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Design and synthesis of new polyphosphorylated upper-rim modified calix[4]arenes as potential and selective chelating agents of uranyl ion

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ABSTRACT

New upper-rim polyphosphorylated calix[4]arenes were designed for decorporation of uranium in case of nuclear contamination. A ligand system containing four preorganized 1-hydroxymethylene-1,1-bis-phosphonic acid moieties anchored onto a calix[4]arene platform has been developed. Three calix[4]-arene-bisphosphonates were efficiently prepared in multi-step syntheses with a variable carbon chain length between the bisphosphonate and the calix[4]arene. Affinity constants towards uranyl ion were determined and compared with those of bis(HEDP) and tris(HEDP) phosphonates, known as efficient ligands for uranyl.

1. Introduction

Uranium is most commonly used as nuclear fuel in fission reactors for civilian purpose. It has been highlighted that the hexavalent uranyl ion (UO_2^{2+}, U(VI)) was the most stable form in both aqueous solutions and serum in vivo.[1] In case of nuclear accident, uranium is at the origin of severe internal contaminations by ingestion or inhalation. In mammalian, uranyl ion is mainly complexed by blood transferrin and by low molecular weight complexing agents such as citrates, bicarbonates and phosphates.[2] Chelation within the blood is usually followed by distribution and retention in target organs such as kidney and bones, this retention is believed to be at the origin of cancer. In this context, uranium must be eliminated from the body by administering non-toxic chelating agents (decorporation). In order to be able to rapidly displace the complexes that are initially formed with the blood components, such chelating agents should display high stability constants and high selectivities towards the uranyl cation. The corresponding uranyl complexes should also be soluble in biological fluids and stable in a pH range from 6 to 8 in order to be subsequently removed from the body by crossing over renal or hepatic barriers.

As part of an ongoing program dealing with the design and synthesis of new ligands for in vivo chelation of actinides, we designed new calix[4]arene-bisphosphonates for the selective decorporation of uranyl ion. The UO_2^{2+} ion is a hard acid according to Pearson's rules and therefore is expected to react preferentially with a hard base. Not surprisingly, the most efficient uranophile chelating functions are oxygen-containing[3] such as hydroxyl-pyridones (HOPO),[3,4] sulfocatecholamides (CAMS)[5] and carba-moylmethylphosphine oxide (CMPO).[6,7] In biological media, carbonate and phosphate ions are the natural ligands of uranyl ion, forming very stable complexes at physiological pH.[8] Many ligands are reported to efficiently complex uranyl ion but, unfortunately, only few of them are able to decorporate uranium in vivo.[9–11] In many cases, significant decreases of the kidney and bones uranyl uptakes have been observed but only when the ligands have been administered immediately after uranyl contamination. Under more meaningful conditions relevant to human treatment, for example, delays of an hour or more, their therapeutic efficiencies are very limited.

Calix[*n*]arenes[12–15] and bisphosphonates[16–22] are both known to complex uranyl ion. Some calix[*n*]arenes such as acid-amide calix[4]arenes[23] and a diacid bis-calix[4]arene have already been

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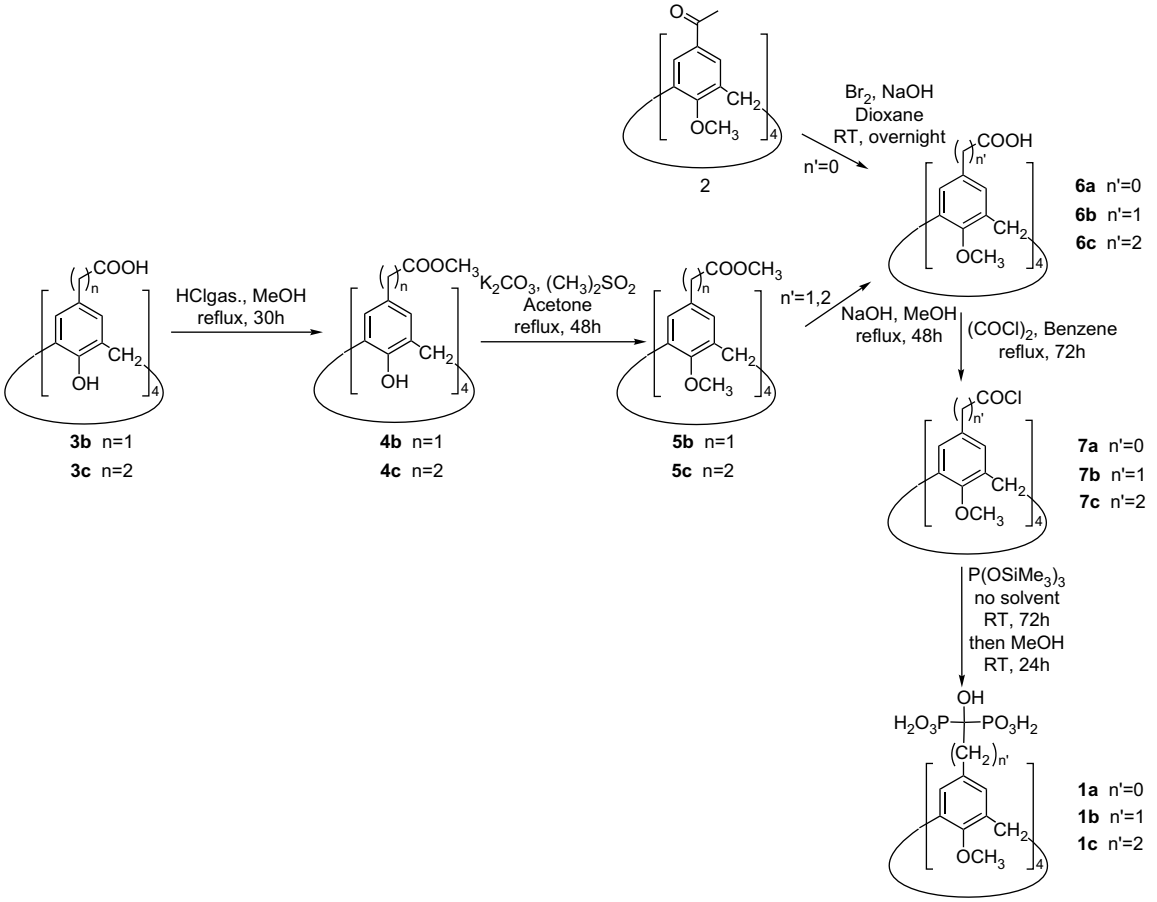
studied as uranophiles.[24] Extraction studies of lanthanides and thorium were reported with CMPO calix[4]arenes.[7] Moreover, HOPO calix[4]arenes were synthesized as a new class of selective extractants of actinide(IV) ions.[25] More recently, CAMS and HOPO calix[4]arenes have been reported to strongly complex UO_2^{2+} in vitro.[26]

