Model studies toward trivalent cation binding by appropriately functionalized calix[4]arenes

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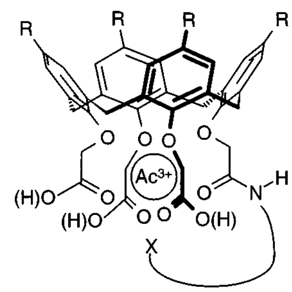
Molecular modeling and molecular dynamics of a series of calix[4]arene tetracarboxylic acids and tricarboxylic acid monoamides revealed that in an aqueous environment the phenolic oxygen atoms do not participate in the complexation of Ac^{3+}. This observation led to the design and synthesis of new calix[4]arene based ionophores, containing multiple glycine units, having an increased number of potential donor sites. Potentiometric titrations in methanol with La^{3+} as a non-radioactive model for Ac^{3+} indicated that, although the level of complexation is high for all ligands, a new calix[4]arene derivative **5** is superior at pH < 4.

Introduction

There is considerable interest in the development of ligands capable of binding radioisotopes, such as $^{225}Ac^{3+}$, being potentially a suitable candidate for radioimmunotherapy[1] with its half-life of 10 days and decay of short-lived α- and β-emitting radionuclides. The binding has to occur in an inert fashion, which means no decomplexation on the human timescale. A hitherto major drawback has been the lack of an adequate chelator for this isotope.[2,3] For its successful application in radioimmunotherapy, the chelator has to complex the radioisotope *in vivo* essentially irreversibly on the human timescale, even in the presence of the abundant serum cations [*e.g.* Ca^{2+} (1.26 mM), Mg^{2+} (0.8 mM), and Zn^{2+} (10^{-5} M)]. Otherwise the metal cation will be rapidly sequestered by serum proteins [*e.g.* transferrin (10^{-5} M) or albumin (10^{-3} M)] leading to irradiation of non-target sites.[4] To achieve such inert complexes, in the calix[4]arene at least three negative charges have to be present. Furthermore, the nine or ten coordination sites of the cation[5] have to be occupied by the ligand as much as possible, to prevent coordination of water molecules, which is often the first step in the decomplexation reaction.

In Fig. 1 the concept of complexation of Ac^{3+} by a calix[4]arene is presented. In addition to the three carboxylic acids, a fourth group at the *lower rim* is used to introduce an additional coordinating group (X in Fig. 1) in order to achieve a high number of coordination sites in the calix[4]arene based ligand **1**.



1 R = Bu^t or H

Fig. 1 Schematic representation of intended Ac^{3+} complexation by calix[4]arenes. X represents an additional coordination site.

Previously, this concept was developed in our group for the complexation of lanthanide ions in *organic media* by calix[4]arene tricarboxylic acid monoamides.[6] These neutral lanthanide complexes show a significantly enhanced luminescence lifetime compared with the free ions in solution, due to efficient shielding and coordination of only one or two methanol molecules to the cation. Computational techniques confirmed this mode of binding.[7] These results are relevant for the development of actinium binding agents, since La^{3+} is a suitable, non-radioactive model for Ac^{3+} (ionic radius of 1.045 Å for La^{3+} *vs.* 1.18 Å for Ac^{3+}).[5] Various calix[4]arene derivatives complex lanthanides but these are in most cases not soluble in water,[8] a prerequisite for *in vivo* applications. Only Ungaro and co-workers[9] reported water-soluble lanthanide–calix[4]arene tetraamide complexes of Tb^{3+} and Eu^{3+}. Recently our group[10] also described water-soluble calix[4]arene based lanthanide complexes and their luminescence properties.

In this paper we report simulations of trivalent cation binding by calix[4]arene based ionophores in water which have guided us in the design and synthesis of new ligands. Experimentally their cation binding properties were determined by potentiometric titrations.

Results and discussion

Simulations of calix[4]arene complexes with trivalent cations; development of a model for Ac^{3+}

Both molecular modeling (MM) and molecular dynamics (MD) can be used to study the behavior of (multiple) molecules. Fossheim and Dahl[11] reproduced the complexation energies of several Gd^{3+}·polyaminocarboxylate complexes, and Horrocks and co-workers[12] performed MM calculations on Eu^{3+}·polyaminocarboxylate complexes. MD studies of Eu^{3+}·calixarene complexes were reported by our group[7,13a] (in methanol) and by Wipff and co-workers[14] (in methanol, acetonitrile, and water).

A problem with simulations of Ac^{3+} or Ln^{3+} complexes is the absence of Lennard–Jones (van der Waals) parameters [σ and ε in eqn. (1)]. In principle one can use as a model Ca^{2+} for which the parameters are known together with a threefold positive charge,[7,13] or one can fit parameters to an X-ray crystal structure.[11] We describe here an approach[15] using free energy perturbation (FEP) calculations that reproduce the

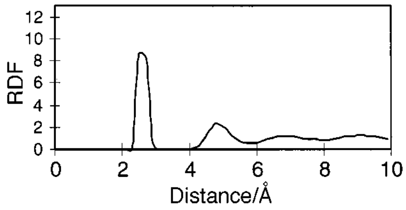


Fig. 2 Radial distribution function for the simulation of the model for Ac^{3+} in water at room temperature.

experimental free energy of hydration of Ac^{3+} by using appropriate Lennard–Jones parameters. The parameters so derived have been used in MM and MD studies of Ac^{3+} complexes of calix[4]arene tricarboxylic acid monoamides **1**. The results have guided us in the design and synthesis of a new generation of calix[4]arenes that are possible chelators for Ac^{3+}.

$$E_{\mathrm{vdW}} = \frac{A_{\mathrm{ij}}}{r_{\mathrm{ij}}^{12}} - \frac{B_{\mathrm{ij}}}{r_{\mathrm{ij}}^{6}} = 4\varepsilon\left[\left(\frac{\sigma}{r_{\mathrm{ij}}}\right)^{12} - \left(\frac{\sigma}{r_{\mathrm{ij}}}\right)^{6}\right] = \varepsilon\left[\left(\frac{R_{\mathrm{min}}}{r_{\mathrm{ij}}}\right)^{12} - 2\left(\frac{R_{\mathrm{min}}}{r_{\mathrm{ij}}}\right)^{6}\right] \quad (1)$$

The free energy of solvation, $\Delta G_{\mathrm{hydr}}(\mathrm{M}^{n+})$, was calculated from eqn. (2). The free energy $\Delta G_{\mathrm{FEP}}(\mathrm{M}^0\rightarrow\mathrm{M}^{3+})$ of charging the

$$\Delta G_{\mathrm{hydr}}(\mathrm{M}^{n+}) = \Delta G_{\mathrm{FEP}}(\mathrm{M}^0\rightarrow\mathrm{M}^{3+}) + \Delta G_{\mathrm{Born}} + \Delta G_{\mathrm{cav}} \quad (2)$$

particle was obtained by Monte Carlo free energy perturbation calculations, ΔG_{Born}[15,16] is simply a correction term for the applied finite cut-off,† and ΔG_{cav} represents the free energy needed for the formation of a "cavity" in water.[17] The electrostatic and van der Waals interactions have been computed with atom-based point charges and Lennard–Jones potentials, respectively. The Lennard–Jones parameters σ and ε were systematically varied to give estimates for Ac^{3+} and were further fine-tuned to give the correct ΔG_{hydr}.

