

# Synthesis and binding properties of calix[4]arene diamide dicarboxylic acids

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Calix[4]arenes diametrically substituted at the lower rim with two carboxylic acid and two tertiary amide binding groups were obtained in good yields and their acid–base properties studied in methanol solution. Complexation studies, performed in methanol by potentiometry, show that mononuclear ( $MLH_z$ ,  $z = 0, 1$ ) or dinuclear ( $M_2L$ ) complexes are formed with alkali metal cations, whereas  $M_xL_zH_z$  ( $x = 1, 2$ ,  $z = 0, 1$ ) species, involving two ligands, are also present with alkaline-earth cations. Both ligands **2** and **3** show a remarkable selectivity for  $Ca^{2+}$  and  $Sr^{2+}$  among alkali and alkaline-earth metal ions.

## Introduction

A rational approach towards the design of ligands for the selective complexation of metal ions is highly desirable and fundamental both in coordination and supramolecular chemistry.<sup>1</sup> Important medicinal and technological areas<sup>2</sup> such as, for example, the treatment of metal intoxication,<sup>3</sup> ligands for magnetic resonance<sup>4</sup> or radiochemical<sup>5</sup> imaging and for luminescent probes,<sup>4b,6</sup> radiotherapeutics,<sup>5a,7</sup> selective extractants in nuclear waste management,<sup>8,9</sup> may greatly benefit from such studies.

For several years, we have been engaged in the synthesis of calixarene-based ligands<sup>10</sup> for the selective complexation of metal ions and recently became interested in the treatment of wastes arising from the reprocessing of nuclear fuel. We have found that calixcrown-6 molecules are extremely selective towards caesium over sodium<sup>11</sup> and, to a lesser extent, towards strontium over sodium extraction,<sup>12</sup> so that their application to decategorization of medium-level waste (MLW) is currently under development. However a higher strontium over sodium selectivity is required. Previous studies have shown that the tetramide of *p*-tert-butylcalix[4]arene **1** (Fig. 1)

is an efficient ligand for alkaline-earth cations, but also strongly complexes sodium ions.<sup>13</sup> The HSAB principle<sup>14</sup> predicts that in order to complex hard cations such as alkaline-earth or trivalent lanthanide ions, the use of hard binding groups such as carboxylic acids is needed.<sup>1,15</sup> This is also clearly confirmed by a recent search in the Protein Database (PDB) which outlines that in calcium binding proteins, one to four carboxylate groups, acting as mono- or bi-dentate ligands, are bound to the metal ion.<sup>16</sup>

Several examples of calix[4]arenes bearing four,<sup>17,18</sup> three,<sup>19</sup> two<sup>10a,17a,18b,20</sup> or one<sup>18b,21</sup> carboxylic acid units at the lower rim have been reported in the literature, together with their binding properties. Recently, Shinkai and coworkers<sup>20a</sup> reported on the extraction properties of the diamide-diacid derivative **2** of *p*-tert-butylcalix[4]arene. This compound shows pH dependent extraction properties and high selectivity for calcium, with strontium being the second best extracted cation among the alkaline-earths. However, no complexation data in homogeneous solution, which could be useful to assess the divalent/monovalent selectivity of the ligand, have been reported. In our current efforts to develop new ligands showing a high  $Sr^{2+}/Na^+$  selectivity, we report

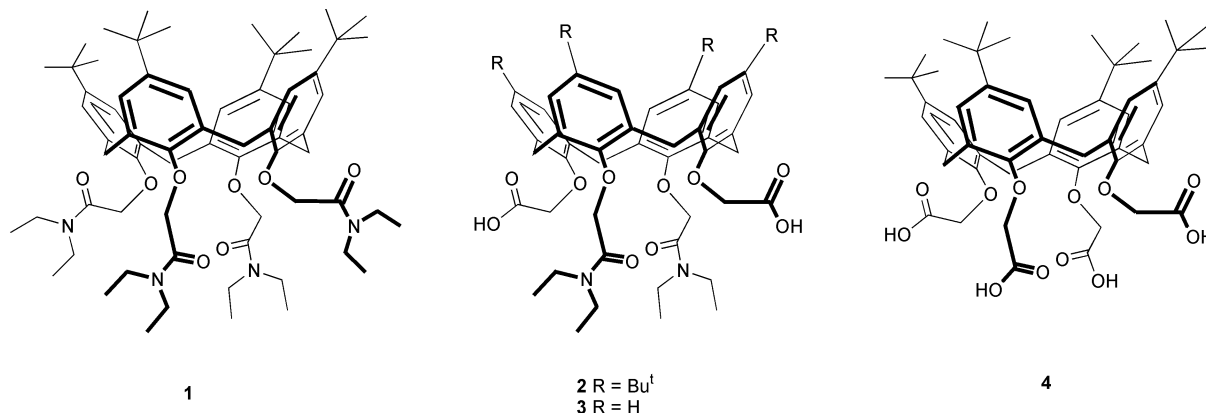


Fig. 1 The calix[4]arenes studied and related ligands.

here, the acid–base properties of the two diamide-diacids **2** and **3** derived from *p*-*tert*-butyl and *p*-dealkylated calix[4]arene, respectively, together with their binding properties in methanol towards alkali and alkaline-earth metal ions. A novel general synthesis for this class of ligands has also been developed.

