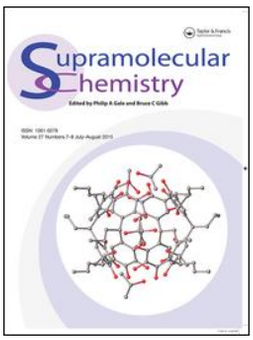

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ARTICLE

Syntheses of ester and amide derivatives of calix[6]arene and their complexation affinities towards La^{3+}, Eu^{3+}, and Yb^{3+}

Marina Tranfić Bakić[a], David Klarić[b], Maria Soledad Espinosa[c], Saša Kazazić[d], Leo Frkanec[e], Paola Alejandra Babay[c] and Nives Galić[b]

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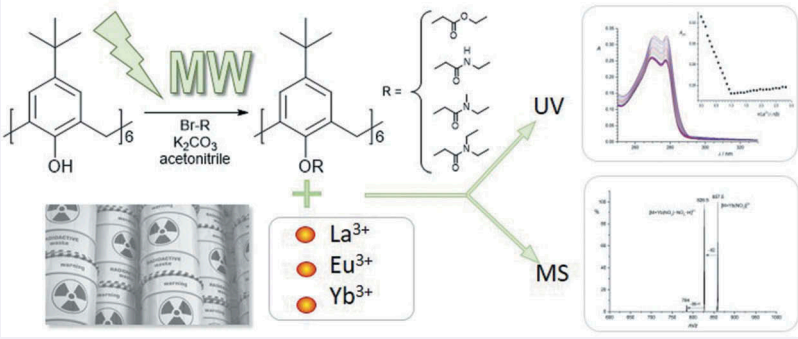
ABSTRACT

One hexaester (**1**) and three hexaamide derivatives (**2**–**4**) of calix[6]arenes were prepared for the first time in one synthetic step, under microwave radiation. Compounds **2** and **3** were novel ones, while ester calix[6]arene derivative **1** and amide derivative **4** were prepared previously, by conventional syntheses. Microwave-assisted syntheses shortened the reaction times from 48 to 2 h. The binding properties of calix[6]arenes towards selected lanthanide cations (La^{3+}, Eu^{3+}, Yb^{3+}) were studied by spectroscopic and mass spectrometric techniques. No complexation was observed with the ester derivative, while compounds **2**–**4** formed 1:1 complexes. Based on spectrophotometric titrations, the stability constants of resulting complexes could only be estimated (lg $K \geq 6$). Calixarene derivatives, as well as their complexes, were analysed by ESI MS and MS/MS spectrometry. Corresponding fragmentation pathways were proposed, and in some cases confirmed by MS^3 experiments. The results obtained by different techniques were in accordance.



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calix[6]arene; lanthanides; complexation; UV spectroscopy; mass spectrometry (MS)

Introduction

Nuclear radioactive waste management is an important and quite challenging step in the development of sustainable and environmentally safe nuclear fuel cycles. Today, the standard for used nuclear fuel processing is PUREX (Plutonium Uranium Refining by Extraction) process, a large-scale actinide solvent extraction separation, which recovers uranium and plutonium for reuse in the production of new nuclear fuel (1, 2). The by-product of this process is radiotoxic waste consisting of nitric acid solutions containing transplutonium long-lived radionuclides. Their separation from nuclear waste and transmutation into short-lived isotopes is currently the preferred strategy in nuclear waste management optimization. Within this process, intra- and inter-group separation of lanthanide (Ln) and actinide (An) families of elements is of significant interest for their reuse as fuel for new generation reactors. Difficulties arise from similar ionic radii and very similar chemical behaviour of these cations, and therefore a quest for ligands that could efficiently and selectively bind and separate them continues (3, 4).

Calixarenes, a family of macrocycles well known for their sensitive and selective cation binding properties

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Supplemental data for this article can be accessed here

(5), emerged as an obvious choice for extraction of radionuclides from nuclear waste. Furthermore, relatively easy functionalization of the lower rim of the calixarene annulus provides means to obtain a wide range of scaffolds which makes them perfect three-dimensional platforms for molecular design (5, 6). This was the reason why their utilization in nuclear waste treatments was proposed some decades ago by *Commissariat à l'énergie atomique et aux énergies alternatives*, France (CEA) (3, 7). Ever since, calixarene-based supramolecular ligands received much attention as potential extractants to be used in nuclear waste partitioning (8). Amongst the first calixarene derivatives studied for this purpose were those incorporating phosphonic groups (9–12), which were proved to be good extractants for separation of lanthanides and actinides in the frame of nuclear reprocessing. Unfortunately, these ligands cannot be completely burned, since they incorporate phosphorous atoms, which is their significant disadvantage. On the other hand, utilization of derivatives consisting only of C, H, O, and N atoms would enable their incineration to gaseous products after use without an increase of secondary solid waste. Having in mind that amide derivatives of calixarenes have been known to have a large coordination affinity towards transition and inner transition metal cations, it is not surprising that they present an interesting alternative (13–15). Although several of such ligands showed good results in respect to complexation and extractions of selected actinides, a quest for more efficient, selective, and sensitive ligands of desired chemical composition and properties is still ongoing.

