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 radio pharmaceutical 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 logK 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 functionelize 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 Sr2+, Ba2+, or Ra2+, 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 [133Ba]Ba2+. 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, [223Ra]RaCl2 (Xofigo®) is the only EMA- and FDA-approved radiopharmaceutical for α-therapeutic applications. [28] [223Ra]RaCl2 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 Ba2+ and Ra2+ 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-tetakis(tert-butyl)-25,27-dihydroxycalix[4]arene-crown-6 (1) was selected as the starting...
material. However, it was proven in extraction studies that its cavity fits best for heavier group 2 metals.\textsuperscript{[2]} For the recent studies, this scaffold was further functionalized with deproto-
nizable groups other than hydroxy groups. These groups are also
known to stably bind (Sr\textsuperscript{2+}), Ba\textsuperscript{2+}, and Ra\textsuperscript{2+} with good se-
lectivity over Mg\textsuperscript{2+} and Ca\textsuperscript{2+}.\textsuperscript{[27]}

Based on compound 1, five calixarenes with distinctively dif-
fering functionalities were chosen to be further investigated
(compounds 3, 5–8). Compound 3 is a simple deproto-
nizable carboxylic acid and the starting compound for following
modifications. The calix derivatives 7 and 8 are easily deproto-
nizable, 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\textsuperscript{2+}. The preparation of all functionalized calixarenes started
from calix(4)crowns-6 derivative 1,\textsuperscript{[31,33,34]} which was further con-
verted 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 bromoceta-
eate, NaI, 50 °C, overnight; b) Me\textsubscript{3}NOH, methanol, 55 °C, overni-
t; c) oxalyl chloride, CDCl\textsubscript{3}, 65 °C, 5 h; d) morpholine, Et\textsubscript{3}N, dichloromethane, room tem-
perature, overnight; e) N-boc-piperazine, Et\textsubscript{3}N, dichloromethane, room temperature, overnight; f) tri-
fluoroacetic acid, dichloromethane, room temperature, 2 h; g) trifluorome-
thanesulfonamide, NaH, THF, room temperature, overnight; h) O-benzylhydroxylamineHCl, pyridine, THF, 35 °C, overni-
t; i) Pd/C–H\textsubscript{2}, acetic acid/meth-
anol (v/v = 1/3), room temperature, overnight.](image)

During the characterization of the calix compounds, the
analysis of the \textsuperscript{1}H NMR spectra of morpholine compound 5
and piperazine derivative 6 indicated an amide rotational barri-
er, which could cause reduced complex stabilities. For a
dereper understanding, compound 11\textsuperscript{[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\textsubscript{3},
[\textsubscript{D}\textsubscript{3}]acetonitrile and/or [\textsubscript{D}\textsubscript{3}]DMSO). The coalescence tempera-
ture \(T_c\) and the difference in chemical shifts expressed as \(\Delta\nu\)
were determined to calculate the rotation barrier \(\Delta G^\ddagger\) of
compounds 5, 6, and 11, according to the Arrhenius equation.\textsuperscript{[36]}
These results are summarized in Table 1.

In general, the rotation barriers for calix derivatives 5 and 6
are higher (\(\Delta G^\ddagger \geq 66\text{kJ mol}^{-1}\)) than for the mono-compound
11 (\(\Delta G^\ddagger = 62.4–65.6\text{kJ mol}^{-1}\)), 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.\textsuperscript{[36]} However, this results from the differ-
ent conformations of the 6-membered ring system. Additional-
ally, a single-crystal X-ray structure analysis was performed on
11. The compound crystallized in the orthorhombic space

![Figure 1. Temperature-dependent \textsuperscript{1}H NMR experiment of 11 measured in
[\textsubscript{D}\textsubscript{3}]acetonitrile (region of interest from 1.90 to 7.40 ppm is shown).](image)

| Compd | Solvent | \(\Delta\nu\) [Hz] | \(k_a\) [s\textsuperscript{-1}] | \(T_c\) [K] | \(\Delta G^\ddagger\) [kJ mol\textsuperscript{-1}] |
|-------|---------|-------------|----------------|---------|----------------|
| 11: OCH\textsubscript{3} | CDCl\textsubscript{3} | n.d. | n.d. | – | – |
| 11: NCH\textsubscript{2} | CDCl\textsubscript{3} | 17.5 | 38.9 | 291.15 | 62.4 |
| 11: OCH\textsubscript{3} | [\textsubscript{D}\textsubscript{3}]DMSO | n.d. | – | 311.15 | – |
| 11: NCH\textsubscript{2} | [\textsubscript{D}\textsubscript{3}]DMSO | n.d. | – | 299.15 | – |
| 11: OCH\textsubscript{3} | CD-CN | 18.6 | 41.3 | 306.15 | 65.6 |
| 11: NCH\textsubscript{2} | CD-CN | 26.5 | 58.9 | 306.15 | 64.7 |
| 5: OCH\textsubscript{3} | CDCl\textsubscript{3} | 86.7 | 192.6 | n.d. | – |
| 5: NCH\textsubscript{2} | CDCl\textsubscript{3} | 152.1 | 337.9 | n.d. | – |
| 5: OCH\textsubscript{3} | [\textsubscript{D}\textsubscript{3}]DMSO | 49.9 | 110.9 | 325.15 | 67.1 |
| 5: NCH\textsubscript{2} | [\textsubscript{D}\textsubscript{3}]DMSO | 41.5 | 92.1 | 325.15 | 67.6 |
| 6: NCH\textsubscript{2} | CDCl\textsubscript{3} | 51.2 | 113.7 | 320.15 | 66.0 |
| 6: NCH\textsubscript{2} | [\textsubscript{D}\textsubscript{3}]DMSO | 135.8 | 301.7 | n.d. | – |
| 6: NCH\textsubscript{2} | [\textsubscript{D}\textsubscript{3}]DMSO | 18.3 | 40.7 | 316.15 | 67.8 |
| 6: NCH\textsubscript{2} | [\textsubscript{D}\textsubscript{3}]DMSO | 33.4 | 74.2 | 325.15 | 68.2 |