Bisphosphonates are known to complex uranium and heavy metals,[18,27] and some are also of prime importance for clinical uses,[28] in particular for bone marrow diseases. Recent investigations conducted by our group showed that bisphosphonates constructed on dipodal scaffolds display significant uranyl removal activities.[29] However, these in vivo activities still need to be improved. In order to obtain more potent bisphosphonate-based uranophiles, we designed new ligands containing four preorganized 1-hydroxymethylene-1,1-bisphosphonic acid moieties anchored onto a calix[4]arene platform. Such ligand should combine two important features that are required to uranyl chelation: first, the rigidity of the calix[4]arene structure, which should allow a favourable preorganization of the ligand around the metal, and second the phosphonate functions, which are hard Lewis bases in accordance to Pearson's rules. In addition, these phosphonate binding sites should increase the solubility of the ligand as well as of the complex in biological media. The syntheses of phosphacalix[4]arenes were recently developed. In 1998, Wieser-Jeunesse et al. reported several syntheses of calix[4]arenes bearing phosphate, phosphonate, phosphine and phosphine oxide groups.[30] More recently, Kazuhiro et al. published the preparation of tetrakis(diphenyl-phosphinoyl-methyl)tetrahydroxycalix[4]arene, by refluxing tetrakis(chloromethyl)tetrahydroxycalix[4]arene with diphenyl ethyl phosphinite in toluene[31] and Matulkova et al. reported in 2005 the synthesis of lower-rim modified calix[4]arenes bearing phosphonic acid groups.[32] Indeed, the reaction of tetrakis(*tert*-butyl)calix[4]arene with ethyl 3-bromopropylphosphonate furnished tetrakis(*tert*-butyl)-3-diethoxyphosphoryl-propoxycalix-[4]arene in 70% yield. The addition of trimethylsilyl bromide followed by methanolysis gave tetrakis(*tert*-butyl)-tetra(dihydroxyphosphoryl-propoxy)calix[4]arene. In 2004, Vovk et al. reported the synthesis of mono and disubstituted calix[4]arene methylene bisphosphonic acids[33] and calix[4]arenes functionalized on the upper-rim with α-hydroxyphosphonic, α-aminophosphonic or methylene bisphosphonic acid groups.[34,35] The inhibition of alkaline phosphatase by these compounds was also studied.[33,36] Besides these studies, the extraction of Am, Eu, Pd and Tc from nitric solutions using phosphorylated calix[*n*]arenes (phosphine oxide, carbamoylphosphine oxide and diphosphine dioxide functions) in *m*-nitrobenzotrifluoride (NBTF) was also investigated.[37]

2. Results and discussion

2.1. Design and synthesis of calix[4]arene-bisphosphonates 1

The syntheses of tetrakis(1-hydroxymethylene-1,1-bisphosphonic acid)tetramethoxycalix[4]arenes **1a–c** are reported in Scheme 1. As previously mentioned, bisphosphonic acids were used as chelating functions and calix[4]arenes as preorganized structures in order to prepare hexadentate ligands specific to the uranyl cation, the fourth bisphosphonate moiety acting as a polar group supposed to increase water solubility. The carbon chain length between the calix[4]arene core and the bisphosphonic heads was modified so as to optimize the ligand properties (n'=0, 1, 2).



Scheme 1.

Starting products in the preparation of compounds **1** were tetrakis(tetraacetyl)tetramethoxycalix[4]arene **2** for $n'=0$ (Scheme 1), tetrakis(carboxymethyl)tetrahydroxycalix[4]arene **3b** for $n'=1$ and tetrakis(carboxyethyl)tetrahydroxycalix[4]arene **3c** for $n'=2$. These derivatives **2**,[38] **3b**[39] and **3c**[40] were obtained from tetrakis(*tert*-butyl)tetrahydroxycalix[4]arene as reported in the literature.

The key step in the synthesis of calix[4]arene-bisphosphonates **1** was the reaction of the adequate acyl chloride with tris-(trimethylsilyl)phosphite. Unfortunately, the silylated phosphorus ester intermediate can be hydrolyzed by phenol functions. To prevent this problem, phenol groups of calix[4]arene **3b** and **3c** were protected by an ether function. First attempts carried out by using sodium hydride and methyl iodide were unsuccessful probably due to the presence of carboxylic acid groups that prevent methylation of the phenol functions. Thus, the carboxylic acid groups of compounds **3b**, and **3c** were first protected as methyl esters, according to the procedure described by Bailly and Burgada,[4] affording esters **4b** and **4c** in 90% yield. These products were analyzed by ^{1}H and $^{13}C\{^{1}H\}$ NMR and IR spectroscopy. ^{1}H NMR spectra showed two doublets about 3.5 and 4.2 ppm corresponding to the methylene groups $ArCH_2Ar$. These chemical shifts are characteristic of a cone conformation as reported by Gutsche et al.[40,41] These data are corroborated by the ^{13}C spectrum, which indicate a signal at 31.8 and 29.9 ppm, respectively, for compounds **4b** and **4c**. So, in $CDCl_3$ solution, ester calix[4]arene **4b** appeared in the cone conformation whereas its analogue **4c** appeared as a mixture of different non-assigned conformers with the cone conformer as the major one.