## Results and discussion

### Synthesis of the ligands

The synthesis of ligands **2** and **3** was achieved by taking advantage of the easy 1,3-(distal) difunctionalization of calix[4]arenes at the lower rim.<sup>22</sup> We preferred to follow a different reaction procedure (Scheme 1) from that reported by Shinkai and coworkers<sup>20a</sup> for the synthesis of ligand **2**. We first prepared compounds **5** and **6**, as previously reported,<sup>23</sup> and subsequently alkylated them with  $\alpha$ -bromoethyl acetate. This reaction was conveniently carried out with  $\text{Na}_2\text{CO}_3$  as the base in dry acetone, at reflux for 3 days. The use of sodium instead of potassium carbonate is due to the fact that reaction with the latter base produced a mixture of different stereoisomers (cone, partial cone and 1,3-alternate). A base having sodium as counter ion is necessary in the alkylation step to obtain exclusively the cone isomer.<sup>22</sup> Although this reaction requires refluxing for three days, it is very convenient since it gives the diesters **7** and **8** in good yields (70%) and with complete stereoselectivity for the cone conformation. This is proven by the presence of only an AX system for the  $\text{ArCH}_2\text{Ar}$  protons ( $\delta \approx 3.2$  and 4.9) in the  $^1\text{H}$  NMR spectra of compounds **7** and **8** and by only one triplet for the corresponding carbon around  $\delta$  32.0, in the  $^{13}\text{C}$  NMR spectra.<sup>24</sup> Subsequent hydrolysis to the diacids **2** and **3** was performed using different conditions such as KOH in  $\text{MeOH-H}_2\text{O}$ ,  $\text{NBu}_4\text{OH}$  in THF or  $\text{K}_2\text{CO}_3$  in  $\text{H}_2\text{O-MeOH}$ . The first reaction conditions are too strong and often also afforded partial hydrolysis of the amide bonds, while the second are too mild and required very long reaction times. We found that the use of  $\text{K}_2\text{CO}_3$  in  $\text{H}_2\text{O-MeOH}$  is to be preferred since it rapidly gives the desired diacids **2** and **3** in quantitative yields.

### Acid–base properties of the ligands

The stepwise protonation constants of the carboxylate forms of the ligands, evaluated using the equation  $K_i = [\text{LH}_i^{(2-i)-}]/([\text{LH}_{i-1}^{(3-i)-}][\text{H}^+])$ , with  $1 \leq i \leq 2$  are given in Table 1. The notation  $\log K_i$ , instead of the acidity  $\text{p}K_a$  values, is preferred for the sake of consistency because they are formation constants similar to the complexation stability constants given below. The two notations are linked by the relationship:  $\text{p}K_{a_i} = \log K_{2-i+1}$ .

For diacid-diamide ligands **2** and **3**,  $\log K_2$  (ca. 8.4) and  $\log K_1$  (ca. 10.3) are slightly higher than the values found for the tetraacid **4** ( $\log K_4 = 8.25$  and  $\log K_3 = 9.19$ ) but lower than those found for the diacid di-*tert*-butylester ( $\log K_2 = 9.5$  and  $\log K_1 = 11.4$ ).<sup>18b</sup> The similarity, within the experimental

**Table 1** Stepwise protonation constants ( $\log K_i \pm \sigma_{n-1}$ ) of the ligands in methanol [ $T = 25^\circ\text{C}$ ,  $I = 0.05 \text{ M}$  ( $\text{NEt}_4\text{ClO}_4$ )]

<i>i</i>	Ligand		
	<b>2</b>	<b>3</b>	<b>4</b> <sup>a</sup>
1	$10.31 \pm 0.02$	$10.22 \pm 0.08$	13.39
2	$8.38 \pm 0.06$	$8.5 \pm 0.2$	10.89
3	—	—	9.19
4	—	—	8.25

<sup>a</sup> From ref. 18b.

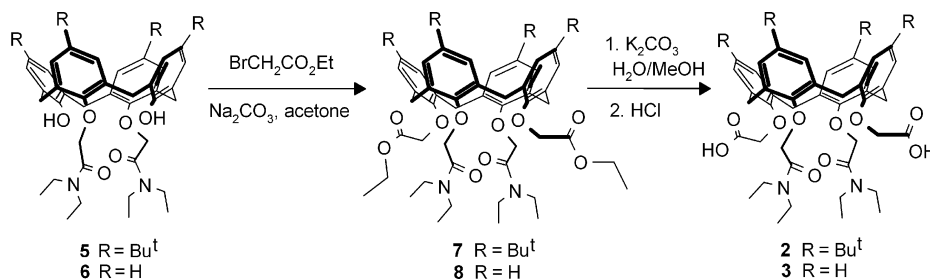
error, of  $\log K_1$  and  $\log K_2$  for ligands **2** and **3** shows no significant influence from the *tert*-butyl groups in the *para* positions, on the acid–base behaviour.

### Complexation studies

The logarithms of the overall apparent stability constants  $\beta_{xyz}$ , expressed as the concentration quotients  $[\text{M}_x\text{L}_y\text{H}_z^{(xm-2y+z)+}]/([\text{M}^{m+}]^x[\text{L}^{2-}]^y[\text{H}^+]^z)$ , are given in Table 2 for alkali and alkaline-earth metal ions.

