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Modified Calix[4]crowns as Molecular Receptors for Barium

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A series of modified calix[4]crown-6 derivatives was synthesized to chelate the heavy group 2 metal barium, which serves as a non-radioactive surrogate for radium-223/-224; radionuclides with promising properties for radiopharmaceutical use. These calixcrowns were functionalized with either cyclic amide moieties or with deprotonizable groups, and the corresponding barium complexes were synthesized. Stability constants of these complexes were measured by using NMR and UV/Vis titration techniques to determine log*K* values of >4.1. Further extraction studies were performed to characterize the binding affinity of calixcrowns to radioactive barium-133. Additionally, the ligands containing cyclic amides were investigated regarding their rotational barriers by using temperature-dependent NMR measurements.

1. Introduction

Calixarenes, in general, belong to an interesting class of compounds.[1–3] They are widely used for the encapsulation of small molecules, ions,[4] pharmaceuticals, and natural compounds[5] like amino acids or proteins.[6] The host–guest chemistry of calixarenes[7] is known for the transportation of pharmacological relevant compounds,[8–10] as reactors for catalysis,[11–13] or to functionalize nanoparticles.[14,15] Other applications involve calixarenes as extracting agents for (radio)metal ions[16,17] in the environment and as chemical sensors[18,19] for the determination of cations[20] and anions.[21] In this regard, a large variety of special functionalized calixarenes was prepared.

Combining crown ethers and calixarenes is beneficial insofar as crown ethers are known to be useful candidates for chelating metal ions.[22–24] Calixcrowns, in contrast to normal calixarene derivatives, lead to higher stability constants and to higher selectivities for metal cations, in most cases.[25] Essentially, in radiopharmacy, high complex stabilities are required to avoid the release of the radiometal from the resulting complex in vivo.[26] This is especially important for the use of group 2 (radio)metal ions like Sr^{2+}, Ba^{2+}, or Ra^{2+}, as there are no suitable ligands known so far.[27] Furthermore, a targeting unit has to be introduced to the ligand to address the motif of biological or pharmacological interest.

The aim of this investigation was the determination of stability constants of calix[4]crowns with barium ions through NMR and UV/Vis titration. Thereby, dependence on their cavity size and further functionalization was explored. Moreover, the ligand-ion-interaction was examined by performing pH-dependent two-phase extraction studies with radioactive $[^{133}Ba]Ba^{2+}$. Barium is not only a metal of radiopharmaceutical interest, but the non-radioactive isotopes could also serve as surrogates for radium-223/-224. These two radium isotopes have suitable half-lives and nuclear decay properties that make them useful tools for α-particle therapy. Until now, $[^{223}Ra]RaCl_2$ (Xofigo®) is the only EMA- and FDA-approved radiopharmaceutical for α-therapeutic applications.[28] $[^{223}Ra]RaCl_2$ directly addresses the bone. To access other targets, chelate complex formation is essential. The obtained results of the barium studies give an idea of the complex formation behavior of radium, as direct studies with radium are not suitable, owing to the high radioactivity and a long half-life.

2. Results and Discussion

A large variety of functionalized calix[4]crown ethers as well as some of their complexes with Ba^{2+} and Ra^{2+} are known from the literature.[27,29–31] Only little is known about the respective complex stability constants. Mainly, extraction studies with these calix compounds and (radio)metals were accomplished.

The basic compound 5,11,17,23-tetrakis(*tert*-butyl)-25,27-dihydroxycalix[4]arene-crown-6 (**1**) was selected as the starting

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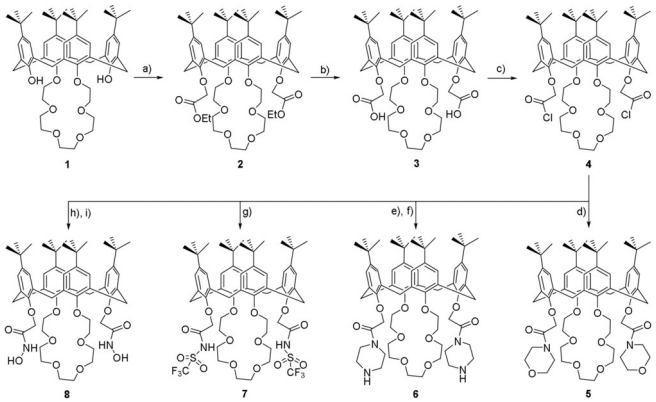
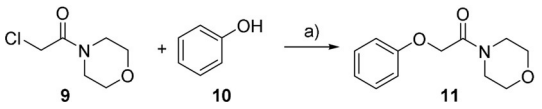
material. However, it was proven in extraction studies that its cavity fits best for heavier group 2 metals.[32] For the recent studies, this scaffold was further functionalized with deprotonizable groups other than hydroxy groups. These groups are also known to stably bind (Sr^{2+}), Ba^{2+}, and Ra^{2+} with good selectivity over Mg^{2+} and Ca^{2+}.[27]

Based on compound **1**, five calixarenes with distinctively differing functionalities were chosen to be further investigated (compounds **3**, **5**–**8**). Compound **3** is a simple deprotonizable carboxylic acid and the starting compound for following modifications. The calix derivatives **7** and **8** are easily deprotonizable, owing to their electron-withdrawing groups. Furthermore, the amide nitrogen atom plays an important role in the ligand–metal coordination. Compounds **5** and **6** were prepared to increase the steric demand in order to avoid the release of Ba^{2+}. The preparation of all functionalized calixarenes started from calix[4]crown-6 derivative **1**,[31,33,34] which was further converted into diester **2**. After saponification, the resulting diacid **3** was reacted with oxalyl chloride to give dichloride **4**. The chloride was reacted with the respective amines and amides without isolation and purification to give calixarenes **5**–**8**. In the case of the piperazine and the hydroxamic derivatives **6** and **8**, a final deprotection step was necessary. The preparation of the calix compounds **2**–**8** is shown in Scheme 1.