The etherification step leading to calix[4]arenes **5b** and **5c** was carried out using dimethyl sulfate and potassium carbonate in refluxed acetone for 48 h. After treatment of the reaction mixture, crude products were precipitated in ether and methanol, respectively, for **5b** and **5c** and filtration gives the expected ether calix[4]arenes in 92 and 90% yields, respectively. Their structures were confirmed by ^{1}H NMR spectra, which showed a characteristic signal about 3.3 ppm for **5b** and 3.7 ppm for **5c** corresponding to the signal of the methyl ether group. $^{13}C\{^{1}H\}$ NMR spectra presented signals between 60.8 and 65.2 ppm, which were assigned to the same function. In $CDCl_3$ solution, the complexity of the ^{1}H NMR spectrum of calix[4]arene **5b** indicated the presence of several conformers. These data were confirmed by the $^{13}C\{^{1}H\}$ NMR spectrum where two signals at 30.7 and 36.2 ppm corresponding to the methylene bridges were observed. According to data reported in the literature,[40,41] these chemical shifts were assigned to the cone and partial cone conformations. As for compound **5c**, it appeared as a mixture of different non-assigned conformers.

Compound **6a** was prepared according to a procedure described by Gutsche and Lin.[38] Ketone **2** in dioxane was stirred at room temperature overnight with bromine and sodium hydroxide to form **6a** in 97% yield.

Compounds **6b** and **6c** were synthesized by methyl ester saponification of compounds **5b** and **5c**, respectively. After 48 h at reflux, the reactive mixture was treated with concentrated hydrochloric acid and precipitated carboxylic acids **6b** and **6c** were filtered and obtained analytically pure in 92 and 87% yields, respectively. Their structures were confirmed by IR spectroscopy with appearance of a broad signal around 3300–3400 cm^{-1} corresponding to the O–H bond of carboxylic acid function. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra in $CDCl_3$ showed characteristic signals of a cone conformation for compound **6b** while acid **6c** appeared as a mixture of different non-assigned conformers. After drying, acids **6** were heated at reflux for 72 h in presence of oxalyl chloride in benzene according to McSkimming et al.[42] The end of the reaction could be monitored by IR spectroscopy, based on the disappearance of the signals about 3300–3400 cm^{-1} (ν_{O-H}) and 1700 cm^{-1} ($\nu_{C=O}$) characteristic of carboxylic acids, replaced by the characteristic absorption of acyl chlorides around 1800 cm^{-1}. After evaporation under reduced pressure, acyl chlorides **7** were obtained quantitatively and used further without purification.

The last step consisted in the reaction of silylated phosphites with acyl chlorides **7** yielding to calix[4]arene-bisphosphonates **1** according to a procedure we have already published.[43] Thus, 10 equiv of tris(trimethylsilyl)phosphite was added to calix[4]arene acyl chlorides **7**, after evaporation of volatile fractions and methanolysis of the silylated intermediates crude calix[4]arene-bisphosphonates **1** were obtained. These crude products were then washed with diethyl ether (to remove phosphorous acid), then with methanol to afford pure products **1a** and **1b** in 70 and 75% yields, respectively. In addition to the purification described above, derivative **1c** was dialyzed with Spectra/Por® Cellulose Ester membrane (MWCO: 500 g mol^{-1}) and obtained in 75% yield. Calix[4]arene-bisphosphonates **1** were fully characterized by IR and $^{31}P\{^{1}H\}$ NMR spectroscopies, the data are reported in Table 1.

IR spectroscopy data confirmed the formation of calix[4]arene-bisphosphonates **1** with the appearance of the characteristic absorptions of phosphonic acid functions around 3400 cm^{-1} (ν_{O-H}), 1250 cm^{-1} ($\nu_{P=O}$) and 1070 cm^{-1} (ν_{P-O}), the disappearance of the acyl chloride absorption band about 1800 cm^{-1}, and the absence of the characteristic signals of carboxylic acids or α-ketophosphonates around 1700 cm^{-1} ($\nu_{C=O}$). This was confirmed by $^{31}P\{^{1}H\}$ NMR data. All spectra showed signals between 16 and 20 ppm, characteristic of 1-hydroxymethylene-1,1-bisphosphonic acids and no typical signal of α-ketophosphonates was observed around 0 ppm. As indicated, calix[4]arene-bisphosphonates **1b** and **1c** were obtained as a mixture of different conformers with the cone conformation as the major one. We tried to separate the two conformers of derivative **1b** by crystallization but without success. Nevertheless, we were able to crystallize (tetraacetyl)tetramethoxycalix[4]arene **5**. When re-dissolved, this intermediate showed several conformational states namely cone, partial cone and 1,3-alternate conformations according to in ^{1}H NMR analysis. During the crystallization process, one conformation became less soluble than the others thus giving a unique conformation in the crystal by equilibrium displacement.[44] This behaviour is a classical way for multi-conformational state compounds to crystallize as a single well-defined specie. This is usually observed in a large variety of compounds as peptides[45] or nucleic acids,[46] although in rare examples, the different conformations can be obtained separately in different crystal habits from the same crystallization medium.[47] Here, we showed that among the possible conformations, the non-symmetric 1,3-alternate one was favoured in the crystalline state for compound **5**.[44] All attempts to improve the NMR analysis at higher temperature, and to displace the equilibrium between the different conformers, were unsuccessful. The characterization of calixarene **1a** in $^{13}C\{^{1}H\}$ NMR was performed and showed a specific triplet at 78.8 ppm corresponding to the central carbon atom of bisphosphonate ($^{1}J_{C-P}=142.0$ Hz). Unfortunately,

