\log(K^{Ra}_{ex}/K^{Sr}_{ex})$	$\log(K^{Ra}_{ex}/K^{Ba}_{ex})$
2	1.7	1.1	< -0.77[a]
3a	3.5	1.7	−0.45
3b	3.3	3.4	0.92
4a	1.9	1.1	−0.060
4b	1.6	1.5	1.1
5	1.1	1.2	< 0.34[a]
6	1.2	1.5	−0.36
7	−1.2	0.22	−0.18
8	< -0.56[a]	< -1.2[a]	< -0.45[a]

[a] Due to the low $^{226}Ra^{2+}$ extraction percentages obtained, this value indicates an upper limit.

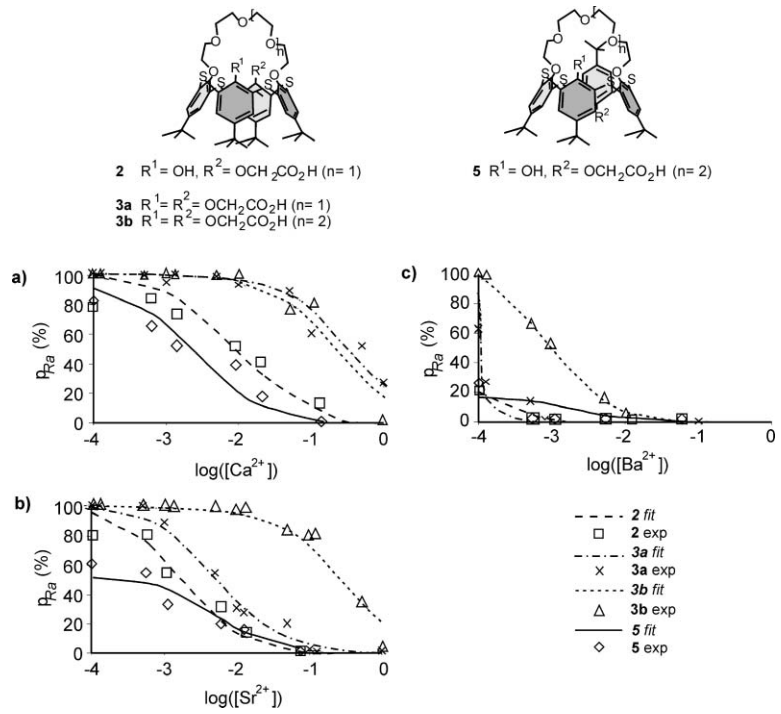


Fig. 3 $^{226}Ra^{2+}$ extraction percentages ($p_{Ra} = [^{226}Ra^{2+}]_{org}/[^{226}Ra^{2+}]_{tot}$ (%)) for ionophores **2, 3a,b**, and **5** (10^{-4} M), as a function of the $M(NO_3)_2$ [M^{2+} = Ca^{2+} (a), Sr^{2+} (b), or Ba^{2+}(c)] concentration, with 2.9×10^{-8} M $^{226}Ra^{2+}$.

The influence of the number of carboxylic acid substituents, the conformation, and the crown bridge on the $^{226}Ra^{2+}$ selectivity of a thiacalix[4]crown was deduced from the $^{226}Ra^{2+}$ extraction abilities of thiacalix[4]crown monocarboxylic acids (**2** and **5**) and thiacalix[4]crown dicarboxylic acids (**3a,b**) (Fig. 3; Table 2).

The Ca^{2+}, Sr^{2+}, and Ba^{2+} extraction constants of the cone (**2**) and partial cone (**5**) thiacalix[4]crown monocarboxylic acids differ; **5** has significantly lower K^{M}_{ex} values for Sr^{2+} and Ba^{2+} (Table 1). Surprisingly, in the presence of Ca^{2+}, their $^{226}Ra^{2+}$ selectivity coefficients [$\log(K^{Ra}_{ex}/K^{M}_{ex})$] clearly differ, 1.7 and 1.1, respectively, while with Sr^{2+} the difference is minor, 1.1 and 1.2, respectively (Table 2). With Ba^{2+} both thiacalix[4]crown-6 derivatives **3b** and **5** are $^{226}Ra^{2+}$ selective, with $\log(K^{Ra}_{ex}/K^{Ba}_{ex})$ values of 0.92 and <0.34,[34] respectively, whereas both thiacalix[4]crown-5 derivatives **2** and **3a** favor Ba^{2+} over $^{226}Ra^{2+}$. Nevertheless, in the presence of Ca^{2+} and Sr^{2+}, both thiacalix[4]crown monocarboxylic acids (**2** and **5**) give significantly lower $^{226}Ra^{2+}$ selectivity coefficients than the thiacalix[4]crown dicarboxylic acids (**3a,b**).[17] The latter, both having the cone conformation, exhibit a clear influence of the size of the crown-ether bridge, with the highest $\log(K^{Ra}_{ex}/K^{M}_{ex})$ values for thiacalix[4]crown-6 dicarboxylic acid (**3b**).