Scheme 1. Synthetic scheme for preparing the calix[4]crowns **2**–**8**. *Reagents and conditions:* a) NaH, ethyl bromoacetate, NaI, 50 °C, overnight; b) Me_4NOH, methanol, 55 °C, overnight; c) oxalyl chloride, CCl_4, 65 °C, 5 h; d) morpholine, Et_3N, dichloromethane, room temperature, overnight; e) *N*-boc-piperazine, Et_3N, dichloromethane, room temperature, overnight; f) trifluoroacetic acid, dichloromethane, room temperature, 2 h; g) trifluoromethanesulfonamide, NaH, THF, room temperature, overnight; h) *O*-benzylhydroxylamine·HCl, pyridine, THF, 35 °C, overnight; i) Pd/C–H_2, acetic acid/methanol (v/v = 1/3), room temperature, overnight.

During the characterization of the calix compounds, the analysis of the ^{1}H NMR spectra of morpholine compound **5** and piperazine derivative **6** indicated an amide rotational barrier, which could cause reduced complex stabilities. For a deeper understanding, compound **11**[35] was synthesized from the starting materials **9** and **10** (Scheme 2), which functions as a mono-structural element of calix derivative **5**. Temperature-dependent NMR experiments were performed (see Figure 1 and the Supporting Information) in different solvents ($CDCl_3$, [D_3]acetonitrile and/or [D_6]DMSO). The coalescence temperature T_C and the difference in chemical shifts expressed as $\Delta\nu$ were determined to calculate the rotation barrier $\Delta G^{\#}$ of compounds **5**, **6**, and **11**, according to the Arrhenius equation.[36] These results are summarized in Table 1.



Scheme 2. Synthetic scheme to prepare 1-morpholino-2-phenoxyethan-1-one (**11**). *Reagents and conditions:* a) NaH, THF, 45 °C, overnight.

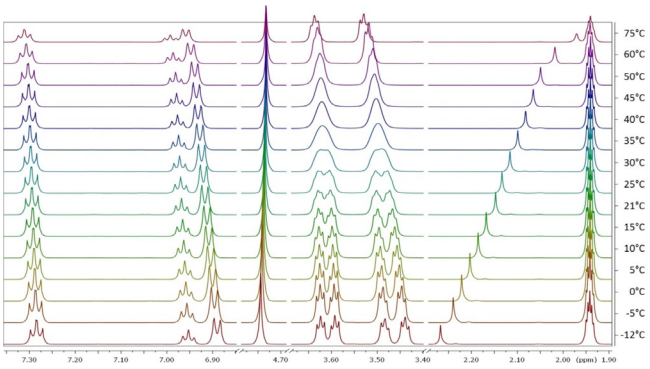


Figure 1. Temperature-dependent ^{1}H NMR experiment of **11** measured in [D_3]acetonitrile (region of interest from 1.90 to 7.40 ppm is shown).

Table 1. Coalescence points T_C and rotation barriers $\Delta G^{\#}$ of functional groups in compounds **5**, **6**, and **11** measured in selected NMR solvents.

Compd.	Solvent	$\Delta\nu$ [Hz]	k_{ex} [s^{-1}]	T_C [K]	$\Delta G^{\#}$ [kJ mol^{-1}]
11: OCH_2	$CDCl_3$	n.d.	–	n.d.	–
11: NCH_2	$CDCl_3$	17.5	38.9	291.15	62.4
11: OCH_2	[D_6]DMSO	n.d.	–	311.15	–
11: NCH_2	[D_6]DMSO	n.d.	–	299.15	–
11: OCH_2	CD_3CN	18.6	41.3	306.15	65.6
11: NCH_2	CD_3CN	26.5	58.9	306.15	64.7
5: OCH_2	$CDCl_3$	86.7	192.6	n.d.	–
5: NCH_2	$CDCl_3$	152.1	337.9	n.d.	–
5: OCH_2	[D_6]DMSO	49.9	110.9	325.15	67.1
5: NCH_2	[D_6]DMSO	41.5	92.1	325.15	67.6
6: $NCH_{2,\ amine}$	$CDCl_3$	51.2	113.7	320.15	66.0
6: $NCH_{2,\ amide}$	$CDCl_3$	135.8	301.7	n.d.	–
6: $NCH_{2,\ amine}$	[D_6]DMSO	18.3	40.7	316.15	67.8
6: $NCH_{2,\ amide}$	[D_6]DMSO	33.4	74.2	325.15	68.2