Table 1
IR and $^{31}P\{^{1}H\}$ NMR data of calix[4]arene-bisphosphonates **1**

Entry	Compound	n'	IR (cm^{-1})	$^{31}P\{^{1}H\}$ NMR (D_2O, ppm)	Conformation
1	**1a**	0	3400 (ν_{O-H}) 1250 ($\nu_{P=O}$) 1060 (ν_{P-O})	16.8 (s)	Cone
2	**1b**	1	3405 (ν_{O-H}) 1250 ($\nu_{P=O}$) 1060 (ν_{P-O})	19.8 (s) 20.4 (s, major)	Nd[a] conformer Cone
3	**1c**	2	3403 (ν_{O-H}) 1255 ($\nu_{P=O}$) 1085 (ν_{P-O})	18.5 (s, major) Signals around 18.5	Cone Nd[a] conformers

[a] Non-determined.

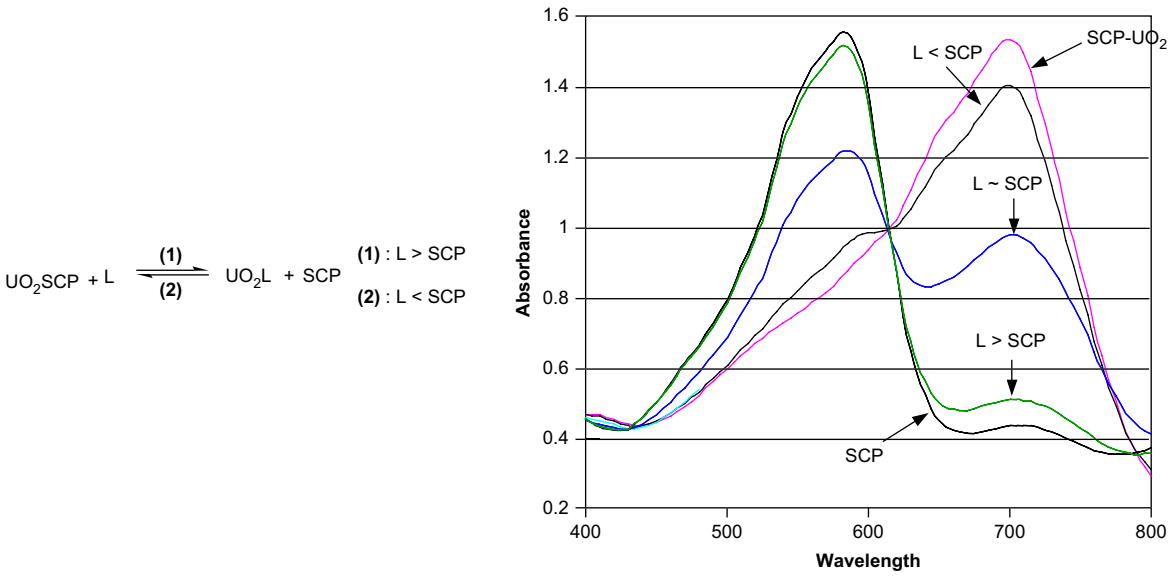


Figure 1.

analysis of derivatives **1b** and **1c** was not possible due to the presence in solution of a mixture of conformers and a lack of solubility in NMR solvents.

2.2. Determination of affinity constants of compounds 1 versus uranyl ion

An efficient ligand for a metal is usually characterized by a strong association constant. Different techniques enable the determination of these constants such as electrochemical methods (potentiometry, conductimetry…), spectroscopy (NMR, photometry, fluorimetry…), mass spectrometry and thermodynamics (calorimetry…). As part of our program, a high-speed colorimetric method has been developed at the CEA.[5,48] It uses sulfochlorophenol (SCP) as a reference ligand, which complexes uranyl ion with a high ultraviolet absorbance. The addition of a stronger ligand than SCP displaces the equilibrium towards the formation of UO_2L (Fig. 1), decreases the absorbance value and changes the colour of the medium.

Tests of competitive displacement of complex UO_2SCP by the synthesized ligands **1** were realized (see Section 4). Affinity constants of these calixarenes **1** were measured at acidic, neutral and basic pH (5.5, 7.4 and 9.0) using the software *HYSS* after a 24-h incubation time for each sample (Table 2). As indicated, the three ligands **1a**–**1c** displaced the UO_2SCP complex with 1 equiv of each ligand at each pH value. These affinity constants were compared to bis(HEDP) and tris(HEDP) (Fig. 2, all compounds from Burgada et al.[21]), which form 1:1 complex with the uranyl ion, as supposed for calix[4]arene-bisphosphonates **1**. Attempts to verify the stoichiometry of **1**/UO_2 complexes using fluorescence assays were unsuccessful. The results were encouraging since each three calix[4]arene-bisphosphonates **1** showed a better affinity constant for uranyl ion than HEDP ($K<10^{13}$ at these pH)[49] and bis(HEDP) at the different pH values. It can be noted that the enhancement of the affinity constant was observed depending on the increase of the pH and on the spacer length separating the calixarene scaffold to the chelating group. The highest complexation was observed with the calix[4]arene **1c** ($n'=2$), which showed comparable results than tris(HEDP). However, the presence of a fourth bisphosphonate moiety seems to not improve the uranyl sequestration potency of the calixarene ligands **1**. Nevertheless, calix[4]arene **1c** displays high uranium binding properties in a wide range of pH. It is noteworthy that these binding properties are also very strong under acidic conditions (the K_{cond} value was too high to be determined precisely by our test at this pH). Acidic pH data are very important because elimination of a metallic complex is often carried out in the kidney where the pH is acidic, and where accumulation of uranium is usually observed.