Since 1990s, when it became more available and more widely used in chemical laboratories, microwave heating technique has emerged as an alternative approach in organic synthesis, offering several advantages over conventional heating, most importantly spectacular acceleration of reactions, higher yields under milder reaction conditions, and higher product purities (16–18). In calixarene chemistry, microwave-assisted chemistry is dominantly used for the synthesis of *p*-alkylcalix[4]arenes by condensation reaction of *p*-alkylated phenols in the presence of formaldehyde, which was shown to be much faster and more efficient compared to conventional procedure (19, 20). Nevertheless, only a few papers describing modifications of the lower calixarene rim utilizing microwave radiation can be found in the literature (21, 22). Research presented by S. K. Nayak and M. K. Choudhary describes previously mentioned advantages of this approach when applied to syntheses of 1,3-dialkyl ethers of calix[4]arene form parent *p-tert*-butylcalix[4]arene. Furthermore, it was shown that microwave-assisted synthesis does not require the utilization of anhydrous reaction conditions, which is of tremendous importance in conventional synthesis, and the obtained calixarene derivatives attained exclusively the *cone* conformation, which is also a very significant advantage (23). To the best of our knowledge, the only example thus far of microwave-assisted modification of the lower rim of calix[6]arenes was described by Galán et al., utilizing NaH as a strong base in DMF (24). Herein, we propose a different microwave-based methodology for modification of the calix[6]arene lower rim by using K_2CO_3, a mild base, in acetonitrile.

UV spectroscopy is a very useful tool for studies of described cation-ligand complexations. On the other hand, mass spectrometry (MS) offers some advantages in studies of non-covalent interactions occurring during complexations, such as specificity, sensitivity, and speed, as well as the possibility of stoichiometry determination (11).

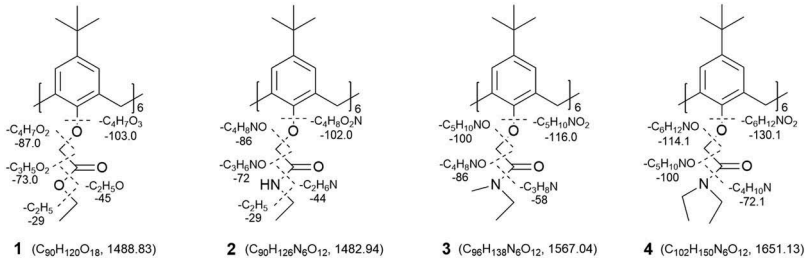
Recently, we have reported the results of studies on binding properties of some peptidocalixarenes as well as ester and amide derivatives of calix[4]arenes towards alkali-metal and selected lanthanide cations (La^{3+}, Ce^{3+}, Eu^{3+}, Yb^{3+}) (25, 26).

In this paper, we present syntheses, UV-Vis spectroscopic and MS investigations of ester and amide derivatives of calix[6]arenes, namely 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-[(ethoxycarbonyl)methoxy]calix[6]arene (**1**), 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(*N*-ethyl-carbamoylmethoxy)calix[6]arene (**2**), 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(*N*-ethyl-*N*-methyl-carbamoylmethoxy)calix[6]arene (**3**), and 5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41,42-hexakis-(*N,N*-diethyl-carbamoylmethoxy)calix[6]arene (**4**) (Scheme 1). Compounds **1, 3**, and **4** were prepared with use of microwave radiation, while synthesis of **2** did not require heating and was performed at room temperature. Coordination properties of the prepared ligands towards selected lanthanide cations (La^{3+}, Eu^{3+}, Yb^{3+}) were studied.

Materials and methods

Chemicals

All reagents used in the syntheses were of the best grade commercially available and were used without further purification. Solvents were purified by standard procedures. Microwave-assisted syntheses were performed in a Milestone START S Microwave Labstation for Synthesis microwave reactor. The power of the microwave radiation ranged from 0 to 500 W and was allowed to vary in order to maintain the set temperature. Reaction course and purity of the products were checked by thin-layer chromatography (TLC) on Merck, DC-Alufolien Kieselgel 60 F254. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AV300 or AV600 MHz spectrometer with $(CH_3)_4Si$ as an internal standard.



Scheme 1. Structures of the studied calix[6]arene derivatives and corresponding fragmentation pathways.

The salts used in the investigations of complexation of synthesized ligands were $La(NO_3)_3 \times 6H_2O$, $Eu(NO_3)_3 \times 6H_2O$, $Eu(CF_3SO_3)_3$ 98%, $Yb(NO_3)_3 \times xH_2O$, (Fluka, p.a. and Sigma Aldrich, 99.99%). The solvents, acetonitrile (Merck, Uvasol) and methanol (Merck, Uvasol), were used without further purification.