In general, the rotation barriers for calix derivatives **5** and **6** are higher ($\Delta G^{\#} \geq 66$ kJ mol^{-1}) than for the mono-compound **11** ($\Delta G^{\#} = 62.4$–65.6 kJ mol^{-1}), independent of the solvent used. This is explainable by the steric demand of the crown ether bridge of the calix or by the calix scaffold itself. Furthermore, two independent barriers were found: one for the amide site and one for the amine or ether site. This behavior was shown for similar compounds.[36] However, this results from the different conformations of the 6-membered ring system. Additionally, a single-crystal X-ray structure analysis was performed on **11**. The compound crystallized in the orthorhombic space

group *Pbca*. Crystal and structure refinement parameters are: $a = 10.7045(3)$, $b = 9.4112(3)$, $c = 21.9636(7)$ Å, $V = 2212.7(1)$ Å^3, $Z = 8$, $T = 123$ K, $2\theta_{max} = 74.2^\circ$, $R1 = 0.040$, $wR2 = 0.112$, GoF = 1.03. The crystals consist of neutral molecules of **11** and the molecular structure is shown in Figure 2.

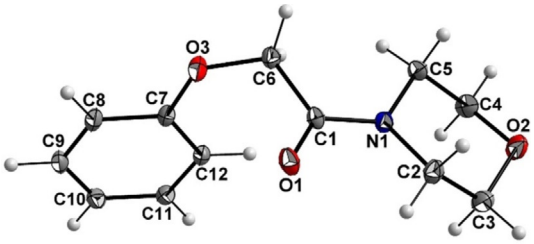


Figure 2. Molecular structure of compound **11** as mono-structural element in the crystal (ORTEP plot, ellipsoids at the 50% probability level at 123 K).

The N1–C1 bond is significantly shorter [1.3542(8) Å] than N1–C2 and N1–C5 [1.4621(8) and 1.4665(8) Å, respectively]. Nitrogen atom N1 points out of the mean plane of the surrounding atoms by only 0.122 Å. It is supposed to be a planar arrangement. Furthermore, the average value of the bond angles around nitrogen atom N1 is calculated to be 119.3°, leading to the result that the C1–N1 contact has, at least to some extent, π-bonding character. This partial double-bond character limits the ability of the molecule to rotate about this bond. In fact, two isomers exist in the solid in a 1:1 ratio. A superimposition of the two isomers is presented in Figure 3. This

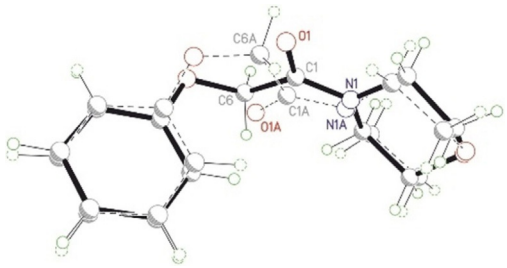
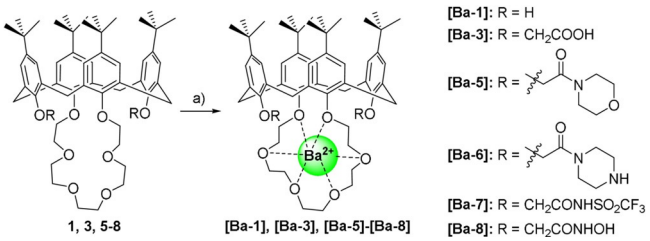


Figure 3. Superimposition fit of the two atropisomers in crystals of **11**, showing different orientations of the carboxylic groups.

was obtained by fitting the morpholine and the phenyl residue of both isomers on top of each other. It is nicely seen from Figure 3 that the two atropisomers differ in the orientation of the carboxylic and with respect to the two attached ring systems. This structural feature is in good accordance with the observed NMR properties.

Preparation of the respective barium complexes **[Ba-1]**, **[Ba-3]**, and **[Ba-5]-[Ba-8]** was executed by adding 1 equivalent of the respective calixarene to 5 equivalents of $Ba(ClO_4)_2$, both dissolved in acetonitrile. The resulting solution was then treated by ultrasound for 1 min at ambient temperature. After removal of the solvent, the residue was treated with chloroform and filtered. $Ba(ClO_4)_2$ is not soluble in chloroform and, thus, the filtrate contained the pure barium complex. Attempts to purify the complexes using column chromatography with silica gel were unsuccessful. After this procedure, only the respective ligand was obtained. To evidence the formation of the complexes, NMR spectra were recorded in $CDCl_3$. The synthesis procedure of the barium complexes is shown in Scheme 3. A comparison of the spectra of ligand **7** and its complex **[Ba-7]** is shown in Figure 4. Selected chemical shifts are listed in Table 2.



Scheme 3. Synthesis of **[Ba-1]**, **[Ba-3]**, and **[Ba-5]-[Ba-8]**. *Reagents and conditions:* a) $Ba(ClO_4)_2$, acetonitrile, ultrasound, room temperature.

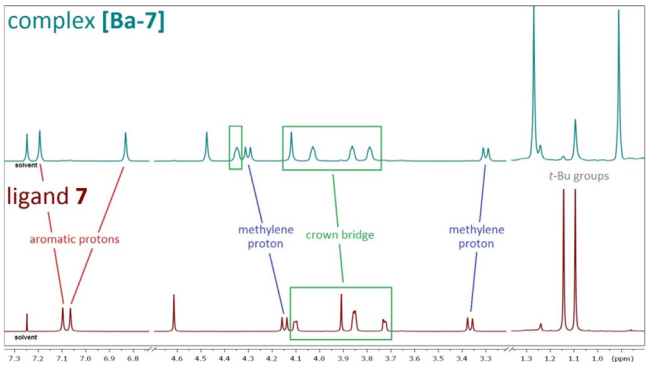


Figure 4. Comparison of ^{1}H NMR spectra from ligand **7** and complex **[Ba-7]**, measured in $CDCl_3$.