The $^{226}Ra^{2+}$ extraction of partial cone thiacalix[4]crown-6 monocarboxylic acid (**5**), together with the complete lack of $^{226}Ra^{2+}$ extraction in the case of thiacalix[4]crown-6 (**1b**), indicates that a carboxylic acid group at the opposite side of the thiacalix[4]arene platform can still partially neutralize $^{226}Ra^{2+}$ cations complexed in the crown-ether bridge. This was proven by NOE spectra of the [Ba(**5**)Pic] complex.[35]

Apparently, the co-extraction of an anion, needed in the case of the thiacalix[4]crown monocarboxylic acids (**2** and **5**), has a negative influence on the $^{226}Ra^{2+}$ selectivity coefficients, compared to the thiacalix[4]crown dicarboxylic acids (**3a,b**). Therefore, the ability to form a neutral [ML] (L = **3a** or **3b**) complex is considered more favorable for selective $^{226}Ra^{2+}$ extraction than a [MLX] (L = **2** or **5**; X = anion) complex.

Hendriksen *et al.* have reported that a calix[4]arene platform functionalized with four carboxylic acid moieties gives stable $^{226}Ra^{2+}$ complexes.[5] Therefore, the effect of the number of carboxylic acid groups on the $^{226}Ra^{2+}$ extraction was studied. The $^{226}Ra^{2+}$ selectivity coefficients of thiacalix[4]arene di- (**6**; Fig. 2a), tri- (**7**), and tetracarboxylic acid (**8**) are given in Table 2.

Since thiacalix[4]arene tetracarboxylic acid (**8**) shows near quantitative extraction of Sr^{2+} and Ba^{2+} (Table 1), but poor $^{226}Ra^{2+}$ selectivity coefficients, it seems that four carboxylic acid groups have a negative influence on the $^{226}Ra^{2+}$ selectivity. Thiacalix[4]arenes with two and three carboxylic acid moieties (**6** and **7**) are rather effective extractants for Ca^{2+} and Sr^{2+} (Table 1), but still show $^{226}Ra^{2+}$ extraction. Only thiacalix[4]arene dicarboxylic acid (**6**) has a $^{226}Ra^{2+}$selectivity in the presence of Ca^{2+}, while thiacalix[4]arene tricarboxylic acid (**7**) and dicarboxylic acid (**8**) show a $^{226}Ra^{2+}$ selectivity in the presence of Sr^{2+}. The $^{226}Ra^{2+}$ selectivity coefficients of thiacalix[4]arene dicarboxylic acid (**6**) towards Ca^{2+} and Sr^{2+}, 1.2 and 1.5, respectively, are similar to those of the thiacalix[4]crown monocarboxylic acids (**2** and **5**; Table 2). This suggests that the presence of two carboxylic acid substituents on a platform is as favorable for the $^{226}Ra^{2+}$ selectivity as the combination of a crown-(6-)ether bridge and one carboxylic acid moiety. However, thiacalix[4]arene dicarboxylic acid (**6**) is not $^{226}Ra^{2+}/Ba^{2+}$ selective, in contrast to thiacalix[4]crown-6 monocarboxylic acid (**5**).

Compared to thiacalix[4]crown-5 dicarboxylic acid (**3a**), only the $^{226}Ra^{2+}/Ca^{2+}$ selectivity of thiacalix[4]arene dicarboxylic acid (**6**) is significantly lower (214 times). On the other hand, thiacalix[4]crown-6 dicarboxylic acid (**3b**), shows significantly higher $^{226}Ra^{2+}$ selectivities than **6** for all competing cations.

Thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**) could provide alternatives for the known thiacalix[4]crown dicarboxylic acids (**3a,b**)[17] and their $^{226}Ra^{2+}$ selectivities were determined under standard conditions (Table 2; for $^{226}Ra^{2+}$ extraction curves, see ESI†). However, the extraction constants of the thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a**), and in particular (**4b**), for Sr^{2+} and Ba^{2+}, are considerably lower than those of the thiacalix[4]crown dicarboxylic acids (**3a,b**; Table 1). In competition experiments with Ca^{2+}, thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**) give significantly lower $^{226}Ra^{2+}$ selectivity coefficients than the thiacalix[4]crown dicarboxylic acids (**3a,b**), *viz.* 1.9 and 1.6 *vs.* 3.5 and 3.3, respectively. In the presence of Sr^{2+}, only thiacalix[4]crown-6 dicarboxylic acid (**3b**) gives a significantly higher selectivity coefficient than

4a and **4b** (3.4 *vs.* 1.1 and 1.5, respectively). In the case of thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**), no distinct crown ether size influence could be observed in the presence of Ca^{2+} and Sr^{2+}. However, the crown-6 derivative **4b** has a $^{226}Ra^{2+}/Ba^{2+}$ selectivity (1.1),[34] which is slightly higher than that of the thiacalix[4]crown-6 dicarboxylic acid **3b** (0.95). In general, the thiacalix[4]crown bis(methylsulfonyl) carboxamides (**4a,b**) show lower selectivities than the thiacalix[4]crown dicarboxylic acids (**3a,b**).