Syntheses

*Microwave-assisted synthesis of 5,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexakis-[(ethoxycarbonyl)methoxy]calix[6]arene (**1**)*

In 5 cm^3 of acetonitrile, 0.39 g of 4-tert-butylcalix[6]arene (5,11,17,23,29,35-hexa-tert-butylcalix[6]arene-37,38,39,40,41,42-hexol) (0.40 mmol), 1.01 g of 2-bromoethyl acetate (6.03 mmol), and 1.67 g of potassium carbonate (12.06 mmol) were suspended and stirred for 2 h at 92°C while exposed to microwave radiation. The organic solvent was evaporated and the reaction mixture was then extracted with dichloromethane/water. The dichloromethane layer was collected and evaporated, and the residue was recrystallized from absolute ethanol to give 560 mg of compound **1** (94% yield). NMR and IR spectra correspond to the literature data (27).

*5,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexakis-(N-ethyl-carbamoylmethoxy)calix[6]arene (**2**)*

In a flask with a stopper, 1.0 g (0.87 mmol) of 55,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexakis-[(ethoxycarbonyl)methoxy]calix[6]arene (**1**) was dissolved in 7 mL of ethylamine. The resulting solution was left in a sealed flask at room temperature until TLC analysis showed the disappearance of starting hexaethyl ester **1** (usually requiring 10–14 days). The reaction mixture was evaporated to dryness, and the residue was triturated with ethanol, filtered and dried. Compound **2** (983 mg) was obtained as a white solid (74% yield).

IR (KBr, ν/cm^{-1}): 2959, 1666, 1533, 1475; ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C), δ/ppm: 0.75–1.46 (m, 72H, $C(CH_3)_3$ and $NHCH_2\underline{CH_3}$), 2.28–4.90 (m, 36H, $ArCH_2Ar$,OCH_2CO, and $NHC\underline{H_2}CH_3$), 5.95–8.50 (m, 18H, ArH and N<u>H</u>); ^{13}C NMR ($CDCl_3$, 300 MHz), δ/ppm: 12.4, 14.5, 14.8, 15.1, 15.4, 29.2, 29.5, 31.2, 31.3, 31.4, 31.5, 31.6, 31.7, 31.8, 34.0, 34.4, 63.3, 71.4, 73.4, 126.9, 128.5, 131.7, 132.2, 132.8, 132.9, 133.3, 145.5, 145.8, 146.0, 146.5, 150.9, 151.9, 152.1, 152.8, 153.3, 154.2, 167.4, 167.7, 168.1, 168.2, 168.6; ^{1}H NMR (DMSO-d_6, 300 MHz, 100°C), δ/ppm: 0.70–1.61 (m, 72H, $C(CH_3)_3$ and $NHCH_2\underline{CH_3}$), 2.55–4.83 (m, 36H, $ArCH_2Ar$,OCH_2CO, and $NHC\underline{H_2}CH_3$), 6.47–8.44 (m, 18H, ArH and N<u>H</u>). MS(MALDI TOF/TOF): m/z = 1483.9524 $[M + H]^+$. ($C_{90}H_{126}N_6O_{12}$, exact mass = 1483.9512).

*Microwave-assisted synthesis of 5,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexakis-(N-ethyl-N-methyl-carbamoylmethoxy)calix[6]arene (**3**)*

In 5 cm^3 of acetonitrile, 0.25 g of 4-*tert*-butylcalix[6]arene (5,11,17,23,29,35-hexa-tert-butylcalix[6]arene-37,38,39,40,41,42-hexol) (0.25 mmol), 680 µL of 2-bromo-*N*-ethyl-*N*-methylacetamide (3.75 mmol), and 1.04 g of potassium carbonate (7.50 mmol) were suspended and stirred for 2 h at 94°C while exposed to microwave radiation. The organic solvent was evaporated and the reaction mixture was then extracted with dichloromethane/water. The dichloromethane layer was collected and evaporated, and the residue was recrystallized from acetonitrile to give 282 mg of compound **3** (72% yield).

IR (KBr, ν/cm^{-1}): 2957, 1659, 1481; ^{1}H NMR ($CDCl_3$, 300 MHz, 25°C), δ/ppm: 0.71–1.42 (m, 54H, $C(CH_3)_3$), 2.38–4.95 (m, 54H, $ArCH_2Ar$, OCH_2CO, $NC\underline{H_2}CH_3$, and $NHCH_2\underline{CH_3}$), 3.32 (s, 18H, $NC\underline{H_3}$), 6.40–6.76 (m, 4H, ArH), 7.23–7.76 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz), δ/ppm: 12.4, 12.6, 12.6, 12.6, 13.1, 14.0, 14.0, 14.1, 14.1, 14.2, 31.4, 31.5, 31.6, 31.7, 31.8, 32.6, 32.7, 32.8, 34.0, 34.2, 34.2, 34.3, 34.3, 34.4, 34.4, 34.5, 41.8, 42.2, 42.3, 42.3, 42.4, 43.3, 43.4, 43.6, 43.8, 43.9, 43.9, 70.3, 71.1, 71.9, 123.5, 128.1, 128.4, 128.7, 129.1, 132.3, 132.4, 132.9, 133.3, 133.5, 145.3, 145.7, 146.3, 154.1, 154.9, 167.2, 167.6; ^{1}H NMR (DMSO-d_6, 300 MHz, 100°C), δ/ppm: 0.70–1.61 (m, 54H, $C(CH_3)_3$), 2.55–4.83 (m, 60H, $ArCH_2Ar$, $NC\underline{H_3}$, $NC\underline{H_2}CH_3$, and $NHCH_2\underline{CH_3}$), 4.23–4.94 (bs, 12H, OCH_2CO), 6.19–7.94 (m, 12H, ArH). MS (MALDI TOF/TOF): m/z = 1569.0530 $[M + H]^+$. ($C_{96}H_{138}N_6O_{12}$, exact mass = 1569.0529)