Table 2. Significant ^{1}H NMR chemical shifts of ligands **3**, **5**, and **7** in comparison with complexes **[Ba-3]**, **[Ba-5]**, and **[Ba-7]**.[a]

	3	[Ba-3]	5	[Ba-5]	7	[Ba-7]
CH_3	1.09/1.26	0.91/1.30	0.85/1.28	0.93/1.28	1.11/1.16	0.92/1.61
$CH_{2,e}$	3.48	3.39	3.15	3.46 (br.)	3.38	3.32
$CH_{2,a}$	4.13	4.26	4.46	4.84 (br.)	4.16	4.32
Ar-H	6.99/7.07	6.83/7.22	6.51/7.05	6.88/7.22	7.08/7.11	6.84/7.20
$CH_2C(O)$	4.71	4.61	4.58	4.84	4.63	4.48
DG	7.89	n.d.	–	–	n.d.	n.d.

[a] DG = deprotonizable group; e = equatorial; a = axial; n.d. = not detected.

In the past, we described a convenient way to determine complex stability constants for calix **1** using ^{1}H NMR measurements.[31] However, determination of the stability constants for the other ligands **5**–**8** was not amenable, owing to the host–guest complexation equilibrium. The equilibrium showed a slow exchange rate compared to the NMR timescale.[37] This leads to two species in the ^{1}H NMR spectrum. Instead, UV/Vis measurements were used. For this purpose, the calix ligand

was dissolved in acetonitrile and aliquots of $Ba(ClO_4)_2$ in acetonitrile were added, which caused a clear change in the absorption. This is shown in Figure 5, based on the example of compound **7** and its complex **[Ba-7]**. Considering one wavelength with a high change in absorption, the stoichiometry of the complex was determined from the diagram titration curve (Figure 6).

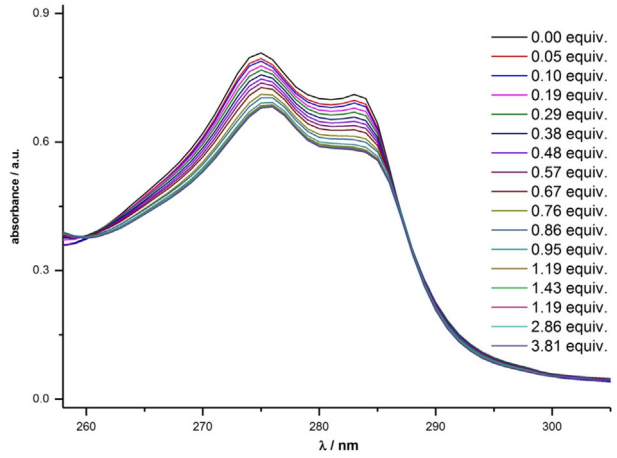


Figure 5. UV/Vis spectra of ligand **7** at different $Ba(ClO_4)_2$ concentrations measured in acetonitrile.

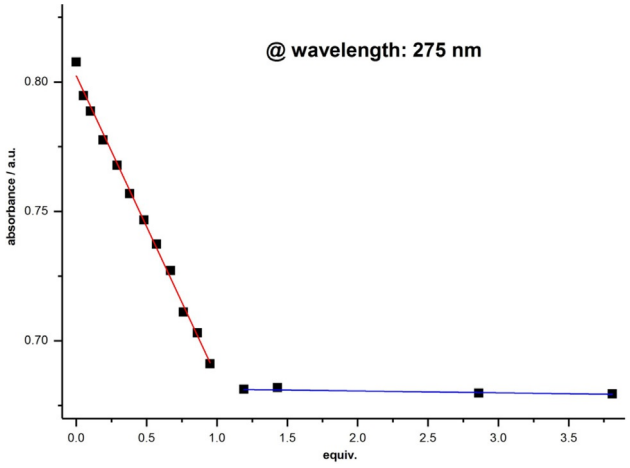


Figure 6. Change of the absorption of ligand **7** at different $Ba(ClO_4)_2$ concentrations, measured in acetonitrile.

All titration experiments showed the presence of a complex with a 1:1 stoichiometry, formed by ligands **5**–**8** with $Ba(ClO_4)_2$. The results are summarized in Table 3 (all titration experiments can be found in the Supporting Information).

The introduction of groups with steric demand seems to have no high influence on the complex stability constant (log*K* = 4.2 for **[Ba-5]** and **[Ba-6]**) compared to the simple calix[4]crown-6 complex **[Ba-1]** (log*K* = 4.1). A significant impact on the stability constant was found when deprotonizable groups were introduced additionally to the crown ether bridge, as proven for **[Ba-3]**, **[Ba-7]**, and **[Ba-8]**. A slightly higher log*K* value of 4.3 was found for diacid **[Ba-3]** and substantially higher log*K* values of > 5 were found for CF_3 complex **[Ba-7]** and hydroxamic acid derivative **[Ba-8]**. Both groups also have quite low pK_a values.[38,39] This leads to the conclusion that these functions serve as anions for Ba^{2+} and, thus, stabilize the whole complex due to the formation of a real ion pair.