Table 2
K_{cond} of calix[4]arene-bisphosphonates **1**, bis(HEDP) and tris(HEDP)[a]

Entry	Compound	log K_{cond}		
		pH=5.5	pH=7.4	pH=9.0
1	**1a**	12.4	16.3	18.0
2	**1b**	13.4	15	<15.0
3	**1c**	>14.0	17.4	18.5
4	Bis(HEDP)	10.3	14.1	17.3
5	Tris(HEDP)	>14.0	17.6	18.8

[a] The K_{cond} values indicated in the table are accurate only hypothesizing a 1:1 ligand/uranyl complex formation.

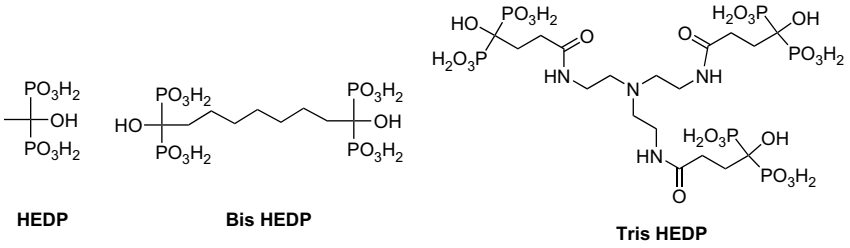


Figure 2.

3. Conclusions

We reported here new and efficient synthetic procedures to obtain original calix[4]arenes bearing 1-hydroxymethylene-1,1-bisphosphonate moieties. The influence of the length of the carbon chain between the calix[4]arene and the chelating group on the chelation properties was also examined (n'=0, 1, 2). If calix[4]arene-bisphosphonate **1a** (n'=0) was obtained, according to NMR spectroscopy, in a cone conformation, analogues with a longer carbon chain (**1b**, n'=1 and **1c**, n'=2) are present in a mixture of several conformers with the cone as the major conformer. These polyphosphorylated upper-rim modified calix[4]arenes appeared as good chelating agents towards uranium, especially compound **1c** highlighting the importance of the ligand spatial preorganization.

Chemical modifications on the lower-rim of calix[4]arenes by a 1-hydroxymethylene-1,1-bisphosphonate group are currently under investigations and will be described in next paper.

Selectivity of these synthesized ligands towards other metals existing in the organism will be soon studied (iron, calcium, zinc…). Moreover, in vivo toxicity tests will be achieved. Preliminary results showed that these ligands are not toxic until 1 mM concentration.

4. Experimental section

4.1. General

Tetrakis(*tert*-butyl)tetrahydroxycalix[4]arene **2** and all other reagents were commercially available. Compounds **2**,[38] **3b**,[39] **3c**,[40] and **6a**[38] were prepared as described in the literature. Solvents were distilled before use. Column chromatography was performed on silica gel 60 A (70/200 μm) from Labosi. Dialysis was realized with Spectra/Por® Cellulose Ester membrane (MWCO: 500 g mol^{-1}). Melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded with a VARIAN Unity Inova 500 MHz (^{1}H: 500.6 MHz, ^{31}P: 200.7 MHz, ^{13}C: 125.9 MHz) spectrometer in $CDCl_3$ or D_2O. Chemical shifts (δ) are given in parts per million. ^{1}H NMR spectra were recorded using tetramethylsilane or HOD as internal standard in $CDCl_3$ or D_2O .^{31}P and ^{13}C NMR spectra were recorded using, respectively, phosphoric acid and methanol as external references. IR spectra were recorded on a PYE UNICAM SP3-300S spectrometer in KBr. Absorptions are given in wavenumbers (cm^{-1}). When a compound is obtained as a mixture of different conformers, only the analytical data of the major one are given. Elemental analyses were realized by the Service Central d'Analyse du CNRS de Vernaison (France). Mass spectra were recorded at the Université de Lyon using electrospray as ionization mode.

4.2. Determination of the 1/UO_2 complexation constants

Uranyl stock solution (20 mM) was prepared by dissolving $UO_2(OAc)_2\cdot 2H_2O$ in 0.1 M perchloric acid. Sulfochlorophenol S (SCP, purchased from Fluka) stock solution (4 mM) was prepared by dissolving SCP in Millipore quality water. All experiments were carried out at 25 °C in buffers with a fixed ionic strength of 0.1 M prepared as follows: MES (for pH 5.5), HEPES (for pH 7.4) or CHES (for pH 9) (acid forms) (12.5 mmol) and *n*-$Bu_4N^+Cl^-$ (112.5 mmol) were dissolved in 1 L of Millipore quality water. Adjustment of the pH was done using *n*-$Bu_4N^+OH\cdot 30H_2O$. Candidate ligands **1** were dissolved in water to get 400 μM solutions.

In each well of a microtiter plate, 100 μM SCP/UO_2^{2+} solution (200 μL, prepared by mixing SCP stock solution (6.25 mL) diluted in 242.5 mL of the appropriate buffer (12.5 mM) with uranyl stock solution (1.25 mL) for 1 h at room temperature) and 400 μM ligand **1** solution (50 μL) were mixed at 25 °C for 36 h. Control experiments (without ligand **1** and without UO_2^{2+}) were made in each plates. All experiments were done in triplicate. Control experiments (SCP alone, SCP/UO_2 and SCP/**1**) were carried out on each plate and used to calculate the percentage of SCP/UO_2 displacement or to control that the competitive ligand did not interfere with the UV–vis properties of SCP. Absorbance measurements were carried out on an absorbance plate reader by staining at 690 nm and 580 nm.