**Alkali metal ions.** For alkali metal ions, the position of the inflection point in the titration curves at 2 equivalents of base for  $C_M/C_L = 1$  indicates the participation of the two carboxylate groups in the complexation. Mononuclear  $\text{ML}^-$  and dinuclear  $\text{M}_2\text{L}$  complexes were found with the two ligands and all the cations, whereas the  $\text{MLH}$  complex was evidenced only with **2** and  $\text{Na}^+$ . The formation of the latter species can be explained by assuming the coordination of the cation to the two amides and to one carboxylate group, while the second carboxylate remains protonated. With the exception of sodium complexes, the 1 : 1 ( $\text{ML}^-$ ) complexes are generally more stable than their analogues with tetradiethylamide derivative **1**. However, they are much less stable than those with the tetracarboxylate derivative **4** (see Table 2). As already seen for the acid–base properties of these ligands, the presence of *tert*-butyl groups at the upper rim does not cause any important differences either on the stoichiometry of the complexes or on their stability, although the dinuclear complexes of  $\text{K}^+$  and  $\text{Cs}^+$  with **2** are more stable than with **3**.

In order to compare the complexing power of the two ligands towards each metal, independently of the type of complexes formed, the calculated percentage of free metal ion was plotted vs. pH (Fig. 2). Both ligands **2** and **3** complex alkali metal ions already at pH 7 and at pH 8, ca. 75% of the total amount of  $\text{K}^+$  and 35% of the  $\text{Na}^+$  are complexed by **2**, whereas, at the same pH, only 40% of the total amount of  $\text{Na}^+$  and 20% of the  $\text{K}^+$  are complexed by **3**. Although this result suggests that the complexation properties do not depend solely on the size complementarity between the hydrophilic cavity and the metal ion, which is the predominant factor in complexation with calix[4]arene amides or esters,<sup>10b</sup> a moderate selectivity of **2** for  $\text{K}^+$  and of **3** for  $\text{Na}^+$  was shown.



**Scheme 1**

**Table 2** Overall stability constants ( $\log \beta_{xyz} \pm \sigma_{n-1}$ )<sup>a</sup> of alkali and alkaline-earth metal ion complexes in methanol [ $T = 25^\circ\text{C}$ ,  $I = 0.05\text{ M}$  ( $\text{NEt}_4\text{ClO}_4$ )]

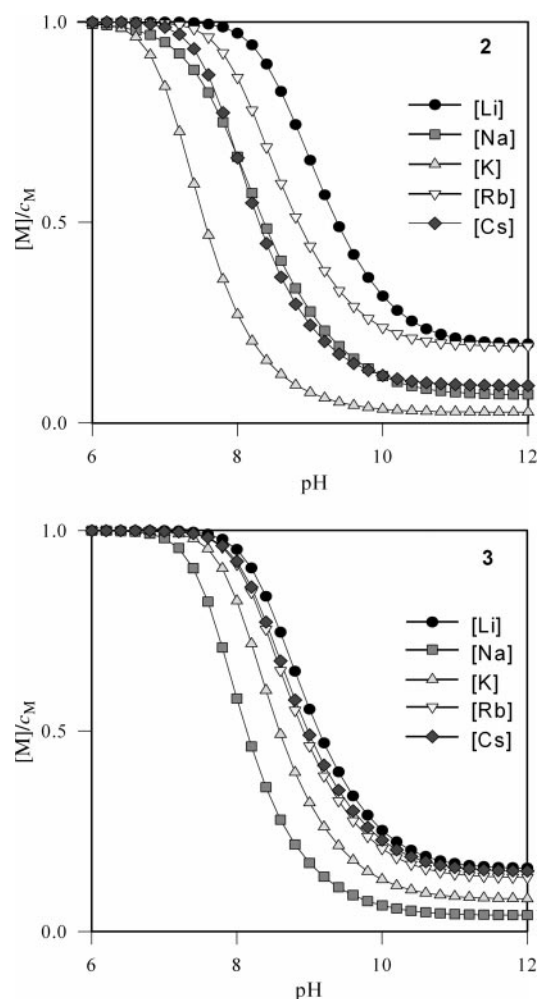
Cation	xyz	Species	2	3	1 <sup>b</sup>	4 <sup>c</sup>
Li <sup>+</sup>	110	ML <sup>-</sup>	4.32 ± 0.05	4.28 ± 0.02	3.9	7.89
	210	M <sub>2</sub> L	—	7.11 ± 0.01	—	—
Na <sup>+</sup>	110	ML <sup>-</sup>	4.59 ± 0.03	4.6 ± 0.1	7.9	9.94
	111	MLH	13.41 ± 0.08	—	—	20.61
K <sup>+</sup>	210	M <sub>2</sub> L	8.15 ± 0.02	8.71 ± 0.06	—	—
	110	ML <sup>-</sup>	4.81 ± 0.02	4.89 ± 0.07	5.8	9.05
Rb <sup>+</sup>	210	M <sub>2</sub> L	9.10 ± 0.03	7.74 ± 0.06	—	—
	110	ML <sup>-</sup>	3.78 ± 0.02	4.23 ± 0.01	3.8	7.72
Cs <sup>+</sup>	210	M <sub>2</sub> L	7.13 ± 0.06	7.44 ± 0.09	—	—
	110	ML <sup>-</sup>	3.2 ± 0.2	3.1 ± 0.2	2.4	6.2
Mg <sup>2+</sup>	210	M <sub>2</sub> L	8.35 ± 0.03	7.50 ± 0.07	—	—
	110	ML	—	6.42 ± 0.07	1.2	11.02
	221	M <sub>2</sub> L <sub>2</sub> H <sup>+</sup>	11.62 ± 0.01	9.97 ± 0.03	—	—
Ca <sup>2+</sup>	221	M <sub>2</sub> L <sub>2</sub> H <sup>+</sup>	—	25.13 ± 0.05	—	—
	110	ML	9.96 ± 0.03	9.9 ± 0.1	≥ 9	22.44
	111	MLH <sup>+</sup>	16.85 ± 0.05	16.7 ± 0.2	—	30.24
	210	M <sub>2</sub> L <sub>2</sub> <sup>2+</sup>	15.43 ± 0.07	13.58 ± 0.01	—	—
Sr <sup>2+</sup>	221	M <sub>2</sub> L <sub>2</sub> H <sup>+</sup>	31.6 ± 0.1	31.69 ± 0.02	—	—
	110	ML	10.78 ± 0.02	9.93 ± 0.02	≥ 9	20.92
	111	MLH <sup>+</sup>	16.36 ± 0.04	16.22 ± 0.03	—	28.69
	210	M <sub>2</sub> L <sub>2</sub> <sup>2+</sup>	14.68 ± 0.07	12.7 ± 0.1	—	—
Ba <sup>2+</sup>	221	M <sub>2</sub> L <sub>2</sub> H <sup>+</sup>	30.9 ± 0.2	30.63 ± 0.03	—	—
	110	ML	9.6 ± 0.1	8.95 ± 0.02	7.2	17.96
	120	ML <sub>2</sub> <sup>2-</sup>	16.38 ± 0.04	14.12 ± 0.09	—	—
	121	ML <sub>2</sub> H <sup>-</sup>	25.23 ± 0.02	23.63 ± 0.02	—	—
	221	M <sub>2</sub> L <sub>2</sub> H <sup>+</sup>	—	28.61 ± 0.04	—	—