Table 3. Stability constants for complexes **[Ba-1]**, **[Ba-3]**, and **[Ba-5]**–**[Ba-8]**.

Complex	R	log*K*	Method
[Ba-1][a]	H	4.6 ± 0.1	NMR
[Ba-1]	H	4.1 ± 0.4	UV
[Ba-3]	CH_2COOH	4.3 ± 0.2	UV
[Ba-5]	$CH_2CON(C_2H_4)_2O$	4.2 ± 0.2	UV
[Ba-6]	$CH_2CON(C_2H_4)_2NH$	4.2 ± 0.1	UV
[Ba-7]	$CH_2CONHSO_2CF_3$	> 5	UV
[Ba-8]	$CH_2CONHOH$	> 5	UV

[a] Data taken from Ref. [31].

For future radiolabeling purposes, extraction studies were first performed by using the radionuclide barium-133 (half-life: 10.5 a) as [^{133}Ba]$BaCl_2$ and functionalized calixarene ligands **5**–**8** as a function of pH (2, 6, and 10). For this experiment, equimolar amounts of carrier added [^{133}Ba]Ba^{2+} and the respective ligand **5**–**8** were used. The results in Table 4 are expressed as relative portions (average values) of the total starting activity in the aqueous phase, which were extracted to the ligand containing chloroform as the organic phase.

Table 4. Barium-133 extraction values [%] of ligands **5**–**8**.

Ligand	pH 2	pH 6	pH 10
5	0[a]	0[a]	4
6	0[a]	1	14
7	58	90	92
8	0[a]	5	47

[a] Value below limit of quantification.

Highest extraction values were found for ligand **7**. Owing to its high electron-withdrawing property, the trifluoromethanesulfonyl residue has a high influence on the deprotonation of the amide. Compared to compounds **5**, **6**, and **8**, there was a high extraction rate even at lower pH values. A slight enhancement of the extraction for compounds **5**, **6**, and **8** was detected at pH 10, which is related to the entire deprotonation of the ligands.

3. Conclusions

A selection of six calixcrown-based ligands **1**, **3**, **5**–**8** was synthesized, including two new compounds, **5** and **6**, to investigate their complexation properties with barium. During the product characterization by using NMR, a rotation barrier was determined for the morpholine ligand **5** and piperazine derivative **6**. Temperature-dependent NMR measurements were per-

formed to further calculate the energy values of the amide rotation barriers of these compounds. Barium complexes were synthesized from ligands **1**, **3**, and **5**–**8**. The characterization of the barium complexes was realized by using UV/Vis and NMR experiments as well as with two-phase extraction studies using [^{133}Ba]$BaCl_2$ as a radioactive compound. From the UV/Vis and NMR data, stability constants were calculated. It was clearly shown that compounds **7** and **8** formed the most stable complexes with barium ions. As a result, the influence of the bulky piperazine and morpholine residues had no benefit on the complex stability compared to the basic compound **1**.

Only compound **7** showed a high extraction rate over a wide pH range in extraction studies with [^{133}Ba]$BaCl_2$. A relative extraction of 90% of the starting radioactivity was determined for physiological conditions (pH 6) and even an extraction of 50% under acidic conditions (pH 2). This experiment proved that the two deprotonizable groups of **7** enhanced the stability of the complex significantly. In particular, the trifluoromethylsulfonyl amide moiety, which is expected to be the most acidic group of our investigation and easy to deprotonate, seemed to form strong ionic interactions.

For the general aim of a radiopharmaceutical usage of barium and radium, further modifications are required. Therefore, it will be necessary to focus on highly acidic functionalities like the trifluoromethylsulfonyl amide group and on a rigid backbone like the calixcrown skeleton. Finally, further functional groups have to be introduced to enable water solubility and biocompatibility.

Experimental Section

General

All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise specified. Anhydrous tetrahydrofuran (THF) was purchased from Acros, anhydrous $Ba(ClO_4)_2$ was purchased from Alfa Aesar, and deuterated solvents were purchased from deutero GmbH. Compounds **1**–**3**, **7**,[33] and **8**[40] were prepared according to the literature. [^{133}Ba]$BaCl_2$ was purchased from Polatom. NMR spectra of all compounds were recorded on an Agilent DD2-400 MHz NMR or an Agilent DD2-600 MHz NMR spectrometer with ProbeOne probe. Chemical shifts of the ^{1}H, ^{19}F, and ^{13}C spectra were reported in parts per million (ppm), using tetramethylsilane (TMS) as an internal standard for ^{1}H/^{13}C and $CFCl_3$ for ^{19}F spectra. Mass spectrometric (MS) data were obtained on a Xevo TQ-S mass spectrometer (Waters) by using electrospray ionization (ESI). The melting points were determined on a Galen III melting point apparatus (Cambridge Instruments & Leica) and are uncorrected. Thin layer chromatography (TLC) detections were performed by using Merck Silica Gel 60 F_{254} sheets. TLC plates were developed by visualization under UV light ($\lambda = 254$ nm). Chromatographic separations were accomplished by using an automated Biotage Isolera Four silica gel column chromatography system and appropriate Biotage KP-SIL SNAP columns. UV/Vis measurements were realized at a Specord 50 by Analytik Jena instrument. Radioactive count rates were detected by the gamma spectrometer ISOMED 2160. Diffraction data were collected with a Bruker Nonius Apex Kappa-II CCD diffractometer, using graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å) and the measurement was performed at −150 °C. The structure was solved by direct methods and refined against F^2 by full-matrix least-squares using the program suites from G. M. Sheldrick.[41,42] All non-hydrogen atoms were refined anisotropically; all hydrogen atoms were placed on geometrically calculated positions and refined by using riding models. CCDC 1817790 contains the supplementary crystallographic data for compound **11**.[43] The calculation of the stability constants was accomplished using the HypSpec 1.1.18 program.