An R_{min} value of 3.980 Å and an ε value of 0.055 kcal mol^{-1} give a ΔG_{hydr} of −778.1 kcal mol^{-1} with a standard deviation of 8.0 kcal mol^{-1}, while the experimentally determined value for Ac^{3+} is −774.9 kcal mol^{-1}.[5]

Evaluation of the suitability of this model was performed by an MD simulation of the cation in a 31 Å cubic water (TIP3P)[18] box. The radial distribution function (RDF) was calculated over 50 ps, and shows the first coordination peak centered at 2.63 Å (Fig. 2). This provides an indication of the distance of the water molecules to the cation (the oxygen atoms of the water molecules in the first hydration shell are positioned at an average distance of 2.63 Å from the cation) and of the number of water molecules in the hydration shells. The first coordination sphere contains ten water molecules, which is in accordance with the literature.[5] Furthermore, these results are in agreement with the RDF value for La^{3+} of 2.58 Å found in X-ray crystal structures.[19]‡

Molecular modeling and molecular dynamics

The fully deprotonated forms of calix[4]arenes **2a**–**d** were subjected to an MM study with this actinium model.§ Calix[4]arene tetracarboxylic acid **2a** is regarded as a possible analogue of 1,4,7,10-tetraazacyclododecanetetraacetic acid (DOTA), a well known ligand for lanthanide cations.[20] Simulations of propylamide **2b** allow the evaluation of the distortion of the symmetry compared to tetracarboxylic acid **2a**, without the introduction of extra potential donor groups, whereas the derivatives **2c** and **2d** do contain such donor groups. In Fig. 3 some examples are shown of typical results of the MM study.¶ A summary of the coordination distances and coordination numbers (the number of oxygen atoms that are positioned at a distance less than 3 Å from the cation) is given in Table 1.

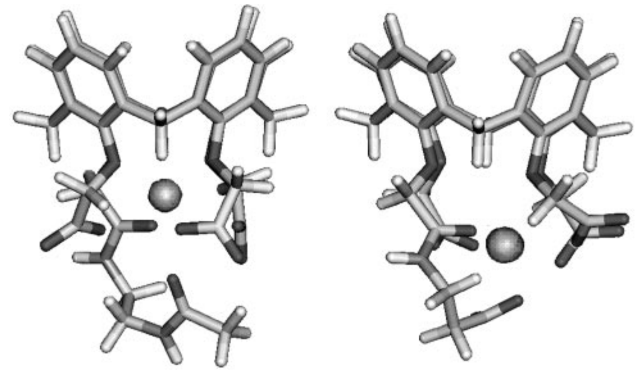
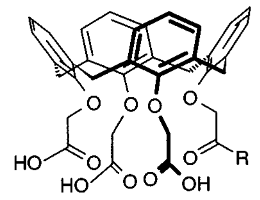


Fig. 3 Energy minimized structures. Left Ac^{3+}·**2c**; right Ac^{3+}·**2d**, for details see the Experimental section.§,¶



2a R = OH
2b R = $NHCH_2CH_2CH_3$
2c R = $NHCH_2CH_2NHC(O)CH_3$
2d R = $NHCH_2CH_2COOH$

In all cases the distance of the cation to the coordinating oxygen atoms of the carboxylic groups and the oxygen atom of the amido group are more or less equal. Larger differences are found for the distance of Ac^{3+} to the phenolic oxygen atoms. In two cases, namely calixarene tetracarboxylic acid **2a** and *N*-acetyl calixarene **2c**, the cation is indeed bound inside the cavity (see Fig. 1), as reflected in average coordination distances of the cation to the phenolic oxygen atoms smaller than 3 Å and a high coordination number. For the calixarene propylamide **2b** and the calixarene tetracarboxylic acid **2d**, the cation is positioned between the carboxylate groups, leading to a larger average distance to the phenolic oxygen atoms. For Ac^{3+}·**2d** this phenomenon is due to the negative charge on the amide side chain, that pulls the cation partially out of the cavity. In *N*-acetyl calixarene **2c** the amide side chain is one atom longer than in calix[4]arene propionic acid **2d**, which allows the acetyl carbonyl group to bend under the cavity and to coordinate better to the cation without pulling it out of the cavity. Due to the distortion of the symmetry in the *N*-propyl derivative **2b** the neutral amido group may position the cation closer to the carboxylate groups. Except in *N*-acetyl calixarene **2c** at least one of the carboxylate groups behaves as a bidentate ligand.

However, in all the MD simulations, the cation was partially pulled out of the cavity into the water layer surrounding the complex. Because of the relatively small partial negative charge

† Interactions further than a certain cut-off distance are not taken into account in the calculations.

‡ To the best of our knowledge the Cambridge Structural Database does not contain information about distances from Ac^{3+} to water molecules in crystal structures.

§ In all cases all carboxylic acid moieties of the calix[4]arenes are deprotonated.

¶ In the case of the negatively charged complexes of Ac^{3+} and calixarene tetracarboxylic acids **2a** and **2d**, a sodium cation is used to obtain a neutral ensemble. For reasons of clarity, the sodium cation is not shown in the figures. In all cases the trivalent cation is bound by the calixarene.

Table 1 Average coordination distances (Å) in gas phase energy minimized Ac^{3+}·calixarene complexes

Calixarene	Ac - - - O_{phenol}	Ac - - - O_2C [a]	Ac - - - OCNH	Ac - - - $O_{amide\ chain}$	Coord. Number
2a	2.78	2.47	—	—	9
2b	3.21	2.51	2.36	—	8
2c	2.73	2.41	2.38	2.38	9
2d	3.59	2.45	2.37	2.46 + 2.48	7

[a] Only the coordinating oxygen atoms (distance < 3 Å) are considered.

Table 2 Coordination abilities of Ac^{3+}·calix[4]arene complexes in MD simulations with explicit solvent

Calix[4]arene	Number of coordinating groups of calixarene	Number of H_2O molecules in first coordination sphere
2a	4	6
2b	4	6
2c	5	5
2d	7	3

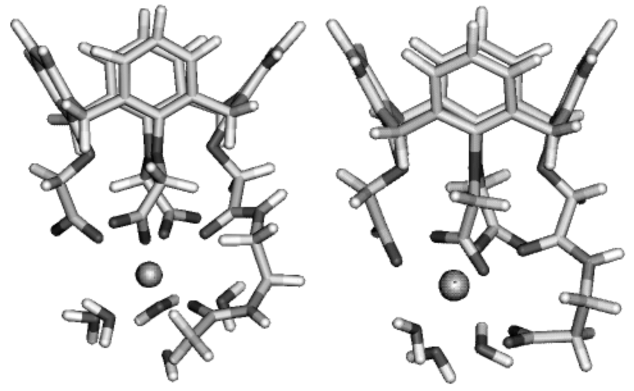


Fig. 4 Snapshots from MD simulations. Left Ac^{3+}·**2c**; right Ac^{3+}·**2d**, for details see the Experimental section.§,¶

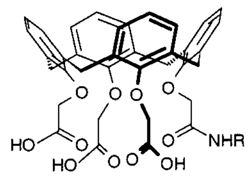
on the phenolic oxygen atoms (−0.23) compared to the charge on the oxygen atoms of the water molecules (−0.83), the water is very competitive. Nevertheless, the carboxylic acid groups (−0.60 charge on the oxygen atoms) and the oxygen atoms of the amide carbonyl groups (−0.55 charge) of the calixarene are in close contact with the cation during the whole simulation time of at least 250 ps (Fig. 4). In addition to the coordination of the carboxylate groups, the coordination sites of the amide linkage contribute to the cation binding. The first coordination sphere of ten is completed with water molecules. In Table 2 a summary is given of the coordination abilities of the simulated Ac^{3+} complexes of calixarenes **2**. For the first three complexes, the mode of complexation is more or less equal: the carboxylate groups behave as monodentates, and the amide carbonyl oxygen atoms, when present, also coordinate to the cation. This leads to the presence of five or six water molecules in the first coordination sphere. In the latter complex, one of the calixarene carboxylate groups and the appended carboxylate group function as a bidentate ligand, giving in total 7-coordination, thus only three water molecules are needed to fill the first coordination sphere. This might be an overoptimistic result. When all carboxylate groups in calix[4]arene **2d** would behave as a monodentate there would be five water molecules around the cation.