*Microwave-assisted synthesis of 5,11,17,23,29,35-hexa-tert-butyl-37,38,39,40,41,42-hexakis-(N,N-diethyl-carbamoylmethoxy)calix[6]arene (**4**)*

In 5 cm^3 of acetonitrile, 0.60 g of 4-*tert*-butylcalix[6]arene (5,11,17,23,29,35-hexa-tert-butylcalix[6]arene-37,38,39,40,41,42-hexol) (0.62 mmol), 1.79 g of 2-bromo-*N,N*-diethylacetamide (9.24 mmol), and 2.55 g of potassium carbonate (18.48 mmol) were suspended and stirred for 2 h at 94°C while exposed to microwave radiation. Organic solvent was evaporated and the reaction mixture was then extracted with dichloromethane/water. The dichloromethane layer was collected and evaporated, and the residue was recrystallized from methanol to give 777 mg of compound **4** (76% yield).

NMR and IR spectra correspond to the literature data (28).

Spectrophotometry and spectrofluorimetry

UV titrations were performed using a Perkin-Elmer λ 25double-beam spectrophotometer, whereas fluorimetric measurements were carried out using a PerkinElmer LS-55 spectrofluorimeter, both equipped with a thermostatting device. UV and fluorescence spectra were obtained at (25.0 ± 0.1) °C using 1 cm optical path length quartz cells. Spectral changes of solutions of ligands were recorded upon stepwise additions of a lanthanide salt solution directly into the measuring cell. Absorbances were collected with an integration time of 0.2 s, whereas fluorescence intensities were sampled with scanning speed of 600 nm min^{-1}, both with a resolution of 0.5 nm. Titrations for each M^{3+}/**L** system (M^{3+} stands for a lanthanide cation and **L** denotes a calix[6]arene ligand) were done at least in triplicate. The obtained data were processed using the HYPERQUAD program (29) and OriginPro 2016. In the course of determinations of stability constants of the complexes, absorption of the nitrate anion was taken into account.

Mass spectrometry

Mass spectra were acquired by Triple Quadrupole 6420 (Agilent Technologies) and Ion trap (Amazon ETD, Bruker Daltonik, Bremen, Germany) instruments. The working conditions for QqQ were as follows: capillary potential = 3.5 kV, fragmentor voltage = 135 V, gas flow (N_2) = 8 dm^3 min^{-1} and temperature 300 °C. Collision energies used were 10–50 V. Collision gas was N_2. The spectra were acquired in positive ion mode from *m/z* 100 to 2000. The Ion trap operated at the following conditions: capillary potential = 4.5 kV, drying gas flow rate: 5 dm^3 min^{-1}; drying gas temperature: 250 °C. Collision energy used for CID fragmentation was in the range 0.2–1.0 V. Helium was used as the collision gas. The spectra were recorded in the *m/z* range 50–2500.

The stock solutions of ligands and metal salts ($c = 1 \times 10^{-3}$ and 5×10^{-3} mol dm^{-3}) were prepared in acetonitrile. The molar ratio Ln^{3+}: ligand were 1:1, 5:1 and 10:1 in solutions measured by QqQ. The ligand concentrations in solutions measured by IT amounted to 1×10^{-6} mol dm^{-3}, while the metal ion concentration was $c(Ln^{3+}) = 5 \times 10^{-5}$ mol dm^{-3}.

Results and discussion

Synthesis

The studied compounds were prepared in one synthetic step from *p*-tert-butylcalix[6]arene, under microwave radiation. Ester and amide subunits were introduced into the lower rim of calix[6]arene by alkylation of phenolic groups with electrophiles. The conventional synthesis of compound **1** was previously described by Arnaud-Neu et al. (27) and synthesis of compound **4** by Casnati et al. (28). Nevertheless, microwave-assisted syntheses presented in this paper showed some advantages compared to conventional syntheses. The dominant positive effect was significantly shorter reaction times. More precisely, while conventional syntheses were performed under reflux for 48 h, reaction mixtures subjected to microwave radiation provided the desired products in only 2 h with similar reaction yields. Another very important advantage was the absence of necessity for anhydrous reaction conditions, facilitating the performing of the reaction.