<sup>a</sup> Arithmetic mean of  $n \geq 4$  determinations;  $\sigma_{n-1}$ : standard deviation on the mean. <sup>b</sup> From ref. 13a. <sup>c</sup> Other protonated species (MLH<sub>n</sub>) were observed [from ref. 18b].

**Alkaline-earth metal ions.** The inflection points in the titration curves with all alkaline-earth metal ions are moved to lower pH than in those of the ligands alone, thus suggesting the formation of very stable complexes. The shift to acidic pH of these points is in the order:  $\text{Ca}^{2+} \approx \text{Sr}^{2+} > \text{Ba}^{2+} > \text{Mg}^{2+}$ . Moreover, the presence of several inflection points suggests the formation of different complex species. With  $\text{Ca}^{2+}$  and  $\text{Sr}^{2+}$ , there is always formation of ML, MLH<sup>+</sup>, M<sub>2</sub>L<sup>2+</sup> and M<sub>2</sub>L<sub>2</sub>H<sup>+</sup> complexes. The existence of the latter species, whose formation reaches at least 20% of the total metal ion concentration, was suggested by the presence of an inflection point at 1.5 equivalents of base in the titration curves for  $C_M/C_L = 1$ . Complexes containing two ligands and two cations have already been found with alkali or alkaline-earth metal ions and calix[4]arene carboxylic acid derivatives both in solution and in the solid state.<sup>21a</sup> With  $\text{Mg}^{2+}$  and **3**, no MLH<sup>+</sup> species is found, whereas only a M<sub>2</sub>L<sup>2+</sup> species is detected with **2**. With  $\text{Ba}^{2+}$ , there is evidence for ML<sub>2</sub><sup>2-</sup> and ML<sub>2</sub>H<sup>-</sup> complexes instead of MLH<sup>+</sup> and M<sub>2</sub>L<sup>2+</sup>. The formation of biligand species is in agreement with the larger size of this cation and has already been demonstrated in extraction experiments with calixarene carboxylate derivatives.<sup>25</sup>

As with alkali metal ions, the absence of *tert*-butyl groups in *para* positions does not produce any drastic changes in the stoichiometry of the complexes. However it leads to significant differences in the stabilities of the complexes which are well illustrated by the distribution curves of both ligands **2** and **3** in the presence of 1 equivalent of  $\text{Sr}^{2+}$  (Fig. 3). These curves show that about 25% of the total metal is involved in the protonated species  $\text{Sr}_2\text{L}_2\text{H}^+$  with **2**, instead of 70% with **3**. The dinuclear neutral complex  $\text{Sr}_2\text{L}_2$  is formed at 40% with **2**, whereas its formation is negligible (< 5%) in these conditions with **3**. The neutral species ML is predominant and totally formed above pH 9 with both ligands.