The difference in acidity of methylsulfonyl carboxamide, compared with carboxylic acid groups, might have enlarged the effective pH range.[36] However, the non-competitive $^{226}Ra^{2+}$ extraction with **3b** and **4b** gave identical curves over a pH range of 4–9 (Fig. 4).[17]

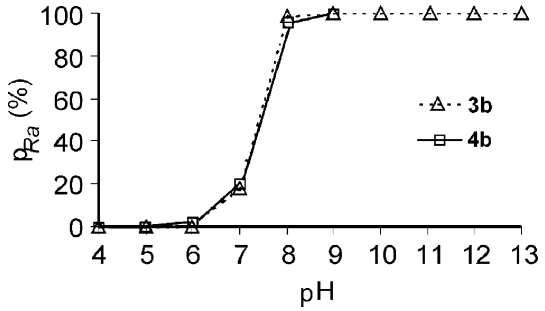


Fig. 4 pH dependent $^{226}Ra^{2+}$ extraction curve of thiacalix[4]crown-6 dicarboxylic acid (**3b**) and thiacalix[4]crown-6 bis(methylsulfonyl) carboxamide (**4b**).

Conclusions

The results of this systematic study clearly show the advantage of bringing together the crown ether and acid components of a synergistic system on a molecular platform, resulting in much higher $^{226}Ra^{2+}$ extraction efficiencies and selectivities. The use of a thiacalix[4]arene with two carboxylic acid groups already gives a high $^{226}Ra^{2+}$ selectivity, a result that is further improved by the introduction of a crown-(6-)ether bridge at the thiacalix[4]arene platform. The latter significantly improves the $^{226}Ra^{2+}$ selectivity compared to that of the mixtures consisting of thiacalix[4]arene dicarboxylic acid (**6**) and dibenzo-21-crown-7, or thiacalix[4]crown-6 (**1b**) and pentadecanoic acid. The thiacalix[4]crown-6 dicarboxylic acid (**3b**) previously reported,[17] is unambiguously the best $^{226}Ra^{2+}$ selective ionophore in the presence of Ca^{2+}, Sr^{2+}, or Ba^{2+}.

Experimental

Synthesis

General methods. All solvents were purified by standard laboratory procedures. All other chemicals were analytically pure and used without further purification. Acetonitrile, acetone, and toluene were dried on molecular sieves, whereas dry THF was obtained after distillation over sodium. *tert*-Butylthiacalix[4]-crown-5 and -6 (**1a,1b**),[18,19] *tert*-butylthiacalix[4]crown-5 and -6 dicarboxylic ethyl esters (**10a,b**),[17] *tert*-butylthiacalix[4]crown-5 and -6 dicarboxylic acid (**3a,b**),[17] *tert*-butylthiacalix[4]arene dicarboxylic ethyl ester (**15**),[25] *tert*-butylthiacalix[4]arene dicarboxylic acid (**6**),[25] *tert*-butylthiacalix[4]arene tetracarboxylic ethyl ester (**17**),[25] and *tert*-butylthiacalix[4]arene tetracarboxylic acid (**8**)[25] were prepared according to the procedure described in the literature. Except for the hydrolysis, all reactions were carried out under an inert argon atmosphere. MALDI-TOF experiments were performed with a dithranol matrix.

^{1}H NMR spectra were obtained on a Varian INOVA 300 spectrometer; ^{13}C NMR spectra were obtained from a Varian Unity 400 spectrometer. Spectra were recorded at 25 °C in $CDCl_3$ and referenced to the residual solvent peak ($CHCl_3$). The HH-NOESY and ROESY spectra (recorded on the 400 MHz spectrometer) were acquired using the standard Varian pulse sequences with mixing times ranging from 100 to 500 ms, 1024 to 2048 data points in t_2 and 128 to 256 increments in t_1. The depicted NOESY spectra of the [Ba(**5**)Pic] complex and **7** (see ESI†), and the ROESY spectrum of **2** (Fig. 1a) were recorded with mixing times of 500 ms, the NOESY spectrum of **5** (Fig. 1b) with a mixing time of 300 ms.

Thin-layer chromatography was performed on aluminium sheets precoated with silica gel 60 F254 (E. Merck); spots were visualized by UV-absorbancy. Chromatographic separations were performed on silica gel 60 (E. Merck, 0.040–0.063 mm, 230–240 mesh) or with preparative thin layer chromatography (Silica gel 60 F_{254}, 2 mm). Melting points are uncorrected.