Although it cannot be proven by MD simulations that the complexes are inert,‖ they give an indication of the mode of binding. In all cases the situation represented in Table 2 is achieved within 100 ps after the start without further changes during the remainder of the 250 ps of the simulation.

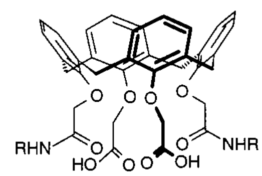
New ionophores; design and synthesis

The MD simulations show that the phenolic oxygen atoms do not participate in the complexation of Ac^{3+} and that the appending coordination site binds to the cation. However, there is no real cavity in which complexation takes place. This led to the design of new ligands in which more than one phenolic ring contains two groups that participate in the complexation of the cation. For a strong interaction, negatively charged groups have to be present. Furthermore, the neutral coordination sites have to compete with the water molecules. The MD simulations of calix[4]arene amides **2b–d** indicate that the oxygen atoms of amide carbonyl groups can do this.

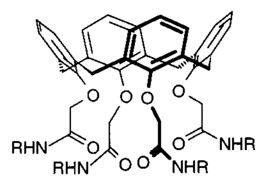
An MD simulation of calix[4]arene tricarboxylic acid monoamide **3** in which the amide side chain contains a glycine



3 R = $CH_2C(O)NHC(CH_2OH)_3$



4 R = CH_2CO_2H



5 R = CH_2CO_2H

unit,** shows that the oxygen atoms of both carbonyl groups are coordinated to the cation.

The MD simulations of calix[4]arenes **4** and **5**, in which respectively two and four glycine units are introduced compared to calix[4]arene tetracarboxylic acid **2**, show cation complexation inside a cavity formed by the carboxylate groups and the oxygen atoms of the amide carbonyl groups (Fig. 5). The distances of the coordinating atoms of calixarenes **4** and **5** to the Ac^{3+} cation are given in Fig. 6. The improved binding is reflected in the number of water molecules in the first coordination sphere of the cation. In the complex with calix[4]arene **4** three water molecules are present during almost the entire simulation, whereas calix[4]arene **5** allows the presence of only two water molecules, of which the second entered after approximately 300 ps. Elongation of the simulation times did not show further changes. It thus seems that the binding abilities of calix[4]arenes **4** and **5** are much improved compared to calix-[4]arenes **2**.

The synthesis route of the possible (according to the MD simulations) Ac^{3+} ionophore, the diglycine calix[4]arene **4**, is

‖ Only a limited time period can be simulated. It is an indication of complex instability if the cation is no longer coordinated to the ligand at the end of a simulation. However, if the cation is still coordinated, it is no guarantee that it will be so when the simulation is prolonged.

** This compound has not been synthesized, but is merely used in an MD simulation study. The idea for this compound stems from our investigations toward water-soluble calix[4]arenes, see ref. 21.

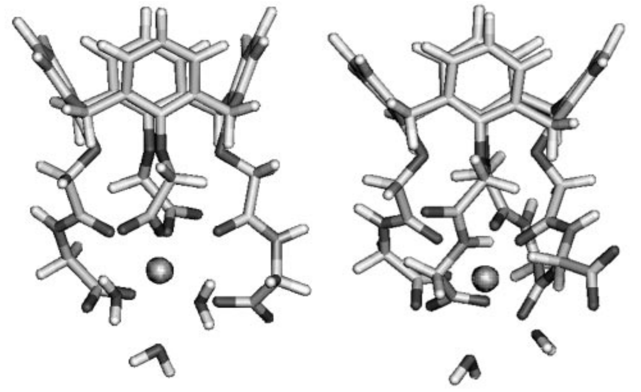
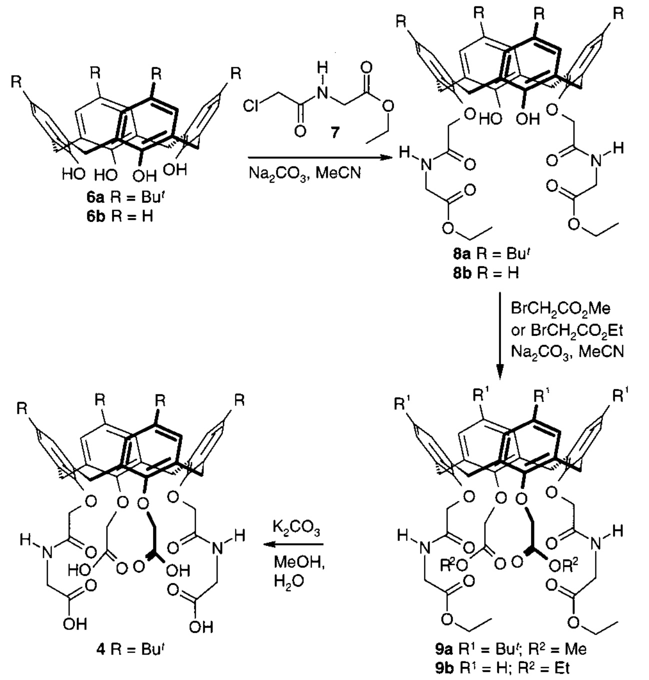
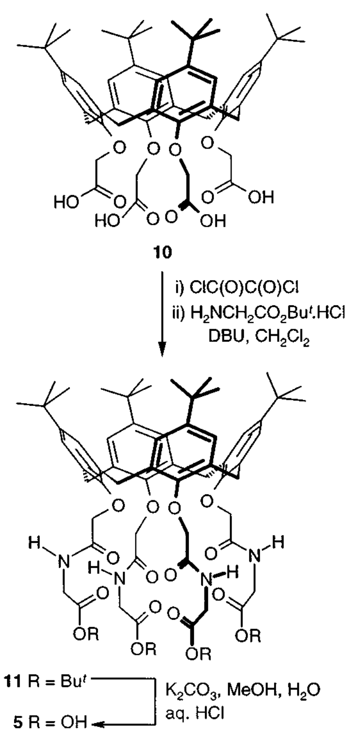


Fig. 5 Snapshots from MD simulations. Left $Ac^{3+}\cdot\mathbf{4}$; right $Ac^{3+}\cdot\mathbf{5}$, for details see the Experimental section.



Scheme 1



Scheme 2

depicted in Scheme 1. Calix[4]arene **6** was dialkylated in about 70% yield with more than two equivalents of the ethyl ester of *N*-(chloroacetyl)glycine **7** to give the 1,3-disubstituted calix[4]arenes **8**. It is possible that steric hindrance between the glycine moieties and the alkylating reagent in the potassium or sodium complex that will be formed when K_2CO_3 or Na_2CO_3 is used as a base prevents further alkylation. However, the remaining two phenolic oxygen atoms could be alkylated with (m)ethyl bromoacetate using Na_2CO_3, affording calix[4]arene tetraesters **9** in almost 70% yield. The cone conformation of **9** is reflected in the characteristic AB system for the methylene groups bridging the aromatic rings in the ^1H NMR spectrum. After mild hydrolysis[6] of the ester groups of calix[4]arene tetraester **9a**[21] diglycine calix[4]arene **4** was obtained.

Tetraglycine derivative **5** was synthesized starting from the known calix[4]arene tetracarboxylic acid **10** (Scheme 2).[22]†† Activation of the carboxylic acid groups with oxalyl chloride afforded its corresponding acid chloride, which was reacted with the *tert*-butyl ester of glycine to give calix[4]arene tetraamide **11** in 65% yield. After mild hydrolysis[6] of the ester groups tetraglycine derivative **5** was obtained in nearly quantitative yield, as was indicated by the presence of only one *tert*-butyl signal in the ^1H NMR spectrum.

