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Lanthanide cation binding properties of homooxacalixarene diethylamide derivatives

Paula M. Marcos ^{a c}, José R. Ascenso ^b, Manuel A.P. Segurado ^{a c}, Peter J. Cragg ^d, Sylvia Michel ^e, Véronique Hubscher-Bruder ^e & Françoise Arnaud-Neu ^e

^a Centro de Ciências Moleculares e Materiais, Faculdade de Ciências da Universidade de Lisboa, Edifício C8, 1749-016, Lisboa, Portugal

^b Instituto Superior Técnico, Complexo I, Avenida Rovisco Pais, 1049-001, Lisboa, Portugal

^c Faculdade de Farmácia da Universidade de Lisboa, Avenida Prof. Gama Pinto, 1649-003, Lisboa, Portugal

^d School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, BN2 4GJ, UK

^e Université de Strasbourg, IPHC, 25 rue Becquerel, 67087, Strasbourg, France, UMR7178, 67037, Strasbourg, France

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Lanthanide cation binding properties of homooxacalixarene diethylamide derivatives

Paula M. Marcos^{a,c,*}, José R. Ascenso^b, Manuel A.P. Segurado^{a,c}, Peter J. Cragg^d, Sylvia Michel^e,
Véronique Hubscher-Bruder^e and Françoise Arnaud-Neu^e

^aCentro de Ciências Moleculares e Materiais, Faculdade de Ciências da Universidade de Lisboa, Edifício C8, 1749-016 Lisboa, Portugal; ^bInstituto Superior Técnico, Complexo I, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal; ^cFaculdade de Farmácia da Universidade de Lisboa, Avenida Prof. Gama Pinto, 1649-003 Lisboa, Portugal; ^dSchool of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton BN2 4GJ, UK; ^eUniversité de Strasbourg, IPHC, 25 rue Becquerel, 67087 Strasbourg, France; CNRS, UMR7178, 67037 Strasbourg, France

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The binding properties of two homooxacalixarene diethylamides (**1b** and **2b**) derived from *p*-tert-butylidihomooxacalix[4]arene and *p*-tert-butylhexahomotrioxacalix[3]arene, respectively, in the cone conformation, for lanthanide cations, were investigated. These properties were assessed by extraction studies of the metal picrates from water into dichloromethane and stability constant measurements in methanol, using spectrophotometric and potentiometric techniques. Microcalorimetric studies of La³⁺, Pr³⁺, Eu³⁺ and Gd³⁺ complexes in the same solvent were also performed. Proton NMR titrations with the representative lanthanides La³⁺, Eu³⁺ and Yb³⁺ were also carried out to establish the sites of interaction of the ligands with the cations. The analogous derivative (**3b**) of *p*-tert-butylcalix[4]arene was also studied and the results of the three compounds are compared. Diethylamide **1b** is the strongest binder, showing some preference for the light lanthanides in extraction, but exhibiting practically no selectivity in complexation. Compound **1b** displays the highest stability constant values ever found with this ligand (log β = 8.6–9.2). In contrast, **2b** shows lower extraction and stability constant values, but it is a more selective ligand, showing a clearer preference for the light lanthanides. Diethylamide **3b** exhibits a similar behaviour to that of its analogue **1b**. Proton NMR titrations confirm the formation of 1:1 complexes between the amides and the cations studied, also indicating that they should be located inside the cavity defined by the phenoxy and the carbonyl oxygen atoms.

Keywords: dihomooxacalix[4]arene; hexahomotrioxacalix[3]arene; diethylamide derivative; lanthanide cation binding; proton NMR titration

Introduction

More than 30 years after the beginning of modern calixarene chemistry, calixarenes (*1–3*) continue to attract much attention as ion receptors and carriers in host–guest chemistry. The parent compounds are readily available and can be further functionalised on the upper and lower rims to give a large variety of derivatives.

In particular, the ability of carbonyl-containing substituents on the lower rim of calixarenes to bind metal ions, predominantly alkali and alkaline earth (*4*), but also transition and heavy metal cations (*5*), has been largely studied. Besides these mono- and divalent cations, research work with trivalent cations, namely lanthanides (*6, 7*), has also been increasingly reported. The growing interest in these elements is mainly due to their use in materials for catalysis, optics, electronics, in luminescent probes, in biology and in medicine as contrast agents for magnetic resonance imaging. The study of the interactions between calixarenes and lanthanides is also motivated by the treatment of radioactive wastes, which requires the extraction of lanthanides and

actinides from acidic effluents, followed by their separation before the disposal or the transmutation of actinides into short-lived radionuclides.