![Scheme 2. Synthetic scheme to prepare 1-morpholino-2-phenoxyethan-1-
one (11). Reagents and conditions: a) NaH, THF, 45 °C, overnight.](image)
group Pbca. Crystal and structure refinement parameters are: 

\[ a = 10.7045(3), \quad b = 9.4112(3), \quad c = 21.9636(7) \text{ Å}, \]

\[ V = 2212.7(1) \text{ Å}^3, \]

\[ Z = 8, \quad T = 123 \text{ K}, \quad 2\theta_{\text{max}} = 74.2^\circ, \quad R1 = 0.040, \quad wR2 = 0.112, \quad \text{GoF} = 1.03. \]

The crystals consist of neutral molecules of 11 and the molecular structure is shown in Figure 2.

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, Ï€-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 superposition of the two isomers is presented in Figure 3. This 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(ClO₄)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(ClO₄)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 CDCl₃. 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.

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

|          | 3      | [Ba-3] | 5      | [Ba-5] | 7      | [Ba-7] |
|----------|--------|--------|--------|--------|--------|--------|
| CH₃      | 1.09/1.26 | 0.91/1.30 | 0.85/1.28 | 0.93/1.28 | 1.11/1.16 | 0.92/1.61 |
| CH₃₄⁺    | 3.48   | 3.39   | 3.15   | 3.46 (br.) | 3.38   | 3.32   |
| CH₂⁺     | 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 |
| CH₂(CO)  | 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 ¹H NMR measurements. 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. This leads to two species in the ¹H 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).

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 demands seems to have no high influence on the complex stability constant (logK = 4.2 for [Ba-5] and [Ba-6]) compared to the simple calix[4]crown-6 complex [Ba-1] (logK = 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 logK value of 4.3 was found for diacid [Ba-3] and substantially higher logK 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. 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.

For future radiolabeling purposes, extraction studies were first performed by using the radionuclide barium-133 (half-life: 10.5 a) as $^{133}$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 $^{133}$BaCl$_2$ 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.

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-

![Figure 5. UV/Vis spectra of ligand 7 at different Ba(ClO$_4$)$_2$ concentrations measured in acetonitrile.](image)

![Figure 6. Change of the absorption of ligand 7 at different Ba(ClO$_4$)$_2$ concentrations, measured in acetonitrile.](image)

| Table 3. Stability constants for complexes [Ba-1], [Ba-3], and [Ba-5]–[Ba-8]. |
|-----------------|-------|-------|
| Complex        | R     | logK  |
| [Ba-1]$^{[a]}$ | H     | 4.6 ± 0.1 | NMR |
| [Ba-1]         | H     | 4.1 ± 0.4 | UV  |
| [Ba-3]         | CH$_3$COOH | 4.3 ± 0.2 | UV  |
| [Ba-5]         | CH$_3$CON(CH$_2$)$_2$O | 4.2 ± 0.2 | UV  |
| [Ba-6]         | CH$_3$CON(CH$_2$)$_2$NH | 4.2 ± 0.1 | UV  |
| [Ba-7]         | CH$_3$CONH$_2$SO$_2$CF$_3$ | > 5 | UV  |
| [Ba-8]         | CH$_3$CONHOH | > 5 | UV  |

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

| 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.
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 \([\text{BaCl}_2]\) 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 \([\text{BaCl}_2]\). 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 trifluoromethylsulfonamide 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 trifluoromethylsulfonamide 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(ClO₄)₂ was purchased from Alfa Aesar, and deuterated solvents were purchased from deutero GmbH. Compounds 1–3, 7, and 8 were prepared according to the literature. \([\text{BaCl}_2]\) 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, using tetramethylsilane (TMS) as an internal standard for 1H and 13C NMR. 436