5,11,17,23-Tetra-*tert*-butyl-26-[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arenemonocrown-5 (9). A suspension of **1a** (200 mg, 0.23 mmol), ethyl bromoacetate (38 mg, 0.23 mmol), and Na_2CO_3 (12 mg, 0.11 mmol) in acetonitrile (40 ml) was refluxed for 64 h. Subsequently, the acetonitrile was removed and the residue dissolved in CH_2Cl_2 (50 ml). The solution was washed with 10% HCl (2 × 100 ml) and water (2 × 100 ml), and dried on $MgSO_4$. After evaporation of the solvent the residue was separated by column chromatography (SiO_2, EtOAc–hexane 2 : 3) to give **9** (130 mg, 59%): mp 241–243 °C; δ_H 8.32 (s, 1H), 7.48 (s, 2H), 7.29 (s, 2H), 7.22 (s, 4H), 5.40 (s, 2H), 4.63–4.70 (m, 2H), 4.44–4.37 (m, 2H), 4.01–4.22 (m, 6H), 3.77–3.97 (m, 8H), 1.26 (t, 3H, *J* 7.3), 1.23 (s, 9H), 1.06 (s, 9H), 0.99 (s, 18H); δ_C 170.0, 158.1, 157.2, 156.5, 147.0, 146.2, 142.0, 134.6, 134.5, 134.1, 133.4, 129.9, 129.5, 121.8, 74.7, 70.5, 70.3, 70.0, 69.8, 60.5, 34.1, 34.0, 31.3, 31.2, 31.0, 14.2; MALDI-TOF *m/z*: 965.9 $[M + H]^+$, 987.9 $[M + Na]^+$, 1003.8 $[M + K]^+$, calcd 965.4 $[M + H]^+$. Found: C, 64.4; H, 7.0. Calc. for $C_{52}H_{68}O_9S_4$: C, 64.7; H, 7.1%.

5,11,17,23-Tetra-*tert*-butyl-26-[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arenemonocrown-6 (11). A suspension of **1b** (479 mg, 0.52 mmol), ethyl bromoacetate (182 mg, 1.09 mmol), and K_2CO_3 (68 mg, 0.49 mmol) in acetonitrile (160 ml) was refluxed for 24 h. Subsequently, the acetonitrile was removed and the residue dissolved in CH_2Cl_2 (150 ml). The solution was washed with 10% HCl (2 × 150 ml) and water (2 × 150 ml), and dried on $MgSO_4$. After evaporation of the solvent the residue was separated by column chromatography (SiO_2, EtOAc–hexane 2 : 3) to give **10b**[17] (218 mg, 38%). Subsequent eluent change to EtOAc yielded **11** (100 mg, 19%): mp 174–179 °C; δ_H 7.83 (s, 1H), 7.61 (s, 4H), 7.44 (d, 2H, *J* 2.6 Hz), 7.23 (d, 2H, *J* 2.6 Hz), 4.59 (s, 2H), 4.44 (m, 2H), 3.96–4.05 (m, 4H), 3.78–3.91 (m, 6H), 3.64–3.73 (m, 10H), 1.43 (s, 9H), 1.33 (s, 9H), 1.07 (s, 18H), 0.99 (t, 3H, *J* 7.1 Hz); δ_C 167.8, 157.1, 156.9, 156.6, 146.9, 146.6, 141.8, 134.7, 133.9, 132.7, 131.2, 129.0, 128.4, 127.0, 121.6, 73.4, 71.1, 70.9, 70.7, 69.9, 67.1, 60.4, 34.5, 34.1, 34.0, 31.5, 30.9, 13.8; MALDI-TOF *m/z*: 1008.6 $[M]^+$, 1030.6 $[M + Na]^+$, 1046.6 $[M + K]^+$, calcd 1008.4 $[M]^+$. Found: C, 64.2; H, 7.2. Calc. for $C_{54}H_{72}O_{10}S_4$: C, 64.2; H, 7.3%.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (16). A suspension of **14** (1.0 g, 1.39 mmol), ethyl bromoacetate (689 mg, 4.17 mmol), and Na_2CO_3 (220 mg, 2.02 mmol) in dry acetone (50 ml) was refluxed for 24 h. Subsequently, the acetone was removed and the residue, containing a mixture of the esters **15, 16**, and **17**, dissolved in CH_2Cl_2 (75 ml). The solution was washed with 10% HCl (2 × 100 ml) and water (2 × 100 ml), and dried on $MgSO_4$. After evaporation of the solvent the residue was separated by column chromatography (SiO_2, dichloromethane) to give **16** (95 mg, 7%): mp 134–137 °C; δ_H 7.61 (s, 2H), 7.58 (s, 2H), 7.01 (d, 2H, *J* 2.6 Hz), 6.98 (d, 2H, *J* 2.6 Hz), 5.34 (s, 2H), 5.22 (s, 2H), 5.17 (s, 2H), 4.83 (s, 1H), 4.77 (s, 1H), 4.28–4.36 (m, 6H),