Lanthanide ions, being hard Lewis acids (*8*), show strong affinity towards hard oxygen donor atoms. Thus, it is expected that calixarenes containing such donor atoms are potential receptors for those cations. Phosphorylated calix[4]arenes, bearing carbamoylmethyl-phosphine oxides (*6a,b, 9, 10*) moieties on the upper and lower rims or phosphine oxide (*11, 12*), as well as calix[4]arene derivatives with lower-rim carbonyl-containing substituents, such as esters (*13*), carboxylic acids (*13–15*) and amides (*16–18*), have been used as extracting agents for lanthanide ions. Also, the larger and more flexible calix[6]-(*18, 19*) and calix[8]arenes (*18–20*) have been investigated, since lanthanide cations require high coordination numbers (*8 or 9*) and, therefore, more donor sites can be favourable to their complexation.

Both dihomooxacalix[4]arene and hexahomotrioxacalix[3]arene, calixarene analogues in which one or all CH₂

*Corresponding author. Email: pmmarcos@fc.ul.pt

in this work and the results of the three derivatives are compared and discussed in terms of the size and conformational effects of the macrocycles.

Extraction studies

The data reveal that amide **1b** displays very high extraction levels for all the cations (% *E* ranges from 41 to 76). These values are significantly higher (more than double) than those obtained for amide **2b** (% *E* ranges from 13 to 34), the maximum difference being observed in the cases of Er³⁺ and Dy³⁺ cations. This behaviour was expected as lanthanides require high coordination numbers (8 or 9) and **2b** possesses only three amide groups, and consequently only six donating sites can surround the cations, compared to the eight sites of tetraamide **1b**. However, **2b** is a more selective extractant agent than **1b** (e.g. $S_{Pr}^{3+}/Yb^{3+} = 2.6$ and 1.8, respectively, where selectivity $S = \%E_{M1}^{3+}/\%E_{M2}^{3+}$). Derivative **1b** also shows a much higher extraction percentage than that of the amide **3b** (% *E* ranges from 12 to 24). Moreover, compared to the extraction percentages of europium picrate (the only data



	La ³⁺	Ce ³⁺	Pr ³⁺	Nd ³⁺	Sm ³⁺	Eu ³⁺	Gd ³⁺	Dy ³⁺	Er ³⁺	Yb ³⁺
Ionic radius ^b /Å	1.03	1.01	0.99	0.98	0.96	0.95	0.94	0.91	0.89	0.87
1b	71	74	76	75	69	75	47	67	57	41
2b	28	34	34	34	31	30	17	18	13	13
3b	12	14	17	19	23	24	20	23	18	18

^b See Ref. (42).

found in the literature) (**4a**) with the larger calix[5] (24% *E*) and calix[6]arene (39% *E*) amide analogues, we verify that **1b** still displays the highest values.

Both amides **1b** and **2b** show similar extraction profiles. They do not display any peak selectivity among the cations, but they clearly discriminate between the light and the heavy lanthanides. The former cations (from La³⁺ to Eu³⁺) are preferred over the latter (with the exception of **1b** with Dy³⁺), and among those, a very slight selectivity can be observed for Pr³⁺, Nd³⁺ and Ce³⁺ with both derivatives, and also for Eu³⁺ with **1b**. Despite the small variations among the ionic radii of the lanthanide ions (0.16 Å from La³⁺ to Yb³⁺), the relative larger size of those cations may account for these differences, as both derivatives have been showing a stronger affinity for the larger cations (21, 22). This extraction trend is, however, the opposite of that found by us for the corresponding ketone derivatives (23). In the case of amide **3b**, the extraction profile is slightly different. This derivative does not display any peak of selectivity either, but shows preference for the middle lanthanides, such as Eu³⁺, Sm³⁺ and Dy³⁺.

Complexation studies

The complexation of some representative lanthanide cations (La³⁺, Pr³⁺, Eu³⁺, Gd³⁺ and Yb³⁺) was followed by UV absorption spectrophotometry and/or competitive potentiometry for ligands **1b**, **2b** and **3b** in methanol.

The logarithms of the stability constants β of the 1:1 complexes formed are given in Table 2. For all these cations except Yb³⁺, the complexation thermodynamic parameters were determined by microcalorimetry with ligands **1b** and **2b** in the same solvent. These data are collected in Table 3.

The first results were obtained with the lanthanide chlorides by spectrophotometry in the presence of tetraethylammonium chloride as the supporting electrolyte. Very significant spectral changes were observed in the spectrum of **1b** during its titration against the metal salts, until the metal-to-ligand concentration ratio reaches 1, indicating the formation of very stable 1:1 complexes (Figure 2). With the hexahomotrioxacalix[3]arene **2b**, much weaker spectral variations could be noticed. In contrast to **1b**, for which only a lower limit could be estimated ($\log \beta \geq 7$), the interpretation of the experimental data for **2b** led to reliable stability constants for the 1:1 complexes (Table 2).