The obtained calixarene derivatives were characterized by spectroscopic methods, elemental analysis, and high-resolution mass spectrometry. The ^1H NMR spectra of all four studied calixarene derivatives in $CDCl_3$ at 25 °C showed very complex signal patterns, containing a large number of peaks, which can be ascribed to structural flexibility of calix[6]arenes (30). Since the exchange between conformations is slow on the NMR timescale, sets of peaks originating from each separate conformer appear in the spectrum. The exception was of compound **1**, whose ^1H NMR spectrum consisted of five broad signals, as described by Arnaud-Neu (27). In this case, a rise in temperature caused faster exchange between conformers and thus sharpening of the signals. Similar was observed for hexaamide diethyl derivative **4** (28). ^1H NMR spectra of newly synthesized calixarene derivatives **2** and **3** were also recorded in DMSO-d_6 at 100°C. In their case, on the contrary, increase in temperature led to merging of peaks into broad signals, indicating that conversion between the conformers, although it did become faster, still was not fast enough to result with a single average peak. This effect was more pronounced in the case of tertiary methyl-ethyl amide derivative **3** than for secondary amide derivative **2**.

The composition of the mixture of conformers was not further investigated. All proceeding measurements were performed with mixtures of conformational isomers as such at 25 °C.

Spectrophotometric titrations and spectrofluorimetry

To investigate the affinity of the studied calixarene derivatives towards selected lanthanide cations, spectrophotometric titrations were performed. The stepwise addition of the acetonitrile solution of $La(NO_3)_3$ to the solution of ligand **1** caused a linear increase in the absorbance (Fig. S1.1 in Supplemental material, SM). The same trend was observed for the complexation of ligand **1** with $Yb(NO_3)_3$ and $Eu(NO_3)_3$ (Figs. S1.2 and S1.3 in SM). On the other hand, upon addition of the solution of europium triflate, insignificant changes in the absorbance spectrum of ligand **1** occurred (Fig. S1.4 in SM). All this pointed towards the conclusion that ligand **1** does not bind the studied cations, and any observed increase in the absorbance can be accounted for by the absorbance of the nitrate anion, which absorbs in the same spectral region as the studied calix[6]arene ligand **1**.

Unlike the ester derivative, amide derivatives **2**, **3**, and **4** showed strong affinity towards the complexation of the studied lanthanide cations. During the corresponding titrations, a sharp break in titration curves at $n(M^+)/n(\mathbf{L}) = 1$ (where M^{3+} denotes any of the studied cations, and **L** calixarene ligands) appeared, suggesting the formation of the complexes with 1:1 stoichiometry and rather strong binding. In all cases, stability constants of the resulting complexes were too high to enable their spectrophotometric determination, and could be only estimated at $\lg K \geq 6$. As examples, titrations of these ligands with La^{3+} are presented in Figures 1, 2, and 3, and their titrations with $Yb(NO_3)_3$, $Eu(NO_3)_3$, and $Eu(CF_3SO_3)_3$ in SM, Figs. S1.5 – S1.13. The same behaviour was observed for complexation of the corresponding calix[4]arene derivatives (ester, secondary ethylamide and tertiary diethylamide) with the same cations (26).

It is known that calix[6]arene derivatives with tertiary amide subunits at the lower rim, such as diethylamine derivative, strongly bind sodium and potassium cations (28, 31), as well as strontium cation (32), resulting with formation of either 1:1 or 1:2 complexes, i.e. two cations occupying the calixarene cavity. The formation of a bimetallic complex was also reported for hexamethoxycalix[6]arene with titanium(IV)cation (33). On the contrary, we found that La^{3+}, Yb^{3+}, and Eu^{3+}, which have comparable ionic radii, form only 1:1 complexes with ligands **2**–**4**. The reason could be mutual repulsion of triply charged ions in close proximity inside a limited space offered by the calixarene cavity, whereas in the previous example, titanium cations are incorporated into calixarene cavity in the form of ($Cl_3TiOTiCl_2$) units, rather than 'naked' Ti^{4+} cations.

During titrations of ligands **2**–**4** with $Eu(NO_3)_3$, after the $n(M^+)/n(\mathbf{L}) = 1$ break in the titration curve, absorption increased significantly, as shown in Figures S1.5, S1.8, and S1.11 in SM. This effect was the result of absorbance of nitrate ions from $Eu(NO_3)_3$ salt as can be seen in Fig.