Conditional constants K_{cond} were calculated using the speciation program Hyss. K_{cond} of the competitive ligands **1** in case of the formation of uranyl-ligand **1** 1:1 complex is defined in the following equation:

$$K_{cond} = [U\mathbf{1}]/([U]([\mathbf{1}]+[H\mathbf{1}]+[H_2\mathbf{1}]+\ldots+[H_n\mathbf{1}])) \quad (1)$$

Affinity constants towards uranyl ion of synthesized ligands **1** were determined by complexation assays realized by Dr. Taran's team at the Commissariat à l'Energie Atomique (CEA).

4.3. General procedure for esters (4)

A solution of carboxylic acid **3b** (400 mg, 0.6 mmol) or **3c** (800 mg, 1.12 mmol) in distilled methanol (25 mL and 50 mL, respectively) was saturated with gaseous hydrochloric acid. The reaction mixture was refluxed for 30 h and then cooled to room temperature. After evaporation under vacuum, the formed solid was dissolved in chloroform (20 mL and 40 mL, respectively) and impurities were filtered. The filtrate was concentrated under reduce pressure and the obtained solid was dried over P_2O_5 to furnish ester **4b** (384 mg, 5.4 mmol, 90%) or **4c** (776 mg, 1.0 mmol, 90%), respectively, as brown solids.

*4.3.1. 5,11,17,23-Tetrakis(carbomethoxymethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4b**)*

Mp=163 °C; IR: ν=3420 (O–H), 2960 (C–H), 1730 (C=O) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ=10.10 (s, 4H, Ar–O*H*), 6.94 (s, 8H, Ar–*H*), 4.20 (br s, 4H, Ar–CH_2–Ar), 3.64 (s, 12H, OCH_3), 3.50 (br s, 4H, Ar–CH_2–Ar), 3.38 (s, 8H, CH_2COO); ^{13}C{^{1}H} NMR (125.9 MHz, $CDCl_3$): δ=172.3 (*C*=O), 148.1 (Ar), 130.1 (Ar), 128.4 (Ar), 127.7 (Ar), 52.2 (OCH_3), 40.4 (*C*H_2COO), 31.8 (Ar–CH_2–Ar). Anal. Calcd for $C_{40}H_{40}O_{12}$: C 67.03, H 6.19. Found: C 67.15, H 6.22.

*4.3.2. 5,11,17,23-Tetrakis(carbomethoxyethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4c**)*

IR: ν=3177 (O–H), 2943 (C–H), 1734 (C=O) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ=10.17–10.08 (s, 4H, Ar–O*H*), 6.87 (s, 8H, Ar–*H*), 4.16 (d, 4H, $^2J_{H-H}$=13.5 Hz, Ar–CH_2–Ar), 3.67 (s, 12H, OCH_3), 3.46 (d, 4H, $^2J_{H-H}$=13.5 Hz, Ar–CH_2–Ar), 2.75–2.54 (m, 16H, CH_2–CH_2–COOH); ^{13}C{^{1}H} NMR (125.9 MHz, $CDCl_3$): δ=173.1 (*C*=O), 147.1, 134.0, 130.7, 128.6, 128.1, 127.7 (Ar), 51.5 (OCH_3), 35.7 (*C*H_2–CH$_2$–COOH), 31.3 (CH$_2$–*C*H_2COOH), 29.9 (Ar–*C*H_2–Ar). Anal. Calcd for $C_{44}H_{48}O_{12}$: C 68.38, H 6.78. Found: C 68.22, H 6.75.

4.4. General procedure for ethers (5)

Potassium carbonate (290 mg, 2.10 mmol for compound **4b** or 1.01 g, 7.32 mmol for compound **4c**) and dimethyl sulfate (210 mg, 1.67 mmol or 1.15 g, 9.13 mmol, respectively) were added to ester **4b** (200 mg, 0.28 mmol) or **4c** (700 mg, 0.91 mmol) in acetone (25 mL or 75 mL, respectively). The reaction mixture was refluxed for 2 days and progress of the reaction was monitored by TLC (CH_2Cl_2/AcOEt 90:10). After cooling at room temperature, the solution was filtered and the obtained solid was washed with acetone. The filtrate was concentrated under vacuum and the crude product was treated with diethyl ether. A white solid appeared and was filtered. This second filtrate was evaporated under reduce pressure too and treated with methanol now. The obtained precipitate was

recovered by filtration to give ether **5b** (198 mg, 0.26 mmol, 92%) or **5c** (676 mg, 0.82 mmol, 90%), respectively, as white solids.

*4.4.1. 5,11,17,23-Tetrakis(carbomethoxymethyl)-25,26,27,28-tetramethoxycalix[4]arene (**5b**)*

IR: ν=2980 (C–H), 1740 (C=O) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ=7.16–6.33 (m, 8H, Ar–*H*), 4.25 (d, 4H, $^2J_{H-H}$=14.0 Hz, Ar–C*H*$_2$–Ar), 3.99 (br s, 4H, C*H*$_2$COO), 3.77 (s, 6H, COOC*H*$_3$), 3.65 (s, 6H, COOC*H*$_3$), 3.29 (s, 12H, OC*H*$_3$), 3.17 (d, 4H, $^2J_{H-H}$=14.0 Hz, Ar–C*H*$_2$–Ar), 3.03 (br s, 4H, C*H*$_2$COO); $^{13}C\{^1H\}$ NMR (125.6 MHz, $CDCl_3$): δ=172.7 (*C*=O), 157.2, 135.1, 134.0, 131.2, 130.0, 129.0, 127.6 (Ar), 61.6 (OCH$_3$), 60.8 (OC*H*$_3$), 52.0 (COOC*H*$_3$), 40.7 (*C*H$_2$COO), 30.7 (Ar–*C*H$_2$–Ar). Anal. Calcd for $C_{44}H_{48}O_{12}$: C 68.38, H 6.78. Found: C 68.49, H 6.76.