4.13 (q, 2H, *J* 7.2 Hz), 1.18–1.37 (m, 9H), 1.30 (s, 9H), 1.26 (s, 9H), 0.86 (s, 18H); δ_C 169.6, 169.1, 168.5, 168.2, 157.2, 156.4, 156.1, 148.6, 148.1, 147.4, 146.5, 142.1, 135.2, 134.4, 133.7, 133.0, 132.4, 129.9, 128.9, 127.1, 121.6, 71.7, 71.5, 71.4, 71.2, 68.6, 34.2, 33.9, 31.8, 31.7, 31.5, 31.4, 31.2, 31.1, 31.0, 30.7, 30.6, 30.2, 14.6, 14.3, 14.1, 13.9, 13.8; MALDI-TOF *m/z*: 978.6 $[M]^+$, 1001.5 $[M + Na]^+$, 1017.5 $[M + K]^+$, calcd 978.4 $[M]^+$. Found: C, 63.8; H, 7.0. Calc. for $C_{52}H_{66}O_{10}S_4$: C, 63.8; H, 6.8%.

General hydrolysis procedure

To a suspension of **9, 11**, or **16** in THF–H_2O (1 : 1) was added an excess of tetramethylammonium hydroxide (TMAH) (25%) in MeOH, whereupon the mixture was refluxed for 12 h. The organic solvents were removed and the residue was dissolved in CH_2Cl_2 (100 ml). The solution was washed with 10% HCl (2 × 100 ml), dried with $MgSO_4$, whereupon the solvent was removed.

5,11,17,23-Tetra-*tert*-butyl-26-carboxymethoxy-2,8,14,20-tetrathiacalix[4]arenemonocrown-5 (2). Reaction of **9** (81 mg, 84 μmol) and TMAH (1.5 ml) in THF–H_2O (20 ml) yielded **2** (64 mg, 81%): mp >250 °C; δ_H 7.97 (s, 1H), 7.75 (s, 2H), 7.64 (s, 2H), 7.03 (d, 2H, *J* 2.6 Hz), 7.00 (d, 2H, *J* 2.6 Hz), 5.58 (s, 2H), 4.31–4.37 (m, 2H), 4.24 (m, 2H), 4.00–4.23 (m, 4H), 3.95 (t, 4H, *J* 5.3 Hz), 3.78–3.88 (m, 4H), 1.35 (s, 9H), 1.33 (s, 9H), 0.83 (s, 18H); δ_C 171.1, 158.1, 157.2, 156.5, 147.6, 147.4, 142.0, 135.7, 134.3, 133.7, 133.5, 129.4, 129.0, 127.8, 122.0, 71.4, 70.7, 70.0, 69.8, 34.4, 34.1, 31.5, 31.3, 30.7, 29.7; MALDI-TOF *m/z*: 937.8 $[M + H]^+$, 959.7 $[M + Na]^+$, 975.7 $[M + K]^+$, calcd 937.3 $[M + H]^+$. Found: C, 64.0; H, 6.9. Calc. for $C_{50}H_{64}O_9S_4$: C, 64.1; H, 6.9%.

5,11,17,23-Tetra-*tert*-butyl-26-carboxymethoxy-2,8,14,20-tetrathiacalix[4]arenemonocrown-6 (5). Reaction of **11** (85 mg, 84 μmol) and TMAH (1.5 ml) in THF–H_2O (16 ml) yielded **5** (70 mg, 85%): mp 241–244 °C; δ_H 7.81 (s, 1H), 7.62 (s, 2H), 7.54 (s, 2H), 7.45 (d, 2H, *J* 2.6), 7.30 (d, 2H, *J* 2.6), 4.59 (s, 2H), 4.28–4.34 (m, 2H), 4.11–4.18 (m, 2H), 3.73–3.83 (m, 6H), 3.72–3.61 (m, 10H), 1.43 (s, 9H), 1.33 (s, 9H), 1.13 (s, 18H); δ_C 167.3, 156.9, 156.5, 153.0, 148.6, 148.4, 142.7, 135.9, 133.5, 130.1, 129.0, 128.9, 128.8, 126.4, 121.2, 73.3, 71.0, 70.9, 70.8, 69.6, 64.4, 34.7, 34.3, 34.1, 31.4, 30.8, 29.7; MALDI-TOF *m/z*: 980.0 $[M + H]^+$, 1002.9 $[M + Na]^+$, 1018.9 $[M + K]^+$, calcd 980.4 $[M + H]^+$. Found: C, 63.7; H, 6.9. Calc. for $C_{52}H_{68}O_{10}S_4$: C, 63.6; H, 7.0%.