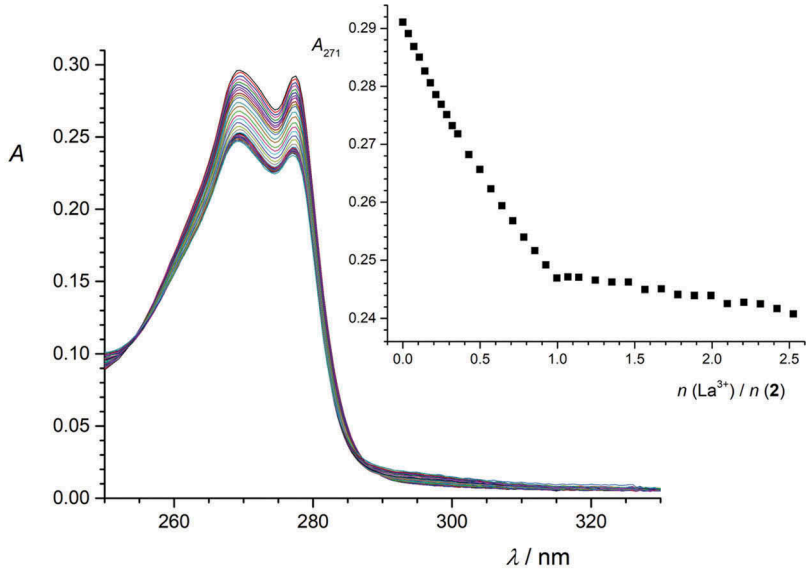


Figure 1. Spectrophotometric titration of **2** ($c = 6.97 \times 10^{-5}$ mol dm^{-3}) with La^{3+} (c ($La(NO_3)_3 \times 6H_2O$) $= 5.02 \times 10^{-4}$ mol dm^{-3}) in acetonitrile. $l = 1$ cm; $\vartheta = (25.0 \pm 0.1)$ °C; the spectra are corrected for dilution. Inset: Dependence of absorbance at 271 nm on La^{3+} concentration.

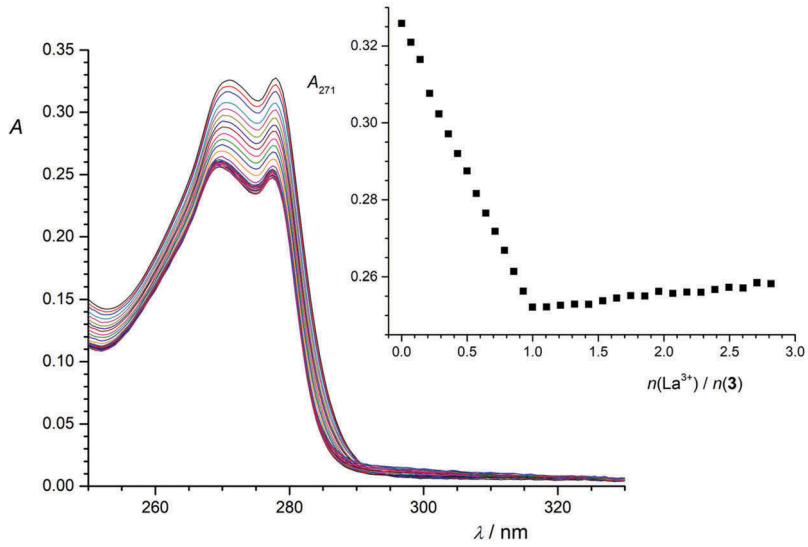


Figure 2. Spectrophotometric titration of **3** (c = 7.23 × 10^{-5} mol dm^{-3}) with La^{3+} (c ($La(NO_3)_3$ × $6H_2O$) = 5.00 × 10^{-4} mol dm^{-3}) in acetonitrile. l = 1 cm; ϑ = (25.0 ± 0.1) °C; the spectra are corrected for dilution. Inset: Dependence of absorbance at 271 nm on La^{3+} concentration.

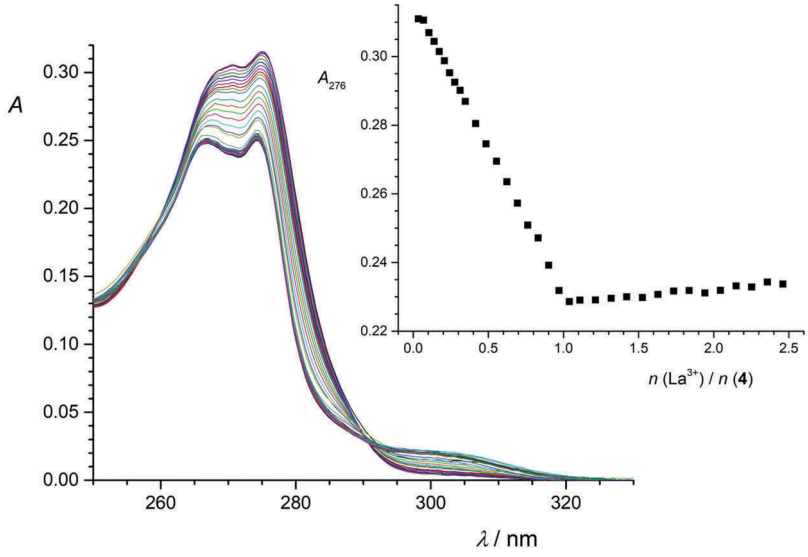


Figure 3. Spectrophotometric titration of **4** (c = 6.51 × 10^{-5} mol dm^{-3}) with La^{3+} (c ($La(NO_3)_3$ × $6H_2O$) = 5.02 × 10^{-4} mol dm^{-3}) in acetonitrile. l = 1 cm; ϑ = (25.0 ± 0.1) °C; the spectra are corrected for dilution. Inset: Dependence of absorbance at 276 nm on La^{3+} concentration.