Potentiometric titrations in methanol

The thermodynamic stabilities of La^{3+} complexes of the new calix[4]arene tetracarboxylic acids **4** and **5** and the known[22,23] derivatives **2a** and **10** were evaluated in MeOH.‡‡

The equilibria of the calix[4]arene based ligands (L^{4-}) are generally described by eqn. (3) for the protonation constants and eqn. (4) for the complexation constants.

$$L^{4-} + zH^{+} \rightleftharpoons LH_z^{(4-z)-} \qquad \beta_{01z} = \frac{[LH_z^{(4-z)-}]}{[L^{4-}][H^{+}]^z} \tag{3}$$

$$xLa^{3+} + yL^{4-} + zH^{+} \rightleftharpoons La_xL_yH_z^{(3x-4y+z)+}$$
$$\beta_{xyz} = \frac{[La_xL_yH_z^{(3x-4y+z)+}]}{[La^{3+}]^x[L^{4-}]^y[H^{+}]^z} \tag{4}$$

The results given in Table 3 show that a large number of different complexes are formed. Besides these complexes, a mononuclear hydroxo complex is formed with calix[4]arenes **5**, **10**, and **2a** and a binuclear monoprotonated complex with calix[4]arenes **4**, **5**, and **10**. Similar stoichiometries have been found for complexes of ligand **10** with other lanthanides (Pr^{3+}, Eu^{3+}, Yb^{3+}).[24] The distribution of all these species with respect to pH are represented in Figs. 7 and 8 for each ligand ($[L] = 5.0 \times 10^{-4}$ M) and one or two equivalents of metal ion (M), respectively. This distribution strongly depends on the experimental conditions, *e.g.* for calix[4]arene **2a** LaL^{-} is the predominant species from pH 8 to 12 for M/L = 1, whereas it is nearly non-existent for M/L = 2.

The degree of complexation is very high for all four ligands (**4**, **5**, **2a**, and **10**), but not exactly the same for each ligand. It is difficult to rank the ligands according to their efficacy, but it is possible to compare the variation of the free metal ion concentrations with respect to pH (Fig. 9). For M/L = 1, our tetra-

†† For synthetic reasons we chose to synthesize the *p*-*tert*-butyl derivatives.

‡‡ Complexes of these compounds with trivalent cations are not soluble in water. Therefore, the experiments have been performed in methanol.

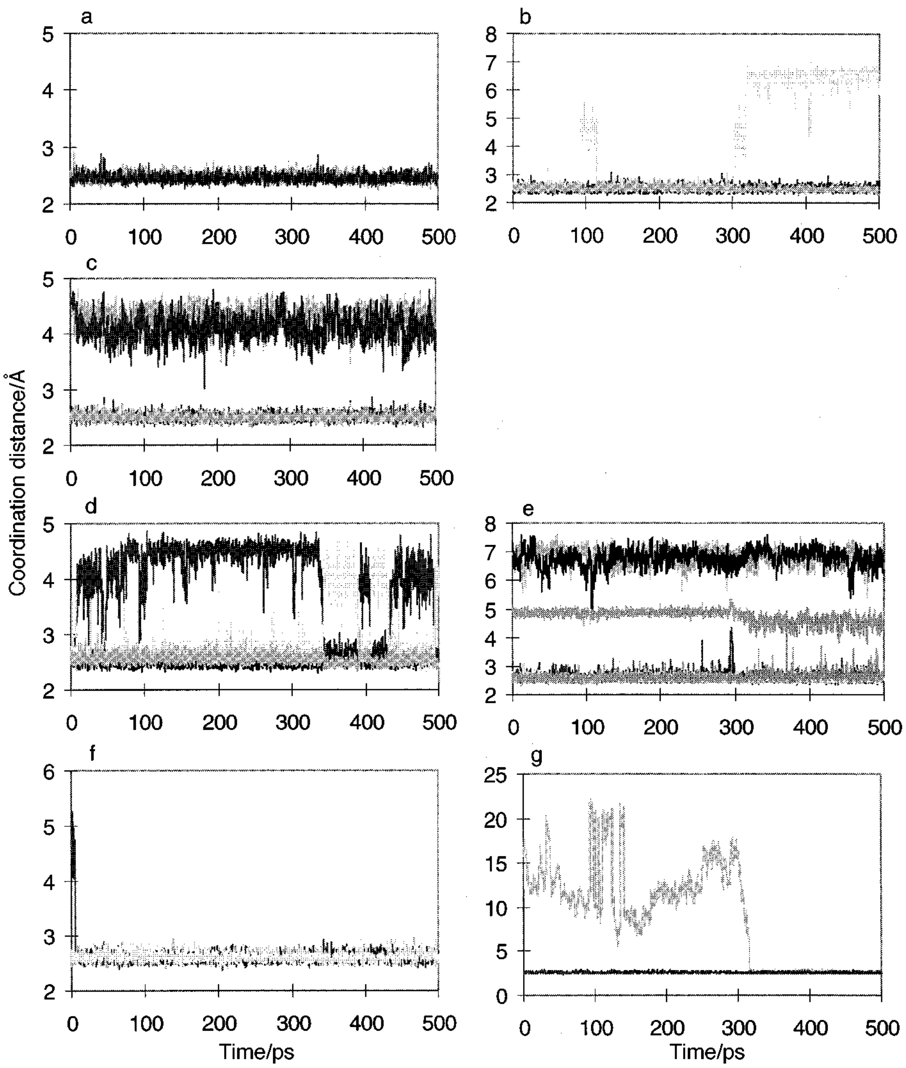


Fig. 6 Coordination distances (Å) of the Ac^{3+} complexes of calixarenes **4** (left) and **5** (right). a and b: oxygen atoms of amide carbonyl groups; c: oxygen atoms of phenoxyacetic acid groups; d and e: oxygen atoms of glycine carboxylate groups; f and g: oxygen atoms of water molecules in the first coordination sphere after 500 ps of simulation time, for details see the Experimental section.

glycine derivative **5** is the best complexing agent in the range $3 < pH < 4$. For $M/L = 2$, a better distinction between the different ligands can be obtained at low pH. Again, calix[4]arene **5** performs the best. However, at higher pH, the four ligands have the same efficacy. These results prove that the insight into the complexation behavior as given by MD studies, can be very useful in the design of new ionophores.[25]

Concluding remarks

We conclude that MM overestimates the shielding properties of the calix[4]arenes and that MD simulations give a much more realistic picture. Simulations with the new model for Ac^{3+} suggest that in aqueous solutions binding with calix[4]arene based ionophores occurs in an outer cavity fashion. The glycine units at the *lower rim* of the calix[4]arene provide additional donor sites for inner cavity binding of trivalent cations.

Potentiometric titrations with La^{3+} and tetraglycine-functionalized calix[4]arene **5** in methanol showed that at low pH values the amount of metal cation bound by this derivative is higher than for calix[4]arene tetracarboxylic acids **2a** and **10**. This means that the predictions of the MD simulations are useful tools for future improvements of the ligand systems. Furthermore, these model studies indicate that this type of functionalization may improve the binding of trivalent cations in water, which is the next step in our investigations toward use of calix[4]arenes as tools for radioimmunotherapy.

Experimental

General

Melting points were determined with a Reichert melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker AC250F spectrometer in the absence of an internal standard. *J* values are given in Hz. FAB mass spectra were obtained with a Finnigan MAT90 mass spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. CH_2Cl_2 was distilled from $CaCl_2$ and stored over molecular sieves (4 Å), CH_3CN was stored over molecular sieves (3 Å), MeOH was distilled over Mg and stored over molecular sieves (4 Å). All other solvents and chemicals were of reagent grade and were used without purification. Silica gel (particle size 0.040–0.063 mm, 230–400 mesh) was obtained from Merck. All reactions were carried out under an argon atmosphere. For reasons of clarity and in order to reduce space, the name calix[4]arene was used instead of the original IUPAC name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Compounds **6a**,**b**[26] and **10**[22] were prepared according to literature procedures.