Synthesis of the Ligands

5,11,17,23-Tetrakis(tert-butyl)-25,27-bis[N,N-(morpholino)carbamoyl]-calix[4]arene-crown-6 (5)

Calix **3** (120 mg, 0.12 mmol) was suspended in CCl_4 (5 mL), oxalyl chloride (900 mg, 7.1 mmol) was added and the mixture was stirred for 5 h at 65 °C. After cooling to room temperature, the solvent was removed, anhydrous dichloromethane (5 mL) was added, and a mixture of morpholine (27 mg, 0.31 mmol) and triethylamine (31 mg, 0.31 mmol) dissolved in 5 mL of dichloromethane was also added. After stirring at room temperature overnight, the mixture was filtered. The filtrate was washed with aqueous HCl (10%, 15 mL), saturated hydrogencarbonate solution (15 mL), and water (3×15 mL). The organic layer was dried, the solvent was removed, and the crude product was purified by using automated column chromatography (solvent: dichloromethane → dichloromethane/methanol 5:1) to give **5** a colorless solid (85 mg, 62%). M.p. 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (s, 18H; *t*Bu), 1.28 (s, 18H; *t*Bu), 3.15 (d, $^{2}J = 12.7$ Hz, 4H; CH_2Ar), 3.42 (s, 4H; OCH_2), 3.55 (s, 4H; NCH_2), 3.59–3.69 (m, 8H; $OCH_2 + NCH_2$), 3.72 (s, 4H; OCH_2), 3.74–3.85 (m, 8H; OCH_2), 4.14–4.27 (m, 8H; OEt), 4.46 (d, $^{2}J = 12.7$ Hz, 4H; CH_2Ar), 4.58 (s, 4H; CH_2), 6.51 (s, 4H; ArH), 7.05 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 31.3$ (*t*Bu), 31.4 (CH_2Ar), 31.8 (*t*Bu), 33.8, 34.2 (2×C_q), 42.0, 46.0, 66.7, 67.0, 69.8, 70.7, 70.8, 71.2, 72.2, 72.8 (10×CH_2), 125.1, 125.7 (2×CH_{Ar}), 132.2, 135.1, 145.0, 145.3, 152.2, 154.5 (6×$C_{q\text{-}Ar}$), 167.4 ppm (C=O); MS (ESI+): *m/z* (%) = 1105 (40) [$M^+ + H$], 1122 (70) [$M^+ + NH_4$], 1127 (100) [$M^+ +$ Na].

5,11,17,23-Tetrakis(tert-butyl)-25,27-bis[N,N-(piperazino)carbamoyl]-calix[4]arene-crown-6 (6)

Calix **3** (430 mg, 0.445 mmol) was dissolved in CCl_4 (30 mL), oxalyl chloride (3.2 g, 25.3 mmol) was added and the mixture was stirred for 5 h at 65 °C. After removal of the solvent, the crude product was dissolved in anhydrous dichloromethane (15 mL) and *N*-Boc-piperazine (207 mg, 1.11 mmol) and triethylamine (112 mg, 1.11 mmol) were added. After stirring at room temperature overnight, the mixture was filtered, the filtrate was washed with aqueous HCl (10%, 20 mL), and saturated hydrogencarbonate solution (20 mL) and water (3×20 mL). The organic layer was dried, the solvent was removed, and the crude product was purified by using automated column chromatography (solvent: dichloromethane → dichloromethane/methanol 7:1) to give **Boc-6** as a colorless solid (310 mg, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (s, 18H; *t*Bu), 1.28 (s, 18H; *t*Bu), 1.45 (s, 18H; Boc-*t*Bu), 3.15 (d, $^{2}J = 12.7$ Hz, 4H; CH_2Ar), 3.31–3.45 (m, 16H; NCH_2), 3.71 (s, 4H; OCH_2), 3.73–3.84 (m, 8H; OCH_2), 4.14–4.27 (m, 8H; OCH_2), 4.46 (d, $^{2}J = 12.7$ Hz, 4H; CH_2Ar), 4.59 (s, 4H; CH_2), 6.50 (s, 4H; ArH), 7.05 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 28.5$, 31.3 (2×*t*Bu), 31.4 (CH_2Ar), 31.8 (*t*Bu), 33.8, 34.2 (2×C_q), 41.6, 45.3 (2×CH_2N), 69.8, 70.7, 70.8, 71.1, 72.2, 80.4 (6×CH_2), 125.1, 125.7 (2×CH_{Ar}), 132.2, 135.0, 145.1, 145.2, 152.1, 154.5 (6×C_q), 154.6 (C=O), 167.3 ppm (C=O); MS (ESI+): *m/z* (%) = 1303 (37) [$M^+ + H$], 1320 (78) [$M^+ + NH_4$], 1325 (100) [$M^+ +$