5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris(carboxymethoxy)-2,8,14,20-tetrathiacalix[4]arene (7). Reaction of **16** (263 mg, 269 μmol) and TMAH (2.5 ml) in THF–H_2O (20 ml) yielded **7** (221 mg, 92%): mp >250 °C; δ_H 7.61 (dd, 4H, *J* 2.6 and 2.6), 7.38 (s, 2H), 7.16 (s, 2H), 5.97 (s, 1H), 5.91 (s, 1H), 4.78 (m, 2H), 4.62 (s, 1H), 4.57 (s, 1H), 1.22 (s, 18H), 1.11 (s, 9H), 0.92 (s, 9H); δ_C 174.5, 170.2, 158.8, 155.0, 148.1, 143.2, 135.5, 134.6, 133.9, 129.2, 128.9, 128.8, 120.8, 34.3, 33.9, 31.6, 31.3, 30.9, 30.5, 29.6; MALDI-TOF *m/z*: 894.3 $[M]^+$, 917.4 $[M + Na]^+$, 933.3 $[M + K]^+$, calcd 894.3 $[M]^+$. Found: C, 61.4; H, 6.1. Calc. for $C_{46}H_{54}O_{10}S_4$: C, 61.7; H, 6.1%.

General procedure for the preparation of *N*-methylsulfonyl carboxamides 4a,b

To a solution of **3a,b** in dry toluene (10 ml) was added oxalyl chloride (2.5 equiv). The solution was refluxed for 12 h, whereupon the toluene was removed at reduced pressure. The residue was dissolved in dry THF (20 ml) and the resulting solution added to a suspension of NaH (60% dispersion in mineral oil) (10 equiv) and methanesulfonamide (2.5 equiv) in dry THF (5 ml). The mixture was stirred at room temperature for 72 h. Excess NaH was carefully neutralized by adding water. After the work up as described for the general hydrolysis procedure, preparative thin layer chromatography (SiO_2, EtOAc) was performed to yield **4a,b**.

5,11,17,23-Tetra-*tert*-butyl-26,28-bis[(methylsulfonyl)carbamoylmethoxy]-2,8,14,20-tetrathiacalix[4]arenemonocrown-5 (4a). Reaction of **3a** (185 mg, 0.19 mmol), oxalyl chloride (69 mg, 54 mmol), sodium hydride (87 mg, 1.86 mmol), and methanesulfonamide (52 mg, 55 mmol) gave **4a** (125 mg, 58%): mp >250 °C; δ_H 11.27 (s, 2H), 7.73 (s, 4H), 7.00 (s, 4H), 5.83 (s, 4H), 4.31–4.33 (m, 4H), 4.06–4.08 (m, 4H), 3.85–3.86 (m, 4H), 3.77–3.79 (m, 4H), 3.19 (s, 6H), 1.35 (s, 18H), 0.84 (s, 18H); δ_C 169.9, 158.2, 157.5, 147.0, 146.9, 135.4, 134.2, 129.5, 128.0, 74.7, 71.1, 70.6, 70.4, 41.5, 34.4, 33.9, 31.4, 30.7, 29.7; MALDI-TOF *m/z*: 1148.4 $[M]^+$, 1170.4 $[M + Na]^+$, 1186.4 $[M + K]^+$, calcd. 1148.3 $[M]^+$. Found: C, 55.8; H, 6.2. Calc. for $C_{54}H_{72}N_2O_{13}S_6 \cdot 0.7\ H_2O$: C, 55.8; H, 6.4%.

5,11,17,23-Tetra-*tert*-butyl-26,28-bis[(methylsulfonyl)carbamoylmethoxy]-2,8,14,20-tetrathiacalix[4]arenemonocrown-6 (4b). Reaction of **3b** (80 mg, 77 μmol), oxalyl chloride (25 mg, 0.19 mmol), sodium hydride (31 mg, 0.77 mmol), and methanesulfonamide (19 mg, 0.19 mmol) gave **4b** (55 mg, 60%): mp >250 °C; δ_H 11.11 (s, 2H), 7.71 (s, 4H), 6.92 (s, 4H), 5.66 (s, 4H), 4.14–4.17 (m, 4H), 4.03–4.06 (m, 4H), 3.86–3.90 (m, 4H), 3.77–3.81 (m, 4H), 3.75 (s, 4H), 3.24 (s, 6H), 1.35 (s, 18H), 0.85 (s, 18H); δ_C 169.5, 158.5, 157.4, 147.0, 146.8, 135.8, 133.3, 129.3, 128.1, 76.4, 71.0, 70.7, 70.5, 70.4, 70.2, 41.3, 34.4, 34.0, 31.4, 30.8, 29.7; MALDI-TOF *m/z*: 1191.9 $[M]^+$, 1213.9 $[M + Na]^+$, 1229.9 $[M + K]^+$, 1235.9 $[M + 2Na]^+$, 1251.9 $[M + Na + K]^+$, 1257.9 $[M + 2K]^+$, calcd. 1192.4 $[M]^+$. Found: C, 56.1; H, 6.5. Calc. for $C_{56}H_{76}N_2O_{14}S_6$: C, 56.3; H, 6.4%.