5,11,17,23-Tetra(*tert*-butyl)-25,27-bis{[(ethoxycarbonyl)-methylcarbamoyl]methoxy}- 26,28-dihydroxycalix[4]arene (8a)

A mixture of calix[4]arene **6a** (1.50 g, 2.31 mmol), anhydrous

Table 3 Stability constants ($\log \beta_{xyz} \pm \sigma_{n-1}$) of La^{3+} complexes of calix[4]arenes **4**, **5**, **10** and **2a** in MeOH, T = 25 °C, I = 0.01 M Et_4NClO_4

Ligand	0 1 z	Protonation (β_{01z})	x y z	Complexation (β_{xyz})
4	0 1 1	12.27 ± 0.06	1 1 0	21.19 ± 0.05
	0 1 2	22.87 ± 0.07	1 1 1	32.07 ± 0.04
	0 1 3	32.29 ± 0.08	1 1 2	37.75 ± 0.04
	0 1 4	40.25 ± 0.08	2 1 0	31.06 ± 0.08
		2 curves, RF = 3.0%	2 1 1	37.52 ± 0.07
			2 1 −2	11.64 ± 0.08
				5 curves (M/L = 0.4, 0.4, 0.6, 1.0, 2.7) ± 500 points, RF = 1.27%
5	0 1 1	11.85 ± 0.06	1 1 0	21.00 (fixed)
	0 1 2	22.08 ± 0.07	1 1 1	32.66 ± 0.04
	0 1 3	31.21 ± 0.08	1 1 2	37.81 ± 0.05
	0 1 4	39.10 ± 0.09	2 1 0	29.9 ± 0.2
		3 curves, RF = 3.2%	2 1 1	38.5 ± 0.2
			1 1 −1	7.1 ± 0.1
			2 1 −2	9.0 ± 0.2
				3 curves (M/L = 0.4, 0.4, 0.6, 1.0, 2.7) ± 500 points, RF = 1.27%
10	0 1 1	13.07 ± 0.02	1 1 0	28.27 ± 0.06
	0 1 2	24.10 ± 0.03	1 1 1	34.84 ± 0.04
	0 1 3	33.76 ± 0.03	1 1 2	38.76 ± 0.10
	0 1 4	42.04 ± 0.03	2 1 0	34.79 ± 0.07
		3 curves, RF = 1.3%	1 1 −1	15.10 ± 0.07
			2 1 −2	14.82 ± 0.08
			2 1 1	39.47 ± 0.09
				5 curves (M/L = 0.5, 0.6, 0.6, 1.4, 1.8) ± 500 points, RF = 2.3%
2a	0 1 1	12.37 ± 0.01	1 1 0	26.00 ± 0.05
	0 1 2	23.05 ± 0.01	1 1 1	33.59 ± 0.04
	0 1 3	32.38 ± 0.02	1 1 2	37.83 ± 0.05
	0 1 4	40.39 ± 0.02	2 1 0	33.98 ± 0.06
		2 curves, RF = 0.6%	1 1 −1	13.89 ± 0.06
			2 1 −2	14.56 ± 0.06
				4 curves (M/L = 0.6, 0.9, 1.3, 1.7) ± 400 points, RF = 2.3%

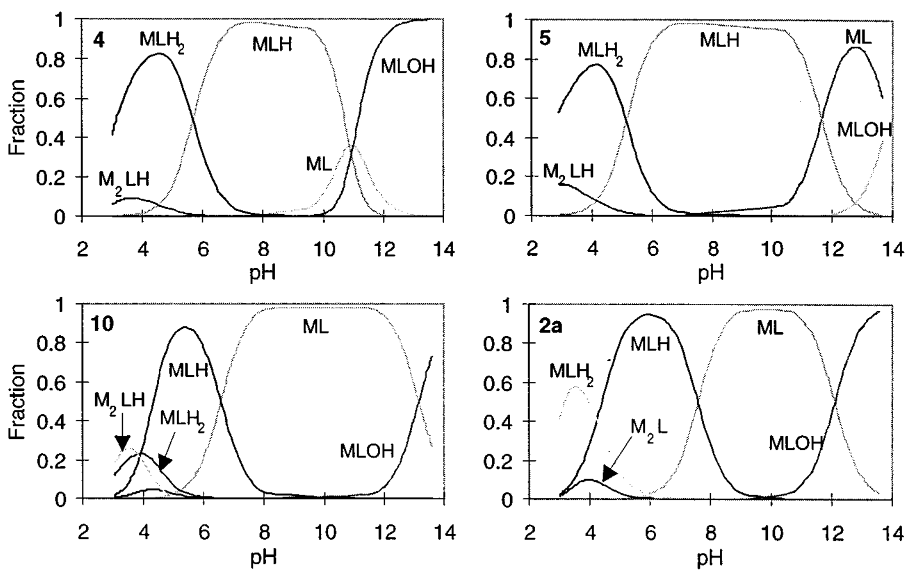


Fig. 7 Distribution (fraction *vs.* pH) of La^{3+}•calix[4]arene complexes (M/L = 1), for details see the Experimental section.

sodium carbonate (1.48 g, 14.0 mmol), *N*-(chloroacetyl)glycine ethyl ester **7** (2.50 g, 13.9 mmol), and sodium iodide (catalytic amount) in acetonitrile (125 cm^3) was refluxed for 72 h. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (150 cm^3) and washed with a saturated aqueous ammonium chloride solution (2 × 100 cm^3) and water (2 × 100 cm^3). After evaporation of the solvent the product was triturated with MeOH for 15 min and filtered and dried to give pure **8a** as a white solid (1.68 g, 78%), mp 249–250 °C (Found: C, 71.90; H, 8.09; N, 3.10. $C_{56}H_{74}N_2O_{10}$ requires C, 71.92; H, 7.98; N, 3.00%); δ_H (250 MHz; $CDCl_3$) 1.04 [18 H, s, $C(CH_3)_3$], 1.24 (6 H, t, *J* 7.1, CH_3), 1.26 [18 H, s, $C(CH_3)_3$], 3.42 (4 H, part of ABq, *J* 13.3, $ArCH_2Ar$), 4.25–4.10 [12 H, m, part of ABq, $NCH_2C(O)$ and OCH_2Me], 4.62 [4 H, s, $OCH_2C(O)$], 6.93 (4 H, s, ArH), 7.08 (4 H, s, ArH), 7.89 (2 H, s, OH) and 9.28 (2 H, t, *J* 5.0, NH); δ_C (62.9 MHz; $CDCl_3$) 14.1 (q, $OCH_2\mathit{C}H_3$), 31.6 and 31.0 [q, $C(\mathit{C}H_3)_3$], 32.2 (t, $ArCH_2Ar$), 34.1 and 33.9 [s, $\mathit{C}(CH_3)_3$], 41.3 [t, $N\mathit{C}H_2C(O)$], 61.4 (t, OCH_2Me), 74.8 [t, $O\mathit{C}H_2C(O)$], 126.2 and 125.5 (d, ArC–H), 148.2, 142.8, 132.4, and 127.1 (s, Ar*C*–C), 149.8 and 149.4 (s, ArC–O) and 169.3 and 169.0 (s, C=O); *m*/*z* 957.9 ([M + Na]$^+$, 100%).