The percentages of free metal ions as a function of pH in methanol (Fig. 4) for **2** and **3** emphasise the high affinity of these ligands for alkaline-earth cations, in particular for  $\text{Ca}^{2+}$  and  $\text{Sr}^{2+}$ , which are quantitatively complexed at pH 6–7.  $\text{Ca}^{2+}$  is slightly better complexed than  $\text{Sr}^{2+}$ . At pH 4.5 and



**Fig. 2** Fraction of calculated free alkali metal ion concentration vs. pH for ligands **2** and **3** ( $C_M = C_L = 10^{-3}\text{ mol dm}^{-3}$ ).

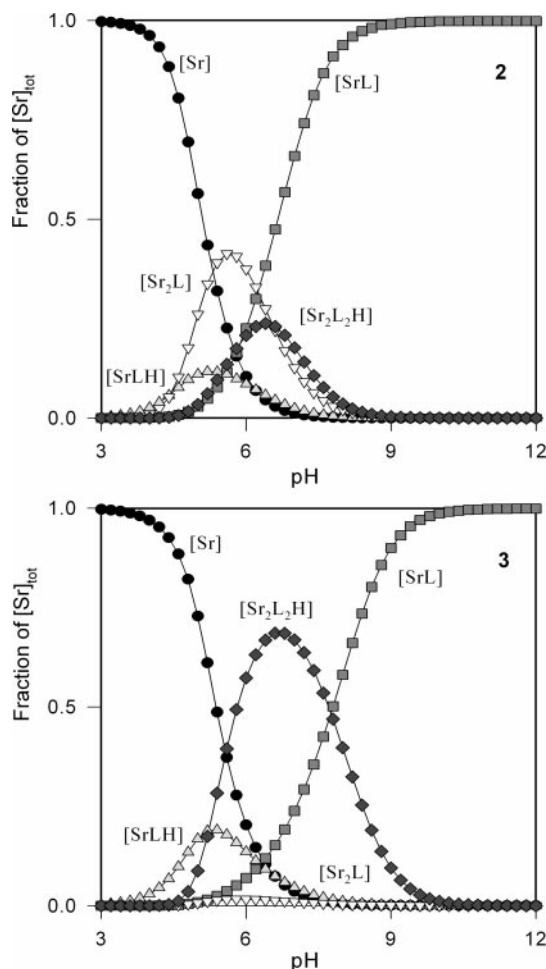


Fig. 3 Distribution curves of strontium complexes with ligands 2 and 3 ( $C_M = C_L = 10^{-3} \text{ mol dm}^{-3}$ ).

$C_M/C_L = 1$ , **2** complexes 50% of the total amount of calcium, 25% of the strontium and 0% of the magnesium and barium ions. These results are consistent with the high extraction selectivity of **2** for  $\text{Ca}^{2+}$  previously shown by Shinkai and coworkers.<sup>20a</sup> The affinity of ligands **2**, **3** and **4** for  $\text{Ca}^{2+}$  and  $\text{Sr}^{2+}$  can be evaluated from the percentages of free metal ion in solution as a function of pH, leading to the following order:  $4 > 2 > 3$  for  $\text{Ca}^{2+}$  and  $2 \approx 4 > 3$  for  $\text{Sr}^{2+}$ .

It is interesting to note, by comparison of the curves in Fig. 2 and 4, that both ligands **2** and **3** present a very high  $\text{Sr}^{2+}/\text{Na}^{+}$  selectivity in the pH range 5–7, as they complex  $\text{Sr}^{2+}$  but not  $\text{Na}^{+}$ .

In conclusion, we have reported the synthesis of two calix[4]arene ligands bearing mixed tertiary amides and carboxylic acids at the lower rim. These compounds show a remarkable selectivity for alkaline-earth ( $\text{Ca}^{2+} \approx \text{Sr}^{2+} \gg \text{Ba}^{2+} > \text{Mg}^{2+}$ ) over alkali metal ions. The high  $\text{Sr}^{2+}/\text{Na}^{+}$  selectivity looks promising especially for the treatment of nuclear waste in weakly acidic or basic conditions.<sup>26</sup>

## Experimental

### General

Melting points were determined on an electrothermal apparatus in sealed capillaries under nitrogen atmosphere.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with an AC300 ( $^1\text{H}$ : 300 MHz,  $^{13}\text{C}$ : 75 MHz) using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Mass spectra were obtained in ESI or CI ( $\text{CH}_4$ ) mode on