As the stability constants obtained with **1b** and metal chlorides were too high, and at the limits of the experimental method, it was decided to follow the complexation of lanthanide nitrates in the presence of Et₄NNO₃ as the supporting electrolyte. Previous studies on phosphorylated calixarene derivatives showed an important decrease in the stability constants in such a more coordinating medium (10). Although much lower values were found with **2b** (for instance, the stability of the lanthanum complex drops from 5.5 to 2.2 log units on

Table 2. Logarithms of the stability constants ($\log \beta \pm \sigma_{n-1}$)^a of lanthanide complexes with **1b**, **2b** and **3b** (methanol, *I* = 0.01 M in Et₄NCl, Et₄NNO₃ or Et₄NClO₄, *T* = 25°C).

Ligand	Method/medium	La ³⁺	Pr ³⁺	Eu ³⁺	Gd ³⁺	Yb ³⁺
1b	Spec./Cl [−]	≥ 7	≥ 7	≥ 7	≥ 7	≥ 7
	Spec./NO ₃ [−]	6.2 ± 0.3	–	6.1 ± 0.2	–	5.5 ± 0.2
	Pot./ClO ₄ [−]	8.88 ± 0.08	9.2 ± 0.3	8.87 ± 0.01	9.0 ± 0.1	8.6 ± 0.2
2b	Spec./Cl [−]	5.5 ± 0.2	4.9 ± 0.1	4.7 ± 0.4	4.3 ± 0.3	3.4 ± 0.1
	Spec./NO ₃ [−]	2.2 ± 0.6	–	2.08 ± 0.04	–	≤ 2
3b	Pot./ClO ₄ [−]	8.86 ± 0.07	8.5 ± 0.7	8.9 ± 0.1	8.9 ± 0.2	8.2 ± 0.4

^a Standard deviation σ_{n-1} on the mean of several experiments.

Table 3. Complexation thermodynamic parameters of lanthanide triflates with **1b**, **2b** and **3b** obtained by microcalorimetric titrations (methanol, *T* = 25°C).

Ligand	Parameter	La ³⁺	Pr ³⁺	Eu ³⁺	Gd ³⁺
1b	log β	8.88 ± 0.08 (6.55) ^a	9.2 ± 0.3	8.87 ± 0.01	9.0 ± 0.1
	−Δ <i>G</i> (kJ mol ^{−1})	50.6 ± 0.4 (37.34) ^a	52 ± 2	50.56 ± 0.06	51.3 ± 0.6
	−Δ <i>H</i> (kJ mol ^{−1})	26.34 ± 0.07 (27.22) ^a	31.77 ± 0.07	24.78 ± 0.01	28 ± 1
	<i>T</i> Δ <i>S</i> (kJ mol ^{−1})	24.3 ± 0.5 (10.12) ^a	21 ± 2	25.78 ± 0.07	23 ± 2
2b	log β	6.05 ± 0.04 (3.0 ± 0.04) ^a	6.31 ± 0.05	6.0 ± 0.1	5.43 ± 0.03
	−Δ <i>G</i> (kJ mol ^{−1})	34.5 ± 0.2 (17.1 ± 0.2) ^a	35.9 ± 0.3	34.2 ± 0.6	30.9 ± 0.2
	−Δ <i>H</i> (kJ mol ^{−1})	−38.9 ± 0.4 (−17.7 ± 0.5) ^a	−35 ± 2	−38.5 ± 0.4	−50.8 ± 0.4
	<i>T</i> Δ <i>S</i> (kJ mol ^{−1})	73.4 ± 0.6 (34.8 ± 0.7) ^a	71 ± 2	73 ± 1	81.7 ± 0.6

^a Titration with La(NO₃)₃.

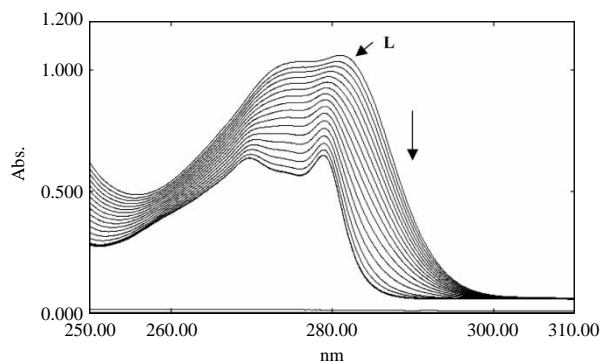


Figure 2. Spectrophotometric titration of **1b** ($C_{1b} = 3.67 \times 10^{-4}$ M) with PrCl_3 ($0 \leq C_{\text{Pr}}/C_{1b} \leq 1.24$) in methanol at 25°C .

changing the counterion from chloride to nitrate), the stability constants remained, however, very high for the complexes of derivative **1b**, with values ranging between 6.2 and 5.5 log units.