S1.5c. The other nitrates ($Yb(NO_3)_3$ and $La(NO_3)_3$) also absorb in this particular region of the spectra but with much lower molar absorptivities. Also, the above mentioned increase in absorbance was not noticed during the titrations with europium triflate.

Finally, the emission spectra of the ligands and their complexes in acetonitrile were also recorded. The wavelength corresponding to absorption maxima (determined from the UV-Vis spectra) was used as excitation wavelength for spectrofluorimetric measurements. Unfortunately, free ligands did not show any significant fluorescence, and the changes upon addition of the cations were too small to provide any insight into the complexation process.

Mass spectrometry

MS and MS/MS spectra of compounds 1-4

To get more insight into the complexation reaction of calixarene derivatives, the mass spectrometry was used. The MS spectra of compounds **1**–**4** in acetonitrile are

shown in SM (Tables S2.1–S2.5, Fig. S1 in SM). Depending on the ligand and instrument used, the most intense signals were assigned to $[M + 2H]^{2+}$, $[M + H + K]^{2+}$ or $[M + Na]^{+}$ (M stands for the calixarene molecule). The peaks corresponding to adducts with impurities already present in the system (Na^+, K^+, NH_4^+) are usually observed in MS spectra of calixarene derivatives (11, 26).

Tandem mass spectrometry was used to determine fragmentation pathways of selected ions: $[M + H]^{+}$, $[M + 2H]^{2+}$, $[M + Na]^{+}$, $[M + K]^{+}$ and $[M + H + K]^{2+}$ whenever it was possible to isolate them. Previously, we have shown that both homolytic and heterolytic cleavage can occur during the collision-induced dissociation of calixarenes (26). Similar cleavage was recorded during fragmentation of compound **1**, heterolytic for $[\mathbf{1} + H]^{+}$ (loss of 28 Da) and homolytic for adducts $[\mathbf{1} + Na]^{+}$, $[\mathbf{1} + K]^{+}$ and $[\mathbf{1} + H + K]^{2+}$. As an example, the fragmentation scheme of $[\mathbf{1} + Na]^{+}$ is given in Figure 4, while MS/MS spectra are shown in Figs S2.2–S2.4 in SM. During adducts fragmentation, loss of part and whole subunit were noticed. In MS/MS spectrum of doubly charged $[\mathbf{1} + H + K]^{2+}$ ion, the formation of singly charged ions and corresponding signals at higher masses was observed.

The fragmentation of protonated amide derivative **2** included the loss of C_2H_6N (–45 Da), C_3H_6NO (–73 Da) and C_4H_8NO group (–85 Da). The MS/MS spectrum at 0.8 V and fragmentation scheme are given in Figs. S2.5 and S2.6 in SM. More energy (1.0 V) was needed to fragment sodiated adduct (Fig. S2.7 in SM).

Higher fragmentation potential (1.2 V) was applied for CID experiments on protonated ligand **3** (Fig. S2.8 in SM). Although the cleavage of calixarene ring and the loss of four subunits were noticed, as well as the part of subunit, the signal of parent ion was still the most intense one, indicating the high stability of compound **3** in the gas phase. This was confirmed by acquiring MS/MS spectrum on triple quadrupole at 70 V (Fig. S2.9 in SM). Proposed fragmentation scheme is given in Fig. S2.10 in SM.

The cleavage of bonds in *α*- and *β*- position to heteroatom in subunits was observed during fragmentation of $[\mathbf{4} + Na]^{+}$ ion resulting with loss of parts of subunit: $C_5H_{10}NO$ (–100 Da), $C_6H_{12}NO$ (–114 Da) and $C_6H_{12}NO_2$ (–130 Da) (Fig. S2.11 and S2.12 in SM).

The fragmentation of protonated amide derivative **2** included the loss of C_2H_6N (–45 Da), C_3H_6NO (–73 Da) and C_4H_8NO group (–85 Da). The MS/MS spectrum at 0.8 V and fragmentation scheme are given in Figs. S2.5 and S2.6 in SM. More energy (1.0 V) was needed to fragment sodiated adduct (Fig. S2.7 in SM).

MS and MS/MS spectra of lanthanide complexes

The MS spectra of complexes recorded by QqQ or IT differ due to different ligand concentrations and Ln^{3+}:ligand molar ratio. However, some general conclusions can be pointed out. In MS spectra acquired by QqQ, dominant signals were those assigned to complexes with Ln^{3+} like $[\mathbf{M} + Ln]^{3+}$, while in MS spectra recorded with IT, the