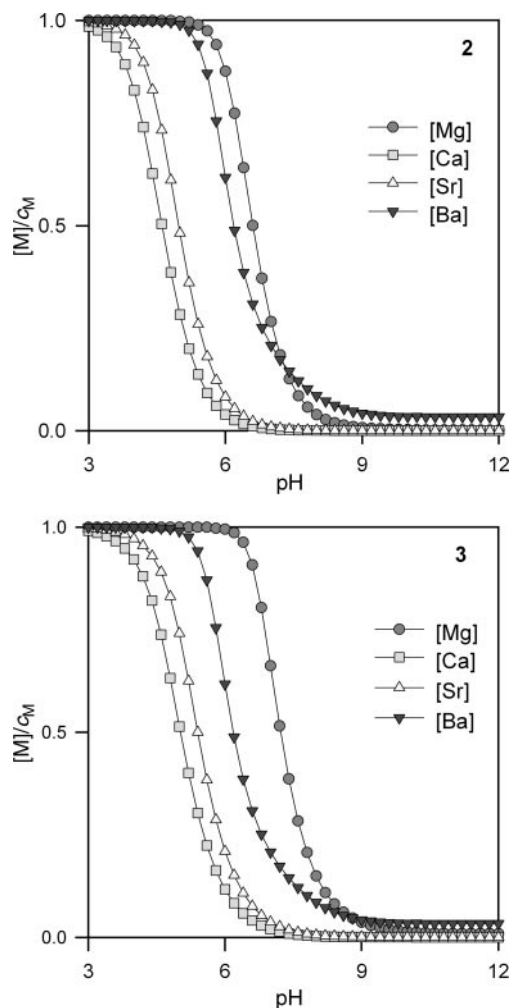


Fig. 4 Fraction of calculated free alkaline-earth metal ion concentration vs. pH for ligands 2 and 3 ( $C_M = C_L = 10^{-3} \text{ mol dm}^{-3}$ ).

a Finnigan Mat SSQ710 instrument. TLC were performed on precoated silica gel plates Merck 60 F<sub>254</sub>. All solvents were purified with standard procedure; dry solvents were obtained by literature methods and stored over molecular sieves. All the reactions were carried out under nitrogen atmosphere. As verified by others,<sup>27</sup> the elemental analysis of calixarenes are very often incorrect because of the inclusion of solvent molecules and can not be considered an appropriate criterion of purity; nevertheless, the identity of the compounds reported has been proven by their spectral data.

### 5,11,17 23-Tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)-methoxy]-26,28-bis[(*N,N*-diethylaminocarbonyl)-methoxy]calix[4]arene **7**

A solution of 0.50 g (0.57 mmol) of diamide **5** and of 0.48 g (4.6 mmol) of  $\text{Na}_2\text{CO}_3$  was stirred under nitrogen in dry acetone (25 ml) at reflux temperature and 30 min later 0.51 ml (4.6 mmol) of ethyl bromoacetate were added. After 3 days the reaction mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was dissolved in 20 ml of  $\text{CH}_2\text{Cl}_2$  and 10% HCl (10 ml), the organic layer separated and then washed with 10% HCl ( $3 \times 10 \text{ ml}$ ). The organic phase was separated and dried over  $\text{MgSO}_4$ . Pure product **7** (0.42 g, 70%) was obtained by crystallisation from a mixture of ethyl ether and hexane. Mp 197–199 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  1752 (OC=O) and 1653 (NC=O);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 0.96 [18 H, s,  $\text{C}(\text{CH}_3)_3$ ], 1.13 [12 H, t,  $J$  5.8,  $\text{NCH}_2\text{CH}_3$ ], 1.16 [18 H, s,  $\text{C}(\text{CH}_3)_3$ ], 1.23 [6 H, t,  $J$  7.1,  $\text{OCH}_2\text{CH}_3$ ], 3.18 (4H, d,  $J$  12.9,  $\text{ArCH}_{\text{eq}}\text{Ar}$ ), 3.38 (8 H, q,  $J$

5.8, NCH<sub>2</sub>CH<sub>3</sub>), 4.13 (4 H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>) 4.73 (4 H, s, OCH<sub>2</sub>CO), 4.94 (4 H, d, *J* 12.9 Hz, ArCH<sub>ax</sub>Ar), 4.99 (4 H, s, OCH<sub>2</sub>CO), 6.62 (4 H, s, ArH), 6.89 (4 H, s, ArH);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 13.1 (q, OCH<sub>2</sub>CH<sub>3</sub>), 14.2, 14.4 (q, NCH<sub>2</sub>CH<sub>3</sub>), 31.3, 31.5 [q, C(CH<sub>3</sub>)<sub>3</sub>], 32.1 (t, ArCH<sub>2</sub>Ar), 33.7, 33.9 [s, C(CH<sub>3</sub>)<sub>3</sub>], 39.9, 41.2 (t, NCH<sub>2</sub>CH<sub>3</sub>), 59.9 (t, OCH<sub>2</sub>CH<sub>3</sub>), 70.9, 72.4 (t, OCH<sub>2</sub>CO), 125.1, 125.5 (d, Ar *meta*), 132.7, 134.2 (s, Ar *ortho*), 144.7, 144.9 (s, Ar *para*), 153.5 (s, Ar *ipso*), 168.4 (s, OCO), 171.2 (s, NCO); MS-Cl: *m/z* 1048 (100, M + 1).