In order to better assess the high stability constants of the complexes with **1b**, potentiometric experiments based on a competition with the Ag^+ cation were then performed with lanthanide trifluoromethanesulphonates (triflates) in the presence of Et_4NClO_4 as the supporting electrolyte. The stability constant of the 1:1 Ag^+ complex has been re-evaluated and the result ($\log \beta = 7.16$) found is in excellent agreement with the value published earlier (21). For comparison, the stability constants of the 1:1 complexes with *p*-tert-butylcalix[4]arene tetra(diethyl)amide **3b** were also determined for Ag^+ and for the selection of lanthanides studied. The values for Ag^+ ($\log \beta = 7.56$) and for Pr^{3+} , Eu^{3+} and Yb^{3+} complexes (Table 2) are consistent with those published earlier (4a, 28).

In order to get a better insight into the origin of the stability of these complexes, the complexation of La^{3+} , Pr^{3+} , Eu^{3+} and Gd^{3+} triflates and of La^{3+} nitrate was followed by microcalorimetric experiments, which allowed the determination of the complexation thermodynamic parameters. Yb^{3+} triflate was not soluble enough to obtain significant heat effects during the titrations of the ligands with this cation. Therefore, no data could be derived in this case. With **1b**, the thermograms were simple, showing exothermic heat signals until a 1:1 stoichiometry was reached, as illustrated in the case of Gd^{3+} (Figure 3). They are consistent with the formation of very stable 1:1 complexes, in agreement with the spectrophotometric and potentiometric results. The enthalpies of complexation, ΔH , determined from the slopes of the cumulative heat effects vs the number of moles of reactant added, and the corresponding entropies of complexation, ΔS , calculated from the Gibbs energy derived from the stability constants obtained from potentiometry, are listed in Table 3. With **2b**, the thermograms are quite different showing endothermic

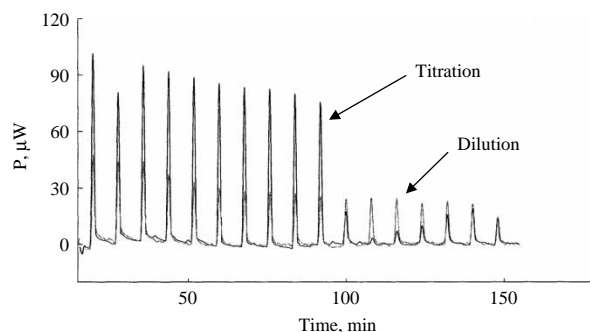


Figure 3. Microcalorimetric titration of $2.5 \mu\text{l}$ of **1b** (4.43×10^{-4} M) by addition of $17 \times 15 \mu\text{l}$ of 6.25×10^{-3} M of $\text{Gd}(\text{CF}_3\text{SO}_3)_3$ in methanol at 25°C .

effects, for example, for Gd^{3+} (Figure 4). In this case, both the logarithm of the stability constants and the enthalpy of complexation could be refined simultaneously (Table 3). The stability constants were found to be slightly higher than those determined by spectrophotometry with chloride counterions. With **3b** and all the lanthanides studied, the thermograms were more complex: they started with exothermic signals, becoming endothermic from a metal-to-ligand concentration ratio of 0.7 and exothermic again, corresponding to the dilution effect, after the 1:1 stoichiometry. They are certainly consistent with several complexation processes, including the formation of a 1:1 complex as with the other ligands studied. They may also show, at some extent, micro-precipitation, which could be the reason why they could not be interpreted.

The main conclusions are the following:

- (1) The dihomooxa derivative **1b** shows a higher affinity for lanthanides than its hexahomotrioxa counterpart **2b**. For instance, the Eu^{3+} complex is at least 2.3 log units higher with **1b** than with **2b** with chloride counterions and 4 log units higher with nitrate counterions. This is consistent with the remarkable

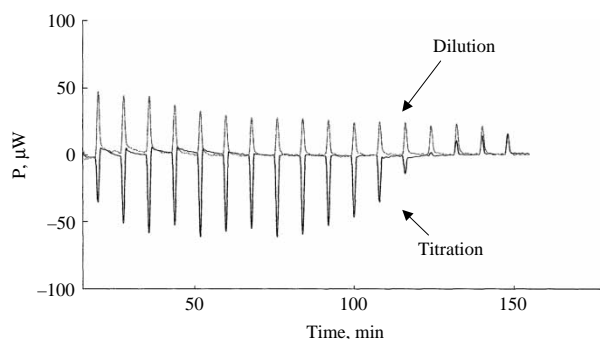


Figure 4. Microcalorimetric titration of $2.5 \mu\text{l}$ of **2b** (4.56×10^{-4} M) by addition of $17 \times 15 \mu\text{l}$ of 6.25×10^{-3} M of $\text{Gd}(\text{CF}_3\text{SO}_3)_3$ in methanol at 25°C .

extraction efficiency of **1b** as compared with **2b**. In contrast, there is no great difference in stability between the complexes with **1b** and its calix[4]arene counterpart **3b**, $\log \beta$ values being in the ranges 9.2–8.6 and 8.9–8.2, respectively.