[Ba(5)Pic] complex formation

A mixture of **5** (9.8 mg, 10^{-2} mmol), $Ba(NO_3)$ (29 mg, 10^{-1} mmol) and LiPic (24 mg, 10^{-1} mmol) in CH_2Cl_2–acetonitrile 1 : 1 (5 ml) was stirred at 40 °C for 1 h. The solvents were evaporated and the residue dissolved in $CDCl_3$ (1 ml), after which the solution was filtered.

Extraction

Materials. The acids (concentrated HCl and HNO_3) and CH_2Cl_2 were of p.a. grade and used as received. The nitrate salts of Ca^{2+} (p.a.), Sr^{2+} (p.a.), and Ba^{2+} (p.a.) were purchased from Acrôs Organics. $^{90}Sr^{2+}$ isotope solutions were purchased from Amersham UK. $^{133}Ba^{2+}$ isotope solutions were purchased from Isotope Products Europe Blaseg GmbH. $^{226}Ra^{2+}$ stock solutions were purchased from AEA Technology QSA GmbH; ^{226}Ra was used due to its long half-life ($t_{1/2} = 1.6 \times 10^3$ y). (**Note**: **^{226}Ra has a very high radiotoxicity and should be handled with care and under radio nuclear supervision.**)

Solutions. All basic experiments were performed using an aqueous phase with pH 8.9 (tris-HCl buffer) and an organic phase containing 10^{-4} M of ionophore in CH_2Cl_2. The different nitrate salt concentrations were obtained by diluting stock solutions to the required concentration. From a carrier free stock solution of $^{90}Sr^{2+}$, a dilution of 2.5 MBq g^{-1} was made in 0.1 M HNO_3. From a 10 μg Ba^{2+} ml^{-1} carrier containing stock solution of $^{133}Ba^{2+}$ in 0.1 M HCl, a dilution of 45 kBq g^{-1} was made in water. From a carrier free stock solution of $^{226}Ra^{2+}$ in 0.5 M HCl, a dilution of 12 kBq g^{-1} (1.4×10^{-6} M) was made in 0.1 M HNO_3.

General extraction procedures. Equal volumes (1.0 ml) of the organic and aqueous solutions were transferred into a screw cap vial with a volume of 4 ml. The samples were shaken (1500 rpm) at ambient temperatures (22–24 °C) for 1 h to ensure complete settling of the two-phase equilibration. After extraction, the solutions were disengaged by centrifugation (1600 rpm for 5 min) and aliquots (0.5 ml) of the organic and aqueous phases were

pipetted out. Experiments were performed in duplicate; average values are reported, with an estimated error of 10–15%.[17]

Non-competitive extraction experiments (Table 1). In the non-competitive extraction experiments, the concentration of $[M(NO_3)_2]$ (M^{2+} = Ca^{2+}, Sr^{2+}, and Ba^{2+}) was varied (0.2–3) × 10^{-4} M compared to the ionophore concentration (10^{-4} M).[37]

ICP-MS monitored extraction procedures (Table 1). The solvent of the aliquot taken from the organic phase was evaporated and the residue destructed in 0.5 ml of concentrated HNO_3. The cation concentrations were measured on a Perkin Elmer Sciex Elan 6000 ICP-MS instrument, using a cross flow nebulizer.[37] The extraction percentage is defined as 100% times the ratio of cation concentration in the organic phase ($[M]_{org}$) and the added cation concentration ($[M]_{tot}$) (eqn. (5)).

$$p_M\% = 100\%([M]_{org}/[M]_{tot}) \quad (5)$$

Tracer monitored extraction procedures (Table 1). The extraction percentages were determined using the appropriate tracer in individual $M^n(NO_3)_n$ [M = Sr^{2+} ($^{90}Sr^{2+}$), or Ba^{2+} ($^{133}Ba^{2+}$)] solutions. In the case of $Sr(NO_3)_2$ the extraction percentages were determined using 2.5 µl of $^{90}Sr^{2+}$ tracer (616 Bq). The activity was determined using a liquid scintillation counter to detect the Cherenkov radiation. In the case of $Ba(NO_3)_2$ the extraction percentages were determined using 10 µl of ^{133}Ba tracer (452 Bq). The gamma-activity was determined using a NaI scintillation counter. The obtained extraction percentages are defined as 100% times the ratio of the activity in the organic phase (A_{org}) and the total activity ($A_{org} + A_{aq}$) (eqn. (6)).

$$p_M\% = 100\%(A_{org}/(A_{org} + A_{aq})) \quad (6)$$

Competitive $^{226}Ra^{2+}$ extraction curves (single competing cation; Figs. 2 and 3 and Table 2). In the competitive extraction experiments, aqueous phase pH 8.9 (tris-HCl), the ratio of competing $M(NO_3)_n$ (M = Ca^{2+}, Sr^{2+}, and Ba^{2+}) salt concentrations compared to a fixed ionophore concentration (1 ml; 10^{-4} M) was altered to provide competing cation-concentration dependent extraction curves. To the aqueous phase, 20 µl of $^{226}Ra^{2+}$ tracer (240 Bq) were added and the gamma-activity was determined with a Ge(Li) scintillation counter. The obtained extraction percentages are defined as 100% times the ratio of activity in the organic phase (A_{org}) and the total activity ($A_{org} + A_{aq}$) (eqn. (6)).