25,27-Bis{[(ethoxycarbonyl)methylcarbamoyl]methoxy}-26,28-dihydroxycalix[4]arene (8b)

A mixture of calix[4]arene **6b** (5.00 g, 11.8 mmol), anhydrous sodium carbonate (7.49 g, 70.7 mmol), *N*-(chloroacetyl)glycine ethyl ester **7** (12.69 g, 70.7 mmol), and sodium iodide (catalytic amount) in acetonitrile (350 cm^3) was refluxed for 72 h. The solvent was evaporated, the residue was taken up in CH_2Cl_2

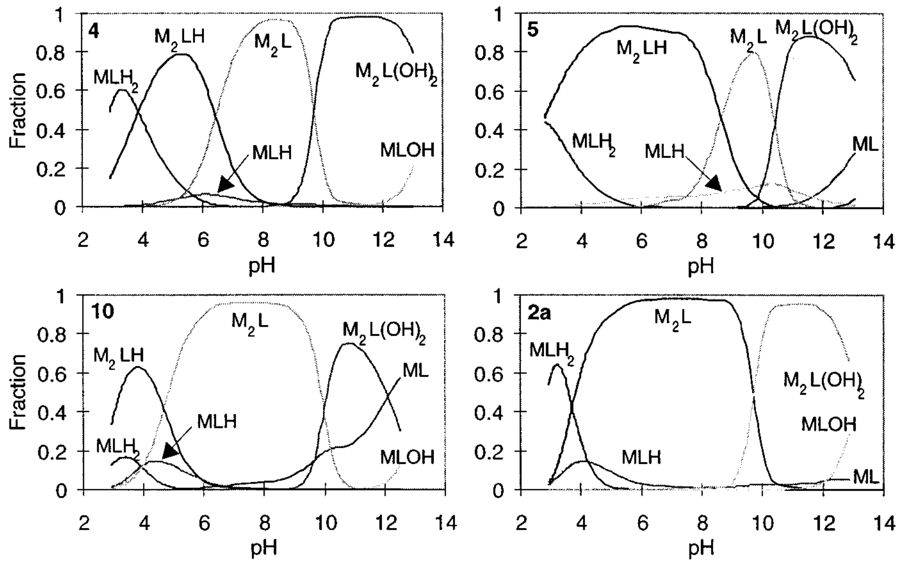


Fig. 8 Distribution (fraction *vs.* pH) of La^{3+}•calix[4]arene complexes (M/L = 2), for details see the Experimental section.

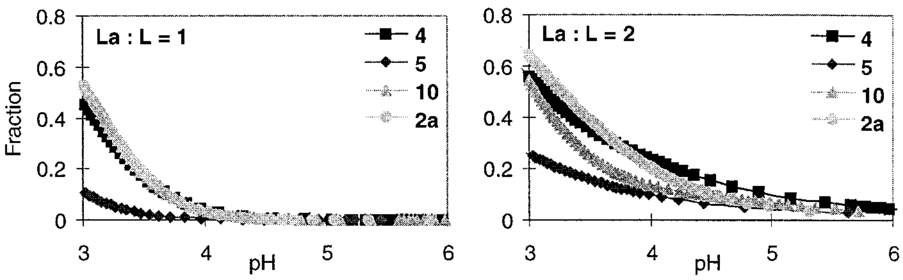


Fig. 9 Free La^{3+} concentrations ($[La]_{free}/[La]_{total}$) *vs.* pH for the different ligands, for details see the Experimental section.

(300 cm^3) and washed with a saturated aqueous ammonium chloride solution (2 × 150 cm^3) and water (2 × 150 cm^3). After evaporation of the solvent the product was triturated with MeOH for 15 min and filtered and dried to give pure **8b** as a white solid (6.36 g, 76%), mp 239–241 °C (Found: C, 67.10; H, 5.92; N, 4.10. $C_{40}H_{42}N_2O_{10}$•$0.1H_2O$ requires C, 67.42; H, 5.97; N, 3.93%); δ_H (250 MHz; $CDCl_3$) 1.25 (6 H, t, *J* 7.2, CH_3), 3.49 (4 H, part of ABq, *J* 13.4, $ArCH_2Ar$), 4.3–4.1 [12 H, m, part of ABq, $NCH_2C(O)$ and OCH_2Me], 4.64 [4 H, s, $OCH_2C(O)$], 7.1–6.7 (12 H, m, ArH), 8.21 (2 H, s, OH) and 9.25 (2 H, t, *J* 4.8, NH); δ_C (62.9 MHz; $CDCl_3$) 14.1 (q, CH_3), 31.7 (t, $ArCH_2Ar$), 41.5 [t, $NCH_2C(O)$], 61.5 (t, OCH_2Me), 74.9 [t, $OCH_2C(O)$], 126.5 and 120.2 (d, ArC–H), 127.4 (s, Ar*C*–CH_2), 129.7 and 128.9 (d, ArC–H), 132.8 (s, Ar*C*–CH_2), 152.3 and 151.4 (s, ArC–O) and 169.2 and 169.1 (s, C=O); *m*/*z* 711.2 ($[M + H]^+$, 100%).

5,11,17,23-Tetra(*tert*-butyl)-25,27-bis{[(ethoxycarbonyl)methylcarbamoyl]methoxy}-26,28-bis[(methoxycarbonyl)methoxy]-calix[4]arene (9a)

A mixture of calix[4]arene **8a** (0.20 g, 0.21 mmol), anhydrous sodium carbonate (0.09 g, 0.86 mmol), and methyl bromoacetate (0.13 g, 0.86 mmol) in acetonitrile (15 cm^3) was refluxed for 72 h. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (50 cm^3) and washed with a saturated aqueous ammonium chloride solution (2 × 25 cm^3) and water (2 × 25 cm^3). After evaporation of the solvent the product was triturated with MeOH for 15 min and filtered and dried to give pure **9a** as a white solid (0.63 g, 68%), mp 81–83 °C (Found: C, 68.88; H, 7.81; N, 2.68. $C_{62}H_{82}N_2O_{14}$ requires C, 68.99; H, 7.66; N, 2.60%); δ_H (250 MHz; $CDCl_3$) 0.92 [18 H, s, $C(CH_3)_3$], 1.11 [18 H, s $C(CH_3)_3$], 1.22 (6 H, t, *J* 7.1, OCH_2CH_3), 3.67 (6 H, s, OCH_3), 4.15–4.05 [8 H, m, $NCH_2C(O)$ and OCH_2Me], 4.51 and 3.21 (8 H, ABq, *J* 13.1, $ArCH_2Ar$), 4.53 [4 H, s, $OCH_2C(O)$], 4.64 [4 H, s, $OCH_2C(O)$], 6.64 (4 H, s, ArH), 6.86 (4 H, s, ArH) and 8.37 (2 H, t, *J* 6.1, NH); δ_C (62.9 MHz; $CDCl_3$) 14.1 (q, OCH_2CH_3), 31.2 [q, $C(CH_3)_3$], 31.3 (t, $ArCH_2Ar$), 31.4 [q, $C(CH_3)_3$], 34.0 and 33.9 [s, $C(CH_3)_3$], 40.8 [t, $NCH_2C(O)$], 51.9 (q, OCH_3), 61.1 (t, OCH_2Me), 74.1 and 72.4 [t, $OCH_2C(O)$], 126.0 and 125.7 (d, ArC–H), 146.0, 145.9, 133.2, and 132.4 (s, Ar*C*–C), 153.4 and 152.5 (s, ArC–O) and 170.5 and 170.3 (s, C=O); *m*/*z* 1101.5 ($[M + Na]^+$, 100%).