- (2) The stability of the complexes is strongly dependent on the medium. As expected from the coordinating properties of the anions towards lanthanides in methanol (29), the complexes are less stable in the presence of nitrate ions than in the presence of the less coordinating chloride, especially perchlorate/triflate anions. For instance, $\log \beta$ of the Eu^{3+} complex with **2b** decreases from 4.7 to 2.08 on going from the chlorides to the nitrates. Similar observations have been made with phosphorylated calixarenes, which have been ascribed to the strong ability of anions such as nitrates, to interact with the lanthanides and to compete with the ligands for their complexation (10).
- (3) The influence of the lanthanide contraction on the complex stability appears to be different according to the ligands. Whereas an irregular variation of stability prevails along the series with **1b** and **3b**, showing no specific trend, there is a clear decrease in the stability of the complexes with **2b**, for instance from 5.5 log units for the La^{3+} complex to 3.4 log units for the Yb^{3+} complex, when chloride is the counterion. Although to a lesser extent with **1b** and **3b**, Yb^{3+} seems to be the least complexed cation by the three ligands. These trends contrast with those observed for classical non-macrocyclic chelating agents (as for example aminopolycarboxylic ligands) (30), where the stability of lanthanide complexes generally increases along the series with the charge density on the cation. Obviously, other factors like the size and the flexibility of the ligands may account for these differences.
- (4) With **1b**, the stabilisation of the complexes is driven by the enthalpy and the entropy changes which vary irregularly from La^{3+} to Gd^{3+} . The former are clearly negative, ranging from -24.78 to $-31.77 \text{ kJ mol}^{-1}$, and the latter clearly positive, ranging from 21 to $25.78 \text{ kJ mol}^{-1}$, hence both being favourable. The situation is quite different with **2b**, since the stabilisation is only due to favourable entropy terms, which are more or less constant (73.4 – 71 kJ mol^{-1}) with the first three cations and increase to 81.7 kJ mol^{-1} with Gd^{3+} . In contrast, the enthalpy contribution is positive and hence unfavourable, especially with Gd^{3+} ($\Delta H = 50.8 \text{ kJ mol}^{-1}$). In fact, with both ligands, the entropic terms are always positive and favourable. This is certainly due to the importance of the solvation of the lanthanides. Another factor, which cannot be neglected, is the ligand solvation. With **2b**, possessing in its macrocyclic skeleton three ethereal oxygen atoms,

solvation is expected to be stronger than with **1b**. This can explain, at least partly, both the low enthalpy and the high entropy terms observed with the former ligand. In the absence of reliable data in methanol for the calix[4]arene counterpart **3b**, these results can be compared to previous data concerning the complexation of alkaline earth cations by **3b** in the same solvent. With these systems involving multicharged cations, the complexation process was also entropically controlled (31).

Changing the counterion from triflate to nitrate also has an influence on ΔH and $T\Delta S$, as seen for the complexation of lanthanum with **1b** and **2b**, which is characterised by slightly more favourable or less unfavourable enthalpic terms and to less positive entropic contributions. These results are consistent with the nitrate anions still interacting with the cation in the complexes.

Proton NMR studies

To obtain further information on the cation-binding behaviour of diethylamides **1b**, **2b** and **3b**, specifically concerning the binding sites, proton NMR titrations were performed in $\text{CDCl}_3/\text{CD}_3\text{OD}$. The cations studied were La^{3+} , Eu^{3+} and Yb^{3+} . Variable amounts of the salts were added to the ligands and the proton spectra were recorded after each addition.

Different situations were found after the addition of the salts to the ligands. The three amides exhibit similar behaviours towards La^{3+} . These titrations show that with $[\text{salt}]/[\text{ligand}]$ ratios lower than 1, both signals of the complexed and uncomplexed ligands are present in the spectra, indicating that on the NMR time scale, the exchange rate between the two species is slow at room temperature. This behaviour reflects the high affinity of these ligands towards La^{3+} as previously observed. Upon reaching 1:1 ratios, all the signals for the free ligands disappear and those of the complexed ligands remain unaltered after subsequent addition of the salt, indicating a 1:1 metal-to-ligand stoichiometry. In the case of ligand **1b**, besides the 1:1 complex, another set of sharp signals with lower intensity can be seen in the spectra, from the addition of the first aliquot of salt (Figure 5). This possibly reflects a 1:2 metal-to-ligand stoichiometry for the second complex (B), since the intensity of B peaks decreases as the addition of the salt proceeds. Similar situations have already been observed by us before (32, 33). In order to confirm the stoichiometry of these complexes, a Job plot based on ^1H NMR data was carried out. The Job plot shown in Figure 6 clearly confirms the formation of a 1:1 metal-to-ligand complex, but no unambiguous stoichiometry can be established from the curve for the weaker complex (B), due to the predominance of complex A (34). Complex B shows a plateau rather than a maximum