Na]. For deprotection, *N*-Boc-calix **Boc-6** (254 mg, 0.195 mmol) was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (2 mL) was subsequently added. After stirring for 2 h, the solvent was removed in an airstream. The crude product was dissolved in dichloromethane (20 mL) and washed three times with NaOH (20 mL, 1 M). The organic layer was dried over Na_2SO_4 to give **6** (221 mg, quant.) without further purification as pale yellow solid. M.p. 139–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (s, 18H; *t*Bu), 1.32 (s, 18H; *t*Bu), 2.79–2.94 (m, 8H; NCH_2), 3.17 (d, $^2J = 12.3$ Hz, 4H; CH_2Ar), 3.46 (s, 4H; NCH_2), 3.66 (s, 4H; NCH_2), 3.73–3.82(m, 12H; OCH_2), 4.14–4.30 (m, 8H; OCH_2), 4.43 (d, $^2J = 12.7$ Hz, 4H; CH_2Ar), 4.49 (s, 4H; CH_2), 6.44 (s, 4H; ArH), 7.09 ppm (s, 4H; ArH). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 31.2$ (*t*Bu), 31.3 (CH_2Ar), 31.8 (*t*Bu), 33.7, 34.2 (2×C_q), 42.6, 45.8, 46.3, 46.6, 69.5, 70.6, 70.7, 71.0, 72.5, 72.9 (10×CH_2), 124.9, 125.7 (2×CH_{Ar}), 131.8, 135.3, 144.9, 145.2, 152.3, 154.6 (6×$C_{q\text{-}Ar}$), 166.9 ppm (C=O); MS (ESI+): *m/z* (%) = 1103 (12) [$M^+ + H$], 1120 (18) [$M^+ + NH_4$], 1125 (100) [$M^+ + Na$].

1-Morpholino-2-phenoxyethan-1-one (11)

Phenol **10** (298 mg, 3.17 mmol) was dissolved in anhydrous THF (15 mL) and NaH (138 mg, 3.45 mmol, 60% in mineral oil) was added. Afterwards, 2-chloro-1-morpholinoethan-1-one **9** (250 mg, 1.67 mmol) dissolved in chloroform (5 mL) was added dropwise and the resulting mixture was allowed to stir at 45 °C overnight. The solvent was removed; the crude was dissolved in dichloromethane (20 mL) and washed with water (2×20 mL). The organic layer was dried over Na_2SO_4, the solvent was removed, and the crude product was purified by using automated column chromatography (solvent: petroleum ether/ethyl acetate 4:1 → 1:1) to give **11** as a colorless solid (160 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.58$–3.68 (m, 8H; $NCH_2 + OCH_2$), 4.69 (s, 2H; CH_2), 6.94 (d, $^3J = 8.1$ Hz, 2H; ArH), 6.99 (t, $^3J = 6.4$ Hz, 2H; ArH), 7.27–7.31 ppm (m, 2H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 42.6$ (OCH_2), 46.1, 66.9, 67.8 (3×CH_2), 114.7 (CH_{Ar}), 121.9 (CH_{Ar}), 129.8 (CH_{Ar}), 157.8 ($C_{q\text{-}Ar}$), 166.7 ppm (C=O).

Synthesis of the Barium Complexes

The respective ligand **5**–**8** (1 equiv) and $Ba(ClO_4)_2$ (5 equiv) were dissolved in acetonitrile. The mixture was treated with ultrasound for 1 min, the solvent was removed, and chloroform was added. Afterwards, the solution was filtered and the filtrate contained the barium complexes in quantitative yield.

[Ba-1]

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (s, 18H; *t*Bu), 1.33 (s, 18H; *t*Bu), 3.41 (d, $^2J = 13.5$ Hz, 4H; CH_2Ar), 3.83–3.95 (m, 8H; OCH_2), 4.04 (s, 4H; OCH_2), 4.13–4.25 (m, 12H; $OCH_2 + CH_2Ar$), 6.48 (s, 2H; OH), 6.61 (s, 4H; ArH), 7.11 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 31.0$ (*t*Bu), 31.6 (CH_2Ar), 31.8 (*t*Bu), 34.0, 34.1 (2×C_q), 69.8, 70.2, 70.4, 71.1, 75.4 (5×CH_2), 125.8, 126.0 (2×CH), 128.5, 131.6, 143.6, 148.1, 149.2, 149.5 ppm (6×$C_{q\text{-}Ar}$).

[Ba-3]

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (s, 18H; *t*Bu), 1.28 (s, 18H; *t*Bu), 3.36 (br. s, 4H; CH_2Ar), 3.80–4.45 (m, 20H; OCH_2), 4.59 (br. s, 4H; CH_2Ar), 5.28 (s, 4H; CH_2), 6.80 (s, 4H; CH_2Ar), 7.26 ppm (s, 4H; ArH). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 30.0$ (CH_2Ar), 31.0 (*t*Bu), 31.6 (*t*Bu), 34.1, 34.4 (2×C_q), 53.6, 67.0, 69.2, 70.6, 70.7, 73.8 (6×CH_2), 126.2, 126.4 (2×CH), 132.8, 134.6, 147.9, 148.1, 152.6 (5×$C_{q\text{-}Ar}$), 174.8 ppm (C=O).