*4.4.2. 5,11,17,23-tetrakis(carbomethoxyethyl)-25,26,27,28-tetramethoxycalix[4]arene (**5c**)*

IR: ν=2960 (C–H), 1740 (C=O) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ=7.05–6.22 (m, 8H, Ar–*H*), 4.24 (br s, 2H, Ar–C*H*$_2$–Ar), 3.98 (br s, 2H, Ar–C*H*$_2$–Ar), 3.76–3.61 (m, 12H, Ar–OC*H*$_3$), 3.08 (s, 12H, COOC*H*$_3$), 3.05 (br s, 2H, Ar–C*H*$_2$–Ar), 2.96 (t, 8H, $^3J_{H-H}$=11.5 Hz, CH$_2$–C*H*$_2$COOCH$_3$), 2.89 (br s, 2H, Ar–C*H*$_2$–Ar), 2.60 (t, 8H, $^3J_{H-H}$=11.5 Hz, *C*H$_2$–CH$_2$COOCH$_3$); $^{13}C\{^1H\}$ NMR (125.6 MHz, $CDCl_3$): δ=176.3 (*C*=O), 173.9, 158.6, 137.2, 128.9, 126.3 (Ar), 65.2 (Ar–OCH$_3$), 57.1 (COOC*H*$_3$), 55.2 (COOC*H*$_3$), 51.6 (COOC*H*$_3$), 36.2 (Ar–CH$_2$–Ar), 30.6 (Ar–*C*H$_2$–Ar), 27.6 (CH$_2$–*C*H$_2$–CO), 23.9 (*C*H$_2$–CH$_2$–CO). Anal. Calcd for $C_{48}H_{56}O_{12}$: C 69.54, H 7.30. Found C 69.33, H 7.32.

4.5. General procedure for carboxylic acids (6)

Ester **5b** (850 mg, 1.11 mmol) or **5c** (250 mg, 0.30 mmol) was added to methanol (10 mL and 15 mL, respectively) and sodium hydroxide (177 mg, 4.43 mmol for **5b** and 50 mg, 1.25 mmol for **5c**) dissolved in water (2 mL). The pH of the solution was controlled about 13–14. The reaction mixture was refluxed for 48 h. After cooling at room temperature, it was poured into iced water (30 mL). The solution was then acidified with concentrated hydrochloric acid to obtain a pH value about 1–2. The appeared white precipitate was filtered, washed with iced water and dried over P_2O_5 to furnish the carboxylic acid **6b** (725 mg, 1.02 mmol, 92%) or **6c** (203 mg, 0.26 mmol, 87%) analytically pure without further purification.

*4.5.1. 5,11,17,23-Tetrakis(carboxymethyl)-25,26,27,28-tetramethoxycalix[4]arene (**6b**)*

Mp=160 °C; IR: ν=3420 (O–H), 2910 (C–H), 1720 (C=O) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ=7.03 (s, 8H, Ar–*H*), 3.63 (s, 8H, Ar–C*H*$_2$–Ar), 3.44 (s, 12H, OC*H*$_3$), 3.11 (s, 8H, C*H*$_2$COOH); $^{13}C\{^1H\}$ NMR (125.6 MHz, $CDCl_3$): δ=177.8 (*C*=O), 156.4 (Ar), 134.7 (Ar), 131.0 (Ar), 127.9 (Ar), 57.6 (OCH$_3$), 42.0 (*C*H$_2$COO), 37.1 (Ar–*C*H$_2$–Ar); ESI-MS (positive mode) *m*/*z* 713.1 [M+H], 735.3 [M+Na], calcd for $C_{40}H_{40}O_{12}$ 712.25. Anal. Calcd for $C_{40}H_{40}O_{12}$: C 67.03, H 6.19. Found C 66.78, H 6.18.

*4.5.2. 5,11,17,23-Tetrakis(carboxyethyl)-25,26,27,28-tetramethoxycalix[4]arene (**6c**)*

IR: ν=3300 (O–H), 2920 (C–H), 1730 (C=O) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ=7.18–6.59 (m, 8H, Ar–*H*), 4.27 (d, 2H, $^2J_{H-H}$=7.0 Hz, Ar–C*H*$_2$–Ar), 3.78 (d, 2H, $^2J_{H-H}$=7.0 Hz, Ar–C*H*$_2$–Ar), 3.73 (s, 6H, Ar–OC*H*$_3$), 3.70 (s, 3H, Ar–OC*H*$_3$), 3.62 (s, 3H, Ar–OC*H*$_3$), 3.10 (t, 8H, $^3J_{H-H}$=11.7 Hz, CH$_2$–C*H*$_2$COOH), 2.80 (t, 8H, $^3J_{H-H}$=11.7 Hz, C*H*$_2$–CH$_2$–COOH), 2.78 (d, 2H, $^2J_{H-H}$=7.0 Hz, Ar–C*H*$_2$–Ar), 2.68 (d, 2H, $^2J_{H-H}$=7.0 Hz, Ar–C*H*$_2$–Ar); $^{13}C\{^1H\}$ NMR (125.6 MHz, $CDCl_3$): δ=180.0 (*C*=O), 156.8, 135.0, 134.0, 129.4, 128.2 (Ar), 60.7 (Ar–OCH$_3$), 38.3 (CH$_2$–*C*H$_2$COOH), 36.0 (*C*H$_2$CH$_2$COOH), 31.0 (Ar–CH$_2$–Ar); ESI-MS (positive mode) *m*/*z* 770.6 [M+2H], calcd for $C_{44}H_{48}O_{12}$ 768.31. Anal. Calcd for $C_{44}H_{48}O_{12}$: C 68.38, H 6.78. Found C 68.17, H 6.77.