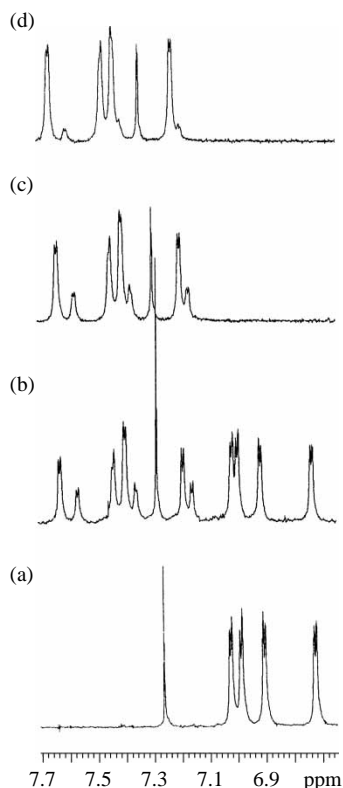


Figure 5. Aromatic region of the ^1H NMR spectra of **1b** in $\text{CDCl}_3/\text{CD}_3\text{OD}$, 22°C and 500 MHz. (a) Free ligand, (b) upon addition of 0.5, (c) 1 equiv. and (d) 3 equiv. of $\text{La}(\text{CF}_3\text{SO}_3)_3$.

between 0.5 and 0.6 mole fraction of **1b**, the same situation found by us before with two ketone derivative analogues and Ca^{2+} and Sr^{2+} cations. In contrast, titrations of diethylamides **1b**, **2b** and **3b** with Eu^{3+} and mainly Yb^{3+}

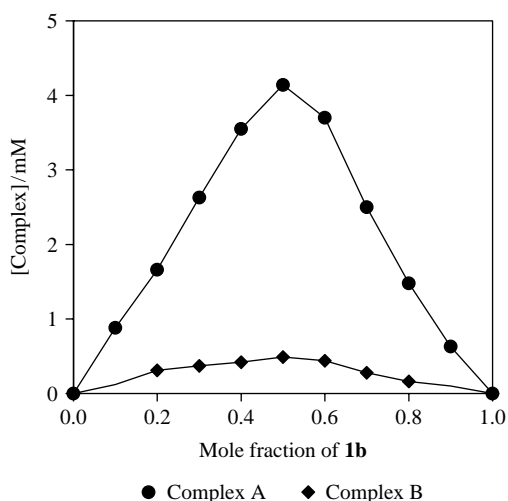


Figure 6. Job's plot based on ^1H NMR data for the system **1b** + La^{3+} ; total concentration $1 \times 10^{-2} \text{ M}$ in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (9:1, v/v).

produce broad and distorted proton signals, which are shifted towards high and low fields. This behaviour is more evident for derivatives **1b** and **3b**, and the shifts observed cover a range greater than 20 ppm. This is consistent with the knowledge that the binding of paramagnetic metal ions, such as Eu^{3+} and Yb^{3+} , causes enhanced shift and relaxation effects on the resonances of the nuclei of the ligands (6c). The results indicate that complexation occurs between the ligands and these cations, and are in agreement with those obtained by spectrophotometry/potentiometry in the present study.

Proton NMR data of the free and complexed ligands are shown in Table 4. The complete interpretation of the spectrum for compound **1b** required an additional COSY spectrum. However, in the case of the weaker complex (B), full proton assignment was not possible due to overlapping of signals arising from both complexed species. Complexation of La^{3+} affects all the proton chemical shifts in ligands **1b**, **2b** and **3b**. In the case of Eu^{3+} and Yb^{3+} , the broad and distorted signals obtained, as already mentioned, prevented a quantitative analysis of the data.

The largest chemical shift changes are recorded for the bridging axial methylene protons (ArCH_2Ar) and the oxygen bridge equatorial methylene protons (CH_2OCH_2), in the case of **2b**, which move upfield, and by the aromatic protons and the methylene protons of the OCH_2CO groups, which move downfield. As observed for other calixarenes, the variation in chemical shift experienced by the equatorial methylene protons (ArCH_2Ar) is downfield and smaller than that of the axial protons, but in the present case it is still very high ($\Delta\delta = 0.52$ and 0.53 ppm for **1b** and 0.60 ppm for **3b**). The CH_2OCH_2 resonances behave differently, as previously reported (21–23). The equatorial methylene protons of the oxygen bridge move upfield and experience larger shift variations than the axial ones. These results suggest that the oxygen bridge conformation changes significantly upon complexation, with the equatorial protons undergoing a higher shielding effect. The smallest variations are observed for the protons of the $\text{N}(\text{CH}_2\text{CH}_3)_2$ and *tert*-butyl groups.