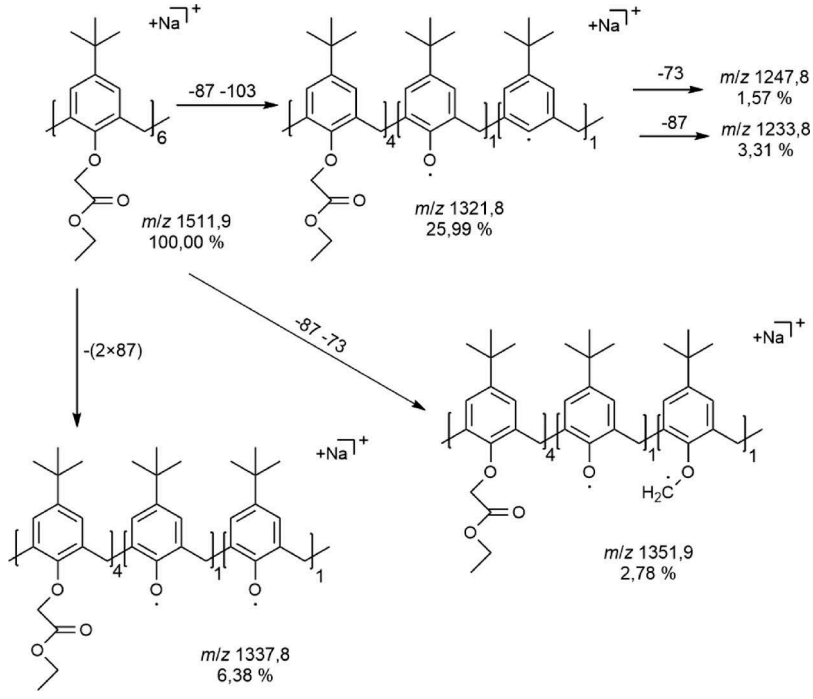


Figure 4. Proposed fragmentation pathway of $[\mathbf{1} + Na]^{+}$ (*m/z* 1512) at 0.8V.

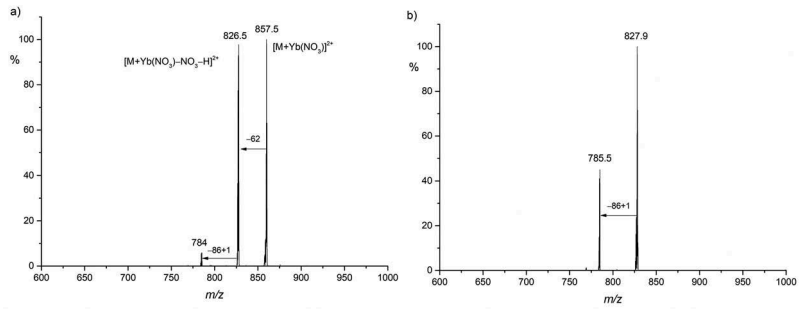


Figure 5. MS^2 (a) and MS^3 (b) spectra of [**2**+ $Yb(NO_3)]^{2+}$ (m/z = 857.5) at 0.20 V.

intense signals were assigned to [**M** + $Ln(NO_3)_2]^{2+}$ or even [**M** + H + K]$^{2+}$ ions (Tables S2.6–2.20 in SM). Due to large cavity in calix[6]arene derivatives, the signals assigned to complexes with two metal salts ([**M** + $Ln(NO_3)$+$Ln(NO_3)_2]^{3+}$ or [**M** + 2× $Ln(NO_3)_2]^{2+}$) were noticed, which was not the case in MS spectra of analogue complexes with derivatives of calix[4]arenes.[17] However, the corresponding intensities were low, except in the case of complexes with Eu^{3+}, indicating that with this particular ion not only 1:1 complex was formed in solution. Among studied ligands, the compound **2** can form intramolecular H-bonds which should be broken upon complexation. As a consequence, the intensities of the signals assigned to [**M** + Ln]$^{3+}$ complexes were less intense than those observed in MS spectra of complexes with compounds **3** and **4**, indicating a stronger binding of metal ions by these ligands. The complexation of lanthanides by ester derivative was not observed at all, which was in agreement with results obtained by UV titrations.

MS/MS measurements were performed on [**M** + Ln]$^{3+}$ and [**M** + $Ln(NO_3)_2]^{2+}$. As example, the MS^2 and MS^3 spectra of ytterbium complex with compound **2** are given on Figure 5, and all other spectra on Figs. S2.16–S2.34 in SM. As can be seen, the loss of nitro group (–63 Da) followed by loss of C_4H_8NO group (–86 Da) was recorded, and confirmed by MS^3 experiment. The cleavage of the bonds next to phenyl oxygen, and loss of adequate fragments of calixarene subunits was recorded for other complexes as well. In general, the complexes were quite stable, and the increase from ~0.2 to 1 V was needed to completely fragment the isolated ions.

During the fragmentation of [**M** + Ln]$^{3+}$ ions, additional loss of *tert*-butyl groups (–57 Da) as well as the loss of one or two calixarene subunits, was recorded.

Conclusions

In this work, we have shown that microwave-assisted synthesis is a suitable method for preparation of ester and amide calix[6]derivatives. Two of four synthesized compounds were not described in the literature previously. The coordination properties of calix[6]arenes towards selected lanthanide cations (La^{3+}, Eu^{3+}, Yb^{3+}) were investigated by spectroscopic and mass spectrometric measurements. No complexation of the cations by the hexaester derivative was observed, while hexaamide derivatives strongly bound lanthanide cations, and can, therefore, be potentially used as good extracting agents.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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