[Ba-5]

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (s, 18H; *t*Bu), 1.28 (s, 18H; *t*Bu), 3.39–3.52 (m, 8H), 3.69–4.16 (m, 36H), 4.23–4.43 (m, 8H), 4.84 (s, 4H; $CO(CH_2)O$), 6.88 (s, 4H; ArH), 7.22 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 30.1$ (CH_2Ar), 31.1, 31.6 (2×*t*Bu), 34.2, 34.5 (2×C_q), 42.9, 45.2, 66.3, 66.5, 68.0, 70.0, 70.8 (7×CH_2), 126.1, 126.6 (2×CH_{Ar}), 133.4, 134.6, 148.1, 148.3, 152.7 (5×$C_{q\text{-}Ar}$), 169.1 ppm (C=O).

[Ba-6]

^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): $\delta = 0.95$ (s, 18H; *t*Bu), 1.29 (s, 18H; *t*Bu), 3.00 (br. s, 6H; NCH_2), 3.37–3.49 (m, 8H; $CH_2Ar + NCH_2$), 3.79 (br. s, 4H; NCH_2), 3.91 (br. s, 4H; OCH_2), 3.97 (br. s, 8H; OCH_2), 4.06 (br. s, 4H; OCH_2), 4.31 (d, $^3J = 13.0$ Hz, 4H; CH_2Ar), 4.37 (br. s, 4H; OCH_2), 6.90 (s, 4H; ArH), 7.23 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$, 57 °C): $\delta = 29.9$ (CH_2Ar), 30.8, 31.4 (2×*t*Bu), 34.0, 34.2 (2×C_q), 43.6, 45.5, 46.0, 67.8, 69.6, 70.6, 77.8 (7×CH_2), 126.0, 126.4 (2×CH_{Ar}), 133.2, 134.4, 148.2, 152.6 (4×$C_{q\text{-}Ar}$), 168.6 ppm (C=O).

[Ba-7]

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.92$ (s, 18H; *t*Bu), 1.61 (s, 18H; *t*Bu), 3.32 (d, $^2J = 12.5$ Hz, 4H; CH_2Ar), 3.78–3.82 (m, 4H; OCH_2), 3.85–3.89 (m, 4H; OCH_2), 4.01–4.06 (m, 4H; OCH_2), 4.13 (s, 4H; OCH_2), 4.32 (d, $^2J = 12.5$ Hz, 4H; CH_2Ar), 4.34–4.38 (m, 4H; OCH_2), 4.48 (s, 4H; CH_2), 6.84 (s, 4H; ArH), 7.20 ppm (s, 4H; ArH). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 29.8$ (CH_2Ar), 31.1, 31.6 (2×*t*Bu), 34.1, 34.4 (2×C_q), 59.7, 66.5, 69.0, 70.9, 71.4, 78.7 (6×CH_2), 120.1 (q, $^1J_{C,F} = 322$ Hz; CF_3), 126.0, 126.3 (2×CH_{Ar}), 133.1, 134.8, 147.7, 148.2, 148.3, 152.3 (6×$C_{q\text{-}Ar}$), 176.1 ppm (C=O); ^{19}F NMR (565 MHz, $CDCl_3$): $\delta = -78.9$ ppm.

[Ba-8]

^{1}H NMR (400 MHz, $CDCl_3$, 57 °C): $\delta = 0.91$ (s, 18H; *t*Bu), 1.28 (s, 18H; *t*Bu), 3.00 (br. s, 6H; NCH_2), 3.30–3.47 (m, 4H; CH_2Ar), 3.77–4.39 (m, 28H; CH_2), 6.85 (s, 4H; ArH), 7.20 ppm (s, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$, 57 °C): $\delta = 29.9$ (CH_2Ar), 31.1, 31.7 (2×*t*Bu), 34.1, 34.4 (2×C_q), 53.6, 67.1, 69.2, 70.8, 70.9 (5×CH_2), 126.1, 126.5 (2×CH_{Ar}), 133.1, 133.2, 134.7, 148.1, 148.2, 152.6 (6×$C_{q\text{-}Ar}$), 173.4 ppm (C=O).

UV/Vis Titration Measurements

A solution of the corresponding ligand was prepared in acetonitrile. The concentration range was chosen to be 1.0 to 2.5 mM, depending on the absorption maxima of the compound. This solution (2.5 mL) was pipetted into a quartz cuvette of 1 cm optical path length. The titration was performed by a stepwise addition of a 25 mM $Ba(ClO_4)_2$ solution in acetonitrile. The absorption spectra were measured in the range of 190 to 400 nm.

Extraction Studies of Ligands 5–8 by using [^{133}Ba]$BaCl_2$

The respective ligands **5**–**8** (1 equiv) were dissolved in 600 µL chloroform. Carrier added [^{133}Ba]$BaCl_2$ (1 equiv, ca. 800 Bq) dis-

solved in 600 μL deionized water was added to the organic phase and treated in an overhead mixer for 1 h at room temperature to reach full equilibrium. pH adjustments were realized by adding NaOH or HCl. Small aliquots of both the organic and the aqueous phase were taken to determine the distribution of the [^{133}Ba]Ba^{2+}. The determination of the radioactivity as count rates was performed by using a gamma spectrometer.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: barium-133 · calixcrowns · extraction · radiolabeling · radium

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