A closer examination of the spectral changes upon complexation indicates that the differences in the chemical shifts between the axial and the equatorial protons of the ArCH_2Ar bridges in ligands **1b** and **3b** ($\Delta\delta = 1.64$, 1.77 ppm for **1b** and 2.10 ppm for **3b**) decrease ($\Delta\delta = 0.46$, 0.39 ppm for **1b** and 0.51 ppm for **3b**), being closer to 0.5 ppm (35). This suggests that the free ligands depart from a distorted cone conformation and adopt a flattened cone conformation after complexation, with their pendant arms moving closer together. If Gutsche's criterion is also applicable to the CH_2OCH_2 bridges, it indicates that ligand **2b** is much more flattened ($\Delta\delta = 0.32$ ppm) than **1b** and **3b**, and stands up when the cation enters into the ionophoric cavity ($\Delta\delta = 0.74$ ppm).

Table 4. Relevant proton chemical shifts (δ , ppm) of ligands **1b**, **2b** and **3b** and their metal complexes.

	<i>t</i> -Bu	ArCH ₂ Ar		CH ₂ OCH ₂		OCH ₂ CO	ArH
		Eq	Ax	Eq	Ax		
1b	0.95, 1.17	3.27, 3.31	4.91, 5.08	4.67	4.89	4.36, 4.78, 4.90, 5.04	6.72, 6.90, 6.99, 7.02
1b + La ³⁺ (A)	1.18, 1.26	3.80, 3.83	4.26, 4.22	4.36	4.94	4.97, 5.04, 5.46, 5.49	7.20, 7.41, 7.45, 7.64
1b + La ³⁺ (B)	1.23, 1.26	^a	^a	4.33	4.90	^a	7.17, 7.37, 7.41, 7.58
2b	1.08	–	–	4.62	4.94	4.57	6.98
2b + La ³⁺	1.15	–	–	4.36	5.10	4.75	7.02
3b	1.07	3.19	5.29	–	–	5.02	6.78
3b + La ³⁺	1.19	3.79	4.30	–	–	5.34	7.34

^a Not possible to assign.

The deshielding effect observed for the aromatic protons indicates the involvement of the phenolic oxygens in complexation, as reported previously (36). The largest shift changes shown by the protons adjacent to the oxygen donor atoms can be explained in terms of variations of both shielding and deshielding effects of the aromatic rings and carbonyl groups upon cation binding to those donor atoms. Therefore, this suggests that the cation must be inside the cavity defined by the phenoxy and carbonyl oxygen atoms and bound through metal–oxygen interactions.

Conclusions

Extraction studies from an aqueous solution in to CH₂Cl₂ and stability constant measurements in methanol have shown that diethylamide **1b** is a very strong binder for lanthanides, showing high extraction percentages and the highest stability constant values ever found with this ligand ($\log \beta = 8.6$ – 9.2). It displays some preference for the light lanthanides (from La³⁺ to Eu³⁺) in extraction, but it does not noticeably discriminate between them (from La³⁺ to Yb³⁺) in complexation. In the case of diethylamide **2b**, the data showed that it is a weaker extractant and exhibits lower $\log \beta$ values, but it is a more selective ligand, showing clearly a positive discrimination for the light lanthanides. The weaker binding power of **2b** may be due to its lack of donating sites compared to **1b**, as lanthanide cations require high coordination numbers. Diethylamide **3b** exhibits a similar behaviour to that of its analogue **1b**, at least in complexation. With **1b**, the complexation process of all the cations is enthalpically and entropically stabilised, since the enthalpy changes are clearly negative, while the entropy changes are positive. In contrast, the complexation process with **2b** is governed by the entropy changes only. Proton NMR titrations corroborated the formation of 1:1 complexes between all the amides and La³⁺ cation, also indicating that the cation should be encapsulated into the cavity defined by the phenoxy and the carbonyl oxygen atoms. In the case of complexation of **1b** with La³⁺, besides the 1:1 complex, minor amounts of another complex with a different ligand-to-metal stoichiometry was formed.

Experimental

Extraction studies

Equal volumes (5 μ l) of aqueous solutions of metal picrates (2.5×10^{-4} M) and solutions of the calixarenes (2.5×10^{-4} M) in CH₂Cl₂ were vigorously shaken for 2 min, and then thermostated in a water bath with mechanical stirring at 20°C overnight. After complete phase separation, the concentration of the picrate ion in the aqueous phase was determined spectrophotometrically ($\lambda_{\max} = 354$ nm). For each cation–calixarene system, the absorbance measurements were repeated at least four times. Blank experiments showed negligible picrate extraction in the absence of a calixarene. The details of the metal picrate preparation have already been described (23).