4.6. General procedure for acyl chlorides (7)

Oxalyl chloride (579 mg, 4.56 mmol for **6a**, 426 mg, 3.36 mmol for **6b** and 396 mg, 3.12 mmol for **6c**) was added to carboxylic acid **6a** (250 mg, 0.38 mmol) or **6b** (200 mg, 0.28 mmol) or **6c** (200 mg, 0.26 mmol) in benzene (10 mL) under argon. The reaction mixture was refluxed for 3 days and the progress of the reaction was monitored by IR spectroscopy. After evaporation of volatile fractions, the corresponding acyl chloride **7** was obtained quantitatively (**7a**, 277 mg, 0.38 mmol; **7b**, 220 mg, 0.28 mmol; **7c**, 219 mg, 0.26 mmol) and used in the next step without further purification.

4.7. General procedure for calix[4]arene-bisphosphonates (1)

Tris(trimethylsilyl)phosphite (1.0 mL, 3 mmol for **1a**; 0.53 mL, 1.59 mmol for **1b**; 0.50 mL, 1.48 mmol for **1c**) is added to calix[4]-arene **7a** (220 mg, 0.30 mmol) or **7b** (125 mg, 0.16 mmol) or **7c** (125 mg, 0.15 mmol) under argon. The reaction mixture was then stirred at 35 °C for 3 days. After evaporation of volatile fractions under reduce pressure, the crude product was hydrolyzed with methanol for 24 h at room temperature. After evaporation of solvent under vacuum, the obtained compound was washed with diethyl ether in order to remove phosphorous acid, then methanol and lyophilized to give calixarene-bisphosphonate **1a** (262 mg, 0.21 mmol, 70%) or **1b** (156 mg, 0.12 mmol, 75%) or **1c** after an additional dialysis (153 mg, 0.11 mmol, 75%), respectively, as white solids.

*4.7.1. 5,11,17,23-Tetrakis(1-hydroxymethylene-1,1-bisphosphonic acid)-25,26,27,28-tetramethoxy-calix[4]arene (**1a**)*

Mp=182–184 °C; IR: ν=3400 (O–H), 2920 (C–H), 1600 (C=C), 1460 (C–H), 1250 (P=O), 1060 (P–O) cm^{-1}; ^1H NMR (500.6 MHz, D_2O): δ=3.53 (s, 12H, OC*H*$_3$), 3.99 (s, 8H, Ar–C*H*$_2$–Ar), 7.65 (s, 8H, Ar–*H*); $^{13}C\{^1H\}$ NMR (125.9 MHz, D_2O): δ=40.1 (Ar–*C*H$_2$–Ar), 61.7 (OCH$_3$), 78.8 (t, $^1J_{P-C}$=142.0 Hz, P–*C*(OH)–P), 131.0 (Ar), 135.2 (Ar), 137.7 (Ar), 158.4 (Ar); $^{31}P\{^1H\}$ NMR (200.7 MHz, D_2O): δ=16.7 (s). Anal. Calcd for $C_{36}H_{48}O_{32}P_8$: C 34.74, H 4.21, P 19.91. Found C 34.65, H 4.20, P 19.87.

*4.7.2. 5,11,17,23-Tetrakis(1-hydroxymethylene-1,1-bisphosphonic acid)-25,26,27,28-tetramethyl-tetramethoxycalix[4]arene (**1b**)*

Mp=180 °C; IR: ν=3405 (O–H), 2940 (C–H), 1640 (C=C), 1475 (C–H), 1250 (P=O), 1060 (P–O) cm^{-1}; ^1H NMR (500.6 MHz, D_2O): δ=3.32 (t, 8H, $^3J_{P-H}$=5.0 Hz, C*H*$_2$–C–OH), 3.56 (s, 12H, OC*H*$_3$), 3.81 (s, 8H, Ar–C*H*$_2$–Ar), 7.22 (s, 8H, Ar–*H*); $^{31}P\{^1H\}$ NMR (200.7 MHz, D_2O): δ=20.4 (s, major conformer). Anal. Calcd for $C_{40}H_{56}O_{32}P_8$: C 36.94, H 4.65, P 19.05. Found C 36.98, H 4.66, P 19.09.

*4.7.3. 5,11,17,23-Tetrakis(1-hydroxymethylene-1,1-bisphosphonic acid)-25,26,27,28-tetraethyl-tetra-methoxycalix[4]arene (**1c**)*

Mp>260 °C; IR: ν=3403 (O–H), 2930 (C–H), 1599 (C=C), 1480 (C–H), 1255 (P=O), 1085 (P–O) cm^{-1}; ^1H NMR (500.6 MHz, D_2O): δ=2.05 (br s, 8H, Ar–C*H*$_2$–Ar), 2.56 (br s, 8H, C*H*$_2$–CH$_2$–C–OH), 3.18 (s, 12H, OC*H*$_3$), 3.59 (br s, 8H, CH$_2$–C*H*$_2$–C–OH), 6.99 (br s, 8H, Ar–*H*); $^{31}P\{^1H\}$ NMR (200.7 MHz, D_2O): δ=18.5 (s, major conformer). Anal. Calcd for $C_{44}H_{64}O_{32}P_8$: C 38.95, H 5.05, P 18.26. Found C 38.19, H 5.03, P 18.31.

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