25,27-Bis{[(ethoxycarbonyl)methylcarbamoyl]methoxy}-26,28-bis[(ethoxycarbonyl)methoxy]calix[4]arene (9b)

A mixture of calix[4]arene **8b** (4.50 g, 6.33 mmol), anhydrous sodium carbonate (2.68 g, 25.3 mmol), and ethyl bromoacetate (2.6 cm^3, 25.3 mmol) in acetonitrile (150 cm^3) was refluxed for 72 h. The solvent was evaporated, the residue was taken up in CH_2Cl_2 (300 cm^3) and washed with a saturated aqueous ammonium chloride solution (2 × 150 cm^3) and water (2 × 150 cm^3). After evaporation of the solvent the product was triturated with MeOH for 15 min and filtered and dried to give pure **9b** as a white solid (3.74 g, 67%), mp 57–59 °C (Found: C, 65.31; H, 6.23; N, 3.22. $C_{48}H_{54}N_2O_{14}$ requires C, 65.30; H, 6.16; N, 3.17%); δ_H (250 MHz; $CDCl_3$) 1.3–1.2 (12 H, m, OCH_2CH_3), 4.2–4.05 [12 H, m, $NCH_2C(O)$ and OCH_2Me], 4.47 [4 H, s, $OCH_2C(O)$], 4.60 and 3.29 (8 H, ABq, *J* 14.2, $ArCH_2Ar$), 4.67 [4 H, s, $OCH_2C(O)$], 6.55–6.36 (6 H, m, ArH), 6.8–6.7 (6 H, m, ArH) and 8.47 (2 H, t, *J* 6.1, NH); δ_C (62.9 MHz; $CDCl_3$) 14.2 and 14.0 (q, OCH_2CH_3), 30.9 (t, $ArCH_2Ar$), 40.6 [t, $NCH_2C(O)$], 61.1 and 61.0 (t, OCH_2Me), 73.9 and 71.7 [t, $OCH_2C(O)$], 129.5, 128.6, 123.5, and 123.3 (d, ArC–H), 134.7 and 133.4 (s, Ar*C*–CH_2), 156.5 and 155.1 (s, ArC–O) and 170.9, 170.1, and 169.7 (s, C=O); *m*/*z* 905.2 ($[M + Na]^+$, 100%).

5,11,17,23-Tetra(*tert*-butyl)-25,27-bis{[(hydroxycarbonyl)-methylcarbamoyl]methoxy}-26,28-bis[(hydroxycarbonyl)-methoxy]calix[4]arene (4)

A solution of K_2CO_3 (0.13 g, 0.93 mmol) in water (2 cm^3) was added to a refluxing solution of calix[4]arene **9a** (0.10 g, 0.093 mmol) in MeOH (10 cm^3). After 30 min of refluxing the mixture was poured into water (150 cm^3), after which the pH was adjusted to about 2 with 1 M HCl. The product was extracted with CH_2Cl_2 (3 × 50 cm^3) to give, after evaporation of the solvent, pure **4** as a white solid (0.086 g, 93%), mp 245–247 °C (decomp.) (Found: C, 61.18; H, 7.29; N, 2.46. $C_{56}H_{70}N_2O_{14}\cdot 6H_2O$ requires C, 60.97; H, 7.49; N, 2.54%); δ_H (250 MHz; THF-d_8) 0.93 [18 H, s, $C(CH_3)_3$], 1.08 [18 H, s, $C(CH_3)_3$], 3.98 [4 H, d, *J* 6.0, $NCH_2C(O)$], 4.38 [4 H, s, $OCH_2C(O)$], 4.53 [4 H, s, $OCH_2C(O)$], 4.62 and 3.14 (8 H, ABq, *J* 12.9, $ArCH_2Ar$), 6.72 (4 H, s, ArH), 6.90 (4 H, s, ArH) and 7.92 (2 H, t, *J* 5.9, NH); δ_C (62.9 MHz; THF-d_8) 33.1 (t, $ArCH_2Ar$), 33.3 and 33.2 [q, $C(CH_3)_3$], 36.1 and 35.9 [s, $C(CH_3)_3$], 42.5 [t, $NCH_2C(O)$], 76.8 and 74.6 [t, $OCH_2C(O)$], 128.0 and 127.9 (d, ArC–H), 148.0, 147.5, 136.3, and 135.4 (s, Ar*C*–C), 155.6 and 154.8 (s, ArC–O) and 173.8, 173.5, and 171.3 (s, C=O); *m*/*z* 1017.4 ($[M + Na]^+$, 40%).

5,11,17,23-Tetra(*tert*-butyl)-25,26,27,28-tetrakis{[(*tert*-butoxycarbonyl)methylcarbamoyl]methoxy}calix[4]arene (11)

A solution of calix[4]arene **10** (1.00 g, 1.13 mmol) was refluxed in oxalyl chloride (20 cm^3) for 2 h. After evaporation of the excess oxalyl chloride, the residue was dissolved in CH_2Cl_2 (50 cm^3). The solution was added dropwise to a cooled solution (0 °C) of the HCl salt of the *tert*-butyl ester of glycine (1.14 g, 6.81 mmol) and DBU (3.4 cm^3, 22.7 mmol) in CH_2Cl_2 (10 cm^3). The mixture was stirred overnight at room temp., after which it was washed with water (2 × 50 cm^3). After evaporation of the solvent pure **11** was obtained after column chromatography (SiO_2, CH_2Cl_2–EtOAc 9 : 1, $R_f = 0.15$) (0.98 g, 65%), mp 222–224 °C (Found: C, 68.24; H, 8.20; N, 4.05. $C_{76}H_{108}N_4O_{16}$ requires C, 68.44; H, 8.16; N, 4.20%); δ_H (250 MHz; $CDCl_3$) 1.01 [36 H, s, $C(CH_3)_3$], 1.39 [36 H, s, $C(CH_3)_3$], 3.99 [8 H, d, *J* 5.9, $NCH_2C(O)$], 4.50 and 3.22 (8 H, ABq, *J* 12.8, $ArCH_2Ar$), 4.51 [8 H, s, $OCH_2C(O)$], 6.75 (8 H, s, ArH) and 7.81 (4 H, t, *J* 5.9, NH); δ_C (62.9 MHz; $CDCl_3$) 28.1 [q, $C(CH_3)_3$], 31.2 (t, $ArCH_2Ar$), 31.3 [q, $C(CH_3)_3$], 33.9 [s, $ArC(CH_3)_3$], 41.6 [t, $NCH_2C(O)$], 74.2 [t, $OCH_2C(O)$], 81.7 [s, $OC(CH_3)_3$], 125.9 (d, ArC–H), 146.1 and 132.7 (s, Ar*C*–C), 152.5 (s, ArC–O) and 170.2 and 169.1 (s, C=O); *m*/*z* 1355.9 ($[M + Na]^+$, 100%).

5,11,17,23-Tetra(*tert*-butyl)-25,26,27,28-tetrakis{[(hydroxy-carbonyl)methylcarbamoyl]methoxy}calix[4]arene (5)

The same procedure as described above for the synthesis of calix[4]arene tetracarboxylic acid **4** was used to obtain calix[4]arene **5**, starting with calix[4]arene tetraester **11** (0.20 g, 0.15 mmol) (0.12 g, 72%), mp 249–251 °C (decomp.) (Found: C, 64.73; H, 7.13; N, 4.85. $C_{60}H_{76}N_4O_{16}$ requires C, 64.97; H, 6.91; N, 5.05%); δ_H (250 MHz; THF-d_8) 1.17 [36 H, s, $C(CH_3)_3$], 4.13 (8 H, d, *J* 5.8, NCH_2), 4.59 [8 H, s, $OCH_2C(O)$], 4.75 and 3.33 (8 H, ABq, *J* 12.9, $ArCH_2Ar$), 6.96 (8 H, s, ArH) and 8.21 (4 H, t, *J* 5.8, NH); δ_C (62.9 MHz; THF-d_8) 29.7 (t, $ArCH_2Ar$), 33.3 [q, $C(CH_3)_3$], 36.0 [s, $C(CH_3)_3$], 42.7 (t, NCH_2), 76.6 [t, $OCH_2C(O)$], 128.0 (d, ArC–H), 147.4 and 135.6 (s, Ar*C*–C), 155.5 (s, ArC–O) and 173.3 and 171.9 (s, C=O); *m*/*z* 1131.5 ($[M + Na]^+$, 30%).