Determination of stability constants

UV absorption spectrophotometric titrations were carried out to obtain the stability constants ($\log \beta$) of the complexes formed between the lanthanide chlorides (and in some cases lanthanide nitrates) and the two ligands **1b** and **2b**. All the experiments were performed in methanol at 25°C in the presence of Et₄NCl as the supporting electrolyte. The detail of the procedure has been published previously (28). The ligand concentrations were in the range 6.4×10^{-5} – 5.7×10^{-4} M and the final cation-to-ligand concentration ratios were in the range 1.5–10, depending on the strength of the complexes. The measurements were treated by the program Specfit (37) to give the stoichiometry and the stability constants of the complexes. For very stable complexes ($\log \beta \geq 7$), i.e. with ligands **1b** and **3b**, potentiometric titrations based on a competition with Ag⁺ as the auxiliary cation, were performed as already described (28). The Ag⁺ concentration was typically around 7.5×10^{-4} M. Similar lanthanide concentrations were used except for Yb³⁺ solutions, which were about 1.6×10^{-4} M. The data were treated using the program SIRKO (38).

The lanthanide (lanthanum, praseodymium, europium, gadolinium and ytterbium) salts used for spectrophotometric measurements were chlorides and in some cases (lanthanum, europium and ytterbium) also nitrates. They

were all purchased from Alfa Aesar (99.99%). Tetraethylammonium chloride (Fluka, purum, $\geq 98\%$) and nitrate (Acros Organics, 99%) supporting electrolyte were used without further purification. The metal salts used for potentiometric measurements were the lanthanide and silver trifluoromethanesulphonates (Alfa Aesar, min 98%). In these cases, tetraethylammonium perchlorate (Fluka, purum, $\geq 99\%$) was used as the supporting electrolyte. All these salts were dried under vacuum at ambient temperature during 48 hours before use. The concentration of the lanthanide stock solutions (*ca.* 10^{-2} M) was standardised by complexometry with EDTA using xylenol orange as the coloured indicator (39). The concentration of Ag^+ solutions was determined by potentiometry with the addition of NaCl. Methanol (Sigma-Aldrich, Chromasolv, water content max 0.03%) was used without further purification.

Microcalorimetric titrations

Microcalorimetric experiments were performed using a 2277 thermal activity monitor microcalorimeter (Thermometric). Titrations were carried out at 25°C on $2.5\ \mu\text{l}$ of the ligand solution in methanol of concentrations ranging from 8.0×10^{-5} to 4.0×10^{-3} M, using a $4\ \mu\text{l}$ glass cell. The heats of complexation were measured after addition of $17 \times 15\ \mu\text{l}$ aliquots of *ca.* 6.0×10^{-3} M lanthanide triflate solutions or *ca.* 5.0×10^{-2} M lanthanum nitrate solutions in the same solvent and then corrected for the heat of dilution of the metal salt determined in separate titrations without the ligands. Chemical calibration of the calorimeter was made by determination of the complexation enthalpy of Rb^+ with 18C6 in methanol as recommended (40). With ligands **1b** and **3b**, the stability constants ($\log \beta \geq 7$) were high enough to consider the complexes formed completely after each addition of the metal ion. In this case, the complexation enthalpy, ΔH , was obtained from the slope of the linear plots of the corrected cumulated heats exchanged vs. the number of moles of the metal added until the 1:1 stoichiometry. With ligand **2b**, which forms less stable complexes with all the cations studied except La^{3+} , $\log \beta$ and ΔH were calculated simultaneously using the program DIGITAM version 4.1 (41). The corresponding complexation entropies were then calculated from the equations $\Delta G = \Delta H - T\Delta S$ and $\Delta G = -RT \ln \beta$, knowing β from spectrophotometry.

Proton NMR experiments

Several aliquots (up to 2–3 equiv.) of the salt solutions (0.25 M) in CD_3OD were added to CDCl_3 solutions (5×10^{-3} M) of the ligands directly in the NMR tube. The salts used were La, Eu and Yb triflates. Due to the low solubility of Eu triflate in MeOH, it was necessary to decrease the concentration of the ligand (2.5×10^{-4} M) and of the salt (4.17×10^{-3} M). The spectra were recorded

on a Bruker Avance III 500 spectrometer after each addition of the salts. The temperature of the NMR probe was kept constant at 22°C . Job's method was performed for diethylamide **1b** and La triflate. The total concentration was maintained at 1×10^{-2} M in $\text{CDCl}_3/\text{CD}_3\text{OD}$ (9:1). The COSY spectrum was the result of 32 transients per increment, in a total of 256.

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