Extraction *vs.* pH curves (Fig. 4). Experiments were performed using fixed concentrations **3b** and **4b** of (10^{-4} M) and $^{226}Ra^{2+}$ (2.9×10^{-8} M). The pH values were set using different buffer solutions: pH 4–6: HCl, pH 7–10: tris-HCl, and pH 10–13: tris-$(CH_3)_3$NOH.

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References and notes

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20 It seems that a difference in reactivity of the two hydroxyl groups of a thiacalix[4]crown allows for selective functionalization, a property that could be useful for the preparation of mixed substituent thiacalix[4]crowns.
21 Attempts to form the cone crown-6 monoester with Na_2CO_3 as a base (2 equiv) only gave partial conversion of thiacalix[4]crown-6 (**1b**) to the partial cone thiacalix[4]crown-6 monoester (**11**). This preferred formation of the partial cone **11** is rather surprizing, since a crown-5-ether bridge only allows for the formation of the monoester in the cone conformation **9**.
22 All conformational assignments are fully confirmed by the complete NOESY data, including those of the *t*-butyl group resonances.
23 In the ^1H NMR spectra of **7** the ArH1 and ArH3 peaks perfectly overlap.
24 The ArH3 NOE interaction with the crown-ether bridge allows assignment of the low field peaks to ArH2a/ArH4a and as a consequence the upfield peaks as ArH2b/ArH4b.
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26 Due to the sharper OH resonance found for the thiacalix[4]arene tricarboxylic ester (**15**), with respect to the corresponding thiacalix[4]arene tricarboxylic acid (**7**), compound **15** was used to assign their conformation.
27 Due to the lack of differences in extraction behavior, described in ref. 17 for the competition of Mg^{2+} cations,only Ca^{2+}, Sr^{2+}, and Ba^{2+} were used as competing cations in this work.
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29 To determine whether pentadecanoic acid is lipophilic enough to remain in the organic phase, its presence in the organic phase was verified with ^1H NMR spectroscopy after extraction with a tris-HCl buffer of pH 8.9. Furthermore, clear organic/aqueous phase separation was obtained after the extraction experiments.
30 Thiacalix[4]crown-5 and -6 (**1a,b**) alone did not give any $^{226}Ra^{2+}$ extraction under the conditions studied.
31 At lower salt concentrations ($<10^{-3}$ M) a third phase was observed with these ionophores.
32 Since the thiacalix[4]crowns (**1a,b**) showed no $^{226}Ra^{2+}$ affinity under the standard conditions used, their extraction constants for Ca^{2+}, Sr^{2+}, and Ba^{2+} were not determined.
33 Since the concentration of $[^{226}Ra^{2+}]_{org}$ can maximally be 2.9×10^{-8} M, compared to a [L] of 10^{-4} M, the selectivity coefficients are not influenced by the fact that p_{Ra} is determined by $[^{226}Ra^{2+}]_{org}/([^{226}Ra^{2+}]_{org} + [^{226}Ra^{2+}]_{aq})$, rather than $[^{226}Ra]_{org}/[^{226}Ra^{2+}]_{tot}$. The precipitation of $^{226}Ra^{2+}$ salts does not influence the selectivity coefficients obtained and as such is not discussed.
34 The relatively high $^{226}Ra^{2+}$ selectivity coefficients are mainly caused by the low Ba^{2+} extraction constants.
35 Partial cone thiacalix[4]crown-6 monocarboxylic acid (**5**) shows NOE cross peaks between the *t*-butyl3 resonances of the inversed aromatic unit of the thiacalix[4]arene and the crown-ether bridge,

while its [Ba(**5**)Pic] complex does not. Nonetheless, NOE interactions between the resonances of the methylene group adjacent to the carboxylic acid moiety and ArH2 and ArH4 (strong) and *t*-butyl2 and *t*-butyl4 (weak) resonances, still confirm the partial cone conformation. Furthermore, the ArH2b and ArH4b peaks shift down field significantly (0.3 ppm) for the [Ba(**5**)Pic] complex. These NMR data suggest outward rotation of the *t*-butyl1 peak, to allow for inward rotation of the carboxylic acid group. To the best of our knowledge this is the first example that in the partial cone conformation a carboxylic acid moiety rotates into the cavity to interact with a cation at the other side of the thiacalix[4]arene platform (see ESI†).

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