Molecular modeling and molecular dynamics

Initial structures as well as visualizations were carried out with Quanta/CHARMm 3.3.§§ The MM and MD calculations were run with CHARMm 23.0.[27] Parameters were taken from Quanta 3.3 and point charges were calculated with the charge template option in Quanta/CHARMm. The ligands were charged to −3 or −4,§ with a small "excess" charge smoothed to non-polar carbons and hydrogens. When four carboxylate groups were present, one sodium cation was introduced in order to obtain a neutral ensemble.¶¶ The actinium cation was represented as an ion with a point charge of +3 and Lennard–Jones parameters of $R_{min} = 3.980$ Å and $\varepsilon = 0.055$ kcal mol^{-1}. The starting structures were minimized by ABNR (Adopted-Basis set Newton-Raphson) until the rms on the energy gradient was ⩽0.01 kcal mol^{-1} Å^{-1}. No cut-off on the non-bonded interactions was applied. A constant relative permittivity with an epsilon of 1 was used.

Details of the MD simulations were as follows. The minimized complexes were placed in a cubic water box of approximately 31 Å dimensions, filled with 1000 TIP3P waters as implemented in CHARMm.[18] Solvent molecules that overlap with the complex were removed (based on heavy atom interatomic distances ⩽2.3 Å). This in general resulted in the removal of one water per non-hydrogen atom of the system under study. Full periodic boundary conditions were imposed. This was done by making 26 images in the $\pm x$, $\pm y$, and $\pm z$ directions. Before running the MD simulations the system was minimized by steepest descent, in order to remove the worst contacts, until the rms on the energy gradient was ⩽1.0 kcal mol^{-1} Å^{-1} or a maximum of 1000 steps was reached. During the simulation the non-bonded list was updated every 20 time steps with a cut-off of 12 Å. Unless otherwise stated, the van der Waals interactions were treated with a switch function between 10 and 11 Å, whereas the shift function was applied to the electrostatic interactions (cut-off 11 Å). A constant relative permittivity and an epsilon of 1 were applied. The system was heated to 300 K in 5 ps, followed by 10 ps equilibration with scaling of the velocities within a temperature window of 10 degrees. After equilibration no scaling of the velocities was applied. The production phase consisted of 250 to 500 ps and coordinates were saved every 200 time steps (NVE ensemble; no systematic deviation from 300 K was observed). The verlet/leapfrog algorithm was used for the numerical integration. The SHAKE algorithm[28] on bonds involving hydrogen was applied, allowing a time step of 1 fs.

Free energy perturbation Monte Carlo (FEP-MC) simulations were performed with the BOSS program.[29] The trivalent cation was placed in the center of a box of approximately 31.2 × 32.1 × 35.6 Å^3 dimensions (cut-off 15 Å). Solvent molecules at distances smaller than 2.5 Å from the solute were removed, leaving 1182 TIP3P waters.[18] The charge was perturbed in the forward and backward directions in 20 equally spaced windows, allowing an estimation of the hysteresis. The ranges of attempts of translational and rotational moves of the waters were 0.20 Å and 20°, giving an acceptance ratio of approximately 40%. The range of translational attempts of the ion was set such that an acceptance ratio of roughly 40% resulted. This means that in a run from +3 to +0 the range in the first window was set to 0.05 Å and in the last window to 0.55 Å. Preferential sampling was applied.[29b] The system was equilibrated first in the NVT ensemble for 1 million configurations, followed by 2 million configurations in the NPT ensemble at 1 atm and 298 K. The averaging was done for 2 million configurations in the NPT ensemble. Full periodic boundary conditions were imposed. This was done by making 26 images in the $\pm x$, $\pm y$, and $\pm z$ directions. The average of forward and backward runs was taken with the standard deviation as a lower bound estimate of the error.

§§ Quanta was bought from Molecular Simulations Inc., Burlington, MA.

¶¶ The sodium cation never disturbed the complex between Ac^{3+} and the calix[4]arene. It either diffused into the solution or was coordinated to one of the carboxylate oxygen atoms.

Table 4 Methanolysis constants ($\log \beta^*_{10-z} \pm \sigma_{n-1}$)[a] of La^{3+}

Species (1 0 − z)	Log β^*_{10-z}	Observations
1 0 −1	−8.17 ± 0.01	2 curves, 200 points
1 0 −2	−18.23 ± 0.03	RF^b = 1.8%
1 0 −3	−29.01 ± 0.03	

[a] Corresponding to the equilibrium between $La^{3+} + z\ CH_3OH$ and $La(OCH_3)_z^{(3-z)+} + z\ H^+$. [b] Hamilton *R*-factor significant for the goodness of the fit.

Potentiometric titrations in methanol

Materials. The solvent, methanol (Carlo Erba with low water content, maximum 0.01%), was used without further purification. The ligand solutions were made from dissolution of a weighted quantity of ligand in methanol. The ionic strength was held constant at 10^{-2} M by the addition of tetraethylammonium perchlorate, recrystallized from methanol. The titrant base used was tetraethylammonium hydroxide made from a dilution of the commercial solution (25% in MeOH, Fluka) and standardized against potassium acid phthalate. The metallic salt used was the trifluoromethanesulfonate $La(SO_3CF_3)_3$, synthesized by reacting lanthanum oxide in slight excess with trifluoromethanesulfonic acid, according to the literature.[30]

Stability constant determination. The stability constants of the complexes were determined potentiometrically using a competitive method with the proton. Measurements have been performed at 25 °C using a combined glass electrode (Ingold) connected to an automatic titrator (716 DMS Titrino). The standard filling solution (saturated aqueous KCl) of the external reference of the combined glass electrode was replaced by a 0.01 M NEt_4Cl solution in MeOH saturated with AgCl. Parameters pH_0 and S of the electrode function [eqn. (5)] were determined from the titration curve of 0.001 M $HClO_4$ in MeOH (obtained by dilution of the commercial concentrated 11.6 M perchloric acid) in the presence of 0.01 M NEt_4ClO_4 by 0.01 M NEt_4OH.

$$pH_{meas} = pH_0 + S\log[H^+] \quad (5)$$

The protonation constants of the ligands β_{01z} and the formation constants of the complexes β_{xyz} corresponding to the general equilibrium of complexation [eqn. (6)] have been determined from pH-metric data during the neutralization by 0.01 M NEt_4OH, under argon, of acidic solutions of the ligands in MeOH with or without metal salts.

$$xLa^{3+} + yL^{4-} + zH^+ \rightleftharpoons La_xL_yH_z^{(3x-4y+z)+} \quad (6)$$

The formation constants β^*_{yz} of the methoxy species of La^{3+} were determined by titrating solutions of lanthanide triflate in methanol with a maximum of five equivalents of NEt_4OH. The program SIRKO,[31] which allows simultaneous adjustment of the constants β_{xyz}, the electrode parameters and component concentrations, was used to interpret the data. Several experiments (between 3 and 5), corresponding to different metal to ligand concentration ratios, in the pH range 3–12, were treated simultaneously. The parameters of the electrode, determined previously, were held constant during the refinement. The autoprotolysis constant of methanol used for the calculations was $pK_{MeOH} = 16.7$. For stability constant determination, the protonation constants β_{01z} obtained from titrations of the ligand in the absence of metal, as well as the formation constants β^*_{y-z} of La^{3+} methoxy species (Table 4), were held constant during the refinement procedure.

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