### 25,27-Bis[(ethoxycarbonyl)methoxy]-26,28-bis[(*N,N*-diethylaminocarbonyl)methoxy]calix[4]arene 8

Compound **8** was prepared following the same procedure as for compound **7** and obtained by crystallisation (70%) from diethyl ether. Mp 193–196 °C;  $\nu_{\max}/\text{cm}^{-1}$  1755 (OC=O) and 1657 (NC=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 1.13 (6 H, t, *J* 7.1, NCH<sub>2</sub>CH<sub>3</sub>), 1.17 (6 H, t, *J* 7.1, NCH<sub>2</sub>CH<sub>3</sub>), 1.25 (6 H, t, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 3.23 (4H, d, *J* 13.8, ArCH<sub>eq</sub>Ar), 3.39 (8 H, q, *J* 7.1, NCH<sub>2</sub>CH<sub>3</sub>), 4.13 (4H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 4.62 (4 H, s, OCH<sub>2</sub>CO), 4.87 (4 H, s, OCH<sub>2</sub>CO), 4.93 (4 H, d, *J* 13.8, ArCH<sub>ax</sub>Ar), 6.28 (4 H, d, *J* 6.7, ArH *meta*), 6.36 (2 H, t, *J* 6.7, ArH *para*), 6.79 (2 H, t, *J* 6.7, ArH *para*), 6.92 (4 H, d, *J* 6.7 Hz, ArH *meta*);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 13.0 (q, OCH<sub>2</sub>CH<sub>3</sub>), 14.2, 14.4 (q, NCH<sub>2</sub>CH<sub>3</sub>), 31.6 (t, ArCH<sub>2</sub>Ar), 39.9, 41.2 (t, NCH<sub>2</sub>CH<sub>3</sub>), 60.1 (t, OCH<sub>2</sub>CH<sub>3</sub>), 70.9, 72.6 (t, OCH<sub>2</sub>CO), 122.5, 122.7 (d, Ar *para*), 128.0, 129.0 (d, Ar *meta*), 133.6, 135.9 (s, Ar *ortho*), 155.9, 156.8 (s, Ar *ipso*), 167.8 (s, OCO), 170.7 (s, NCO); MS-ESI: *m/z* 824 (100, M + 1).

### 5,11,17 23-Tetra-*tert*-butyl-25,27-bis(carboxymethoxy)-26,28-bis[(*N,N*-diethylaminocarbonyl)methoxy]calix[4]arene 2

A solution of K<sub>2</sub>CO<sub>3</sub> (0.66 g, 4.8 mmol) in water (4 ml) was added to a refluxing solution of compound **7** (0.5 g, 0.48 mmol) in MeOH (30 ml). After 2 h the mixture was cooled to room temperature and the organic solvent removed under reduced pressure. Water (150 ml) was added and the pH was adjusted to about 2 with 1 M HCl. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 ml) to give, after the evaporation of the solvent, pure **2** as a white solid (0.43 g, 90%). Mp 255–257 °C;  $\nu_{\max}/\text{cm}^{-1}$  1757 (OC=O) and 1655 (NC=O);  $\delta_H$ (300 MHz; CDCl<sub>3</sub>) 0.86 [18 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.17 (12 H, t, *J* 7.0, NCH<sub>2</sub>CH<sub>3</sub>), 1.31 [18 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.27 (4H, d, *J* 13.0, ArCH<sub>eq</sub>Ar), 3.33 (4 H, q, *J* 7.0, NCH<sub>2</sub>CH<sub>3</sub>), 3.41 (4 H, q, *J* 7.0, NCH<sub>2</sub>CH<sub>3</sub>), 4.57 (4 H, s, OCH<sub>2</sub>CO), 4.61 (4 H, d, *J* 13.0 Hz, ArCH<sub>ax</sub>Ar), 4.77 (4 H, s, OCH<sub>2</sub>CO), 6.60 (4 H, s, ArH), 7.12 (4 H, s, ArH);  $\delta_C$ (75 MHz; CDCl<sub>3</sub>) 12.9, 14.5 (q, NCH<sub>2</sub>CH<sub>3</sub>), 31.0 (t, ArCH<sub>2</sub>Ar), 31.3, 31.6 [q, C(CH<sub>3</sub>)<sub>3</sub>], 33.7, 34.1 [s, C(CH<sub>3</sub>)<sub>3</sub>], 40.7, 41.7 (t, NCH<sub>2</sub>CH<sub>3</sub>), 72.7, 72.8 (t, OCH<sub>2</sub>CO), 125.4, 126.0 (d, Ar *meta*), 132.2, 134.7 (s, Ar *ortho*), 146.0, 146.8 (s, Ar *para*), 151.3, 153.1 (s, Ar *ipso*), 167.3 (s, OCO), 170.6 (s, NCO); MS-Cl: *m/z* 991 (60, M + 1).