1. **Synthesis of the Ligands**

Calix 3 (300 mg, 0.12 mmol) was suspended in CCl₄ (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 hydrogen carbonate 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. 1H NMR (400 MHz, CDCl₃): δ = 0.85 (s, 18H; Boc-CH₂), 1.28 (s, 18H; Boc-CH₂), 3.15 (d, J = 12.7 Hz, 4H; CH₂Ar), 3.42 (s, 4H; O-CH₂), 3.55 (s, 4H; N-CH₂), 3.59–3.69 (m, 8H; OCH₂-CH² N-CH₂), 3.72 (s, 4H; OCH₂), 3.74–3.85 (m, 8H; OCH₂), 4.14–4.27 (m, 8H; OEt), 4.46 (d, J = 12.7 Hz, 4H; CH₂Ar), 4.58 (s, 4H; CH₂), 6.51 (s, 4H; ArH), 7.05 ppm (s, 4H; ArH); 13C NMR (101 MHz, CDCl₃): δ = 31.3 (Boc(CH₂Ar), 31.8 (Boc-CH₂), 33.8, 34.2 (2 CH₂), 42.0, 46.0, 66.7, 67.0, 69.8, 70.7, 70.8, 71.2, 72.2, 72.8 (10 CH₂), 125.1, 125.7 (2 CH₂Ar), 132.2, 135.1, 145.0, 145.3, 152.2, 154.5 (6 CH₂Ar); 167.4 ppm (CO; MS (ESI+): m/z (%): 1105 (40) [M⁺ + H⁺], 1122 (70) [M⁺ + NH₄⁺], 1127 (100) [M⁺ + Na⁺].

Calix 5 (340 mg, 0.445 mmol) was dissolved in CCl₄ (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 hydrogen carbonate 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%). 1H NMR (400 MHz, CDCl₃): δ = 0.84 (s, 18H; Boc-CH₂), 1.28 (s, 18H; Boc-CH₂), 1.45 (s, 18H; Boc-CH₂), 3.15 (d, J = 12.7 Hz, 4H; CH₂Ar), 3.31–3.45 (m, 16H; NCH₂), 3.71 (s, 4H; OCH₂), 3.73–3.84 (m, 8H; OCH₂), 4.14–4.27 (m, 8H; OCH₂), 4.46 (d, J = 12.7 Hz, 4H; CH₂Ar), 4.59 (s, 4H; CH₂), 6.50 (s, 4H; ArH), 7.05 ppm (s, 4H; ArH); 13C NMR (101 MHz, CDCl₃): δ = 28.5, 31.3 (2 CH₂O), 31.4 (CH₂Ar), 31.8 (Boc-CH₂), 33.8, 34.2 (2 CH₂), 41.6, 45.3 (2 CH₂N), 69.8, 70.7, 70.8, 71.1, 72.2, 80.4 (6 CH₂), 125.1, 125.7 (2 CH₂Ar), 132.2, 135.0, 145.1, 145.2, 152.1, 154.5 (6 CH₂Ar); 167.3 ppm (C=O; MS (ESI+): m/z (%): 1303 (37) [M⁺ + H⁺], 1320 (78) [M⁺ + NH₄⁺], 1325 (100) [M⁺ + Na⁺].
Na). For deprotection, N-Boc-calix 

**Book-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 solution 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$_2$SO$_4$ 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, 18 H; rBu), 1.32 (s, 18 H; rBu), 2.79–2.94 (m, 8 H; NCH$_2$), 3.17 (d, $J = 12.3$ Hz, 4H; CH$_2$Ar), 3.46 (s, 4 H; NCH$_3$), 3.66 (s, 4 H; NCH$_3$), 3.73–3.82 (m, 12H; OCH), 4.14–4.30 (m, 8 H; OCH$_2$), 4.43 (d, $J = 12.7$ Hz, 4 H; CH$_2$Ar), 4.49 (s, 4 H; CH$_2$), 6.44 (s, 4 H; ArH), 7.09 ppm (s, 4 H; ArH).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 31.2$ (rBu), 31.3 (CH$_2$Ar), 31.8 (rBu), 33.7, 34.2 (2 × C$_6$H$_5$), 42.6, 45.8, 46.3, 46.6, 69.5, 70.6, 70.7, 71.0, 72.5, 72.9 (10 × CH$_3$), 124.9, 125.7 (2 × CH$_2$Ar), 131.8, 135.3, 144.9, 145.2, 152.3, 154.6 (6 × C$_{6}$H$_{5}$), 166.9 ppm (C=O); MS (ESI+): m/z (%) = 1103 (12) [M$^+$ + H$^+$], 1120 (18) [M$^+$ + NH$_4^+$], 1125 (100) [M$^+$ + Na$^+$].

**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 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, $J = 8.1$ Hz, 2H; ArH), 6.99 (t, $J = 6.4$ 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$_3$), 114.7 (CH$_2$), 121.9 (CH$_2$), 129.8 (CH$_2$), 157.8 (C$_{6}$H$_{5}$), 166.7 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 $^{133}$BaCl$_2$**

The respective ligands 5–8 (1 equiv) were dissolved in 600 μL chloroform. Carrier added $^{133}$BaCl$_2$ (1 equiv, ca. 800 Bq) dis-

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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 \([133\text{Ba}]\text{Ba}^{2+}\). 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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