### 25,27-Bis(carboxymethoxy)-26,28-bis[(*N,N*-diethylaminocarbonyl)methoxy]calix[4]arene 3

The product **3** was prepared following the same procedure as for compound **2** and obtained as a white solid (95%). Mp 229–231 °C;  $\nu_{\max}/\text{cm}^{-1}$  1749 (OC=O) and 1653 (NC=O);  $\delta_H$ (300 MHz; CD<sub>3</sub>OD) 1.16 (6 H, t, *J* 7.3, NCH<sub>2</sub>CH<sub>3</sub>), 1.19 (6 H, t, *J* 7.3, NCH<sub>2</sub>CH<sub>3</sub>), 3.27 (4H, d, *J* 12.9, ArCH<sub>eq</sub>Ar), 3.40 (8 H, q, *J* 7.3, NCH<sub>2</sub>CH<sub>3</sub>), 3.43 (8 H, q, *J* 7.3, NCH<sub>2</sub>CH<sub>3</sub>), 4.72 (4 H, s, OCH<sub>2</sub>CO), 4.75 (4 H, s, OCH<sub>2</sub>CO), 4.87 (4 H, d, *J* 12.9, ArCH<sub>ax</sub>Ar), 6.49 (2 H, t, *J* 7.3, ArH *para*), 6.56 (4 H, d, *J* 7.3, ArH *meta*), 6.85 (2 H, t, *J* 7.3, ArH *para*), 7.02 (4 H, d, *J* 7.3 Hz, ArH *meta*);  $\delta_C$ (75 MHz; CD<sub>3</sub>OD) 11.5, 12.9 (q, NCH<sub>2</sub>CH<sub>3</sub>), 30.4 (t, ArCH<sub>2</sub>Ar), 40.0, 41.4 (t, NCH<sub>2</sub>CH<sub>3</sub>), 71.2, 72.3 (t, OCH<sub>2</sub>CO), 122.7, 123.1 (d, Ar *para*), 128.0, 128.6 (d, Ar *meta*), 133.4, 135.1 (s, Ar *ortho*), 154.6, 155.4 (s, Ar *ipso*), 166.2 (s, OCO), 171.4 (s, NCO); MS-Cl: *m/z* 767 (70, M + 1).

## Physicochemical measurements

**Materials.** The solvent methanol (Carlo Erba, max. 0.01% water) was used without any further purification. The ionic strength was held constant at  $5 \times 10^{-2}$  M by addition of NEt<sub>4</sub>ClO<sub>4</sub> (Acros) twice recrystallised from bidistilled water and dried under vacuum for 24 h at room temperature. The titrant base used was NEt<sub>4</sub>OH made from dilution of the commercial solution (25% in MeOH, Fluka) and standardised against potassium acid phthalate. The metallic salts were chosen according to their solubilities in the solvent: LiCl (Fluka, purum), NaCl (Merck, p.a.), KCl (Merck, p.a.) RbCl (Fluka, puriss.), CsCl (Merck, p.a.), Mg(ClO<sub>4</sub>)<sub>2</sub> · xH<sub>2</sub>O (Merck, p.a.), Ca(ClO<sub>4</sub>)<sub>2</sub> · 4H<sub>2</sub>O (Fluka, purum), SrCl<sub>2</sub> · 6H<sub>2</sub>O (Aldrich, 99%), Sr(NO<sub>3</sub>)<sub>2</sub> (Merck, p.a.), Ba(ClO<sub>4</sub>)<sub>2</sub> (Prolabo, rectapur). All these salts were dried under vacuum for 24 h before use. The stock solutions of all the alkaline-earth metal ions were standardised by complexometric titrations with EDTA in the presence of the appropriate indicator.<sup>28</sup>

The ligands were used as the free acids. Their solutions were made from dissolution of a known quantity in methanol.

**Stability constant determination.** Stability constants were determined potentiometrically using a competitive method with the proton. The concentrations of free hydrogen ions, [H<sup>+</sup>], were measured using a combined glass electrode (Ingold) connected to an automatic titrator (Titroprocessor Mettler) at 25 °C. The standard filling solution (saturated aqueous KCl) of the external reference of the combined glass electrode was replaced by a solution of 0.04 M NEt<sub>4</sub>ClO<sub>4</sub> + 0.01 M NEt<sub>4</sub>Cl in MeOH saturated with AgCl. The electrode was calibrated at pH =  $-\log[H^+] = 2$  with a solution of  $10^{-2}$  M HClO<sub>4</sub> in MeOH obtained by dilution of the commercial concentrated *ca.* 11.6 M perchloric acid. As the junction potentials vary exponentially with  $-\log[H^+]$ , the following correction relationship was used:

$$-\log[H^+]_{\text{real}} = -\log[H^+]_{\text{meas}} + a + b[H^+]_{\text{meas}}$$

The parameters *a* and *b* were determined by measuring the pH of a methanolic solution of  $10^{-3}$  M HClO<sub>4</sub> in the presence of  $4.9 \times 10^{-2}$  M NEt<sub>4</sub>ClO<sub>4</sub> or by modelling the experimental titration curve of HClO<sub>4</sub> by a strong base (NEt<sub>4</sub>OH) through the program SIRKO.<sup>29</sup> The working solutions were made up as follows. Precise volumes of a stock solution of the metallic salt were added to 20 ml of a stock solution of ligand in methanol in 25 ml flasks. The ligand concentrations *C<sub>L</sub>* ranged from  $10^{-3}$  M to  $7.5 \cdot 10^{-4}$  M. 10 ml aliquots of these solutions (*I* = 0.05 M in NEt<sub>4</sub>ClO<sub>4</sub>) were titrated with NEt<sub>4</sub>OH in a thermostatted cell (25 ± 0.05 °C) under an atmosphere of argon. For each determination at least four experiments were performed with different metal/ligand concentration ratio ( $0.5 \leq C_M/C_L \leq 2$ ) to promote the formation of different species. The data have been interpreted by the program SIRKO, which refines the overall stability constants  $\beta_{xyz}$ . The protonation constants of the carboxylated forms of the ligands, obtained from titration of the ligand in the absence of metal ions, were set to fixed values during the refinement procedure. The autoprotolysis constant of methanol used for the calculations was  $pK_{\text{MeOH}} = 16.7$ .

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