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Elias Bou Maroun[a]; Agnès Hagège[a]; Christian Basset[b]; Eric Quéméneur[b]; Claude Vidaud[b]; Zouhair Asfari[a]
[a] Laboratoire de Chimie Analytique et Minérale, UMR 7178 ULP/CNRS/IN2P3 (LC4), ECPM, Strasbourg Cedex, France [b] CEA IBEB, SBTN, Marcoule Research Center, Bagnols-sur-Cèze, France

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Synthesis of phosphorylated calix[4]arene derivatives for the design of solid phases immobilising uranyl cations

Elias Bou Maroun[a], Agnès Hagège[a], Christian Basset[b], Eric Quéméneur[b], Claude Vidaud[b] and Zouhair Asfari[a]*

[a]*Laboratoire de Chimie Analytique et Minérale, UMR 7178 ULP/CNRS/IN2P3 (LC4), ECPM, Strasbourg Cedex, France;* [b]*CEA IBEB, SBTN, Marcoule Research Center, Bagnols-sur-Cèze, France*

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With the aim of developing supports for uranyl cations immobilisation, new 1,3-alternate calix[4]arenes bearing both phosphonic acid functions as chelating sites and *N*-succinimide-4-oxabutyrate as the anchoring arm were synthesised in good yields. The coupling of such calixarenes to a gel was performed and a successful immobilisation of uranyl cations was obtained.

Keywords: phosphorous-calix[4]arenes; uranyl cations immobilisation; solid supports; anchoring arms

1. Introduction

Uranium, especially under its uranyl ion form (UO_2^{2+}), is widespread in the environment, not only as naturally occurring in various minerals but also resulting from both nuclear civil and military uses. Regarding the complexity of biological matrices, studying its speciation *in vivo* still requires innovative tools. Thus, the design and synthesis of macrocyclic ligands that could preorganise uranyl chelating functions is of primary importance in the development of such tools.

Among them, calixarenes represent an interesting class of macrocycles. On the one hand, they might adopt pseudoplanar configuration. However, in contrast to homooxacalix[4]arenes and tetrathiacalix[4]arenes (*1–3*), the crystal structure of the complex between the simple calix[4]arene and UO_2^{2+} evidenced that the 1,3-oxygen atom distance is far from the ideal distance required for an internal complex (*3*). On the other hand, calix[4]arenes can adopt a 1,3-alternate conformation, where the uranyl cation binding sites can be remote from the anchoring arm designed for a covalent bond to a polymer support.

Calix[4]arenes functionalised by various complexing groups were then used as extractants of uranyl ion, i.e. carboxylic acid (*4–8*), carboxylic acid-amide (*9*, *10*), ester (*11*), hydroxamate (*12*), or semicarbazone functions (*13*). Phosphoryl groups have also been proved to be suitable for uranyl cation complexation. The solvent extraction of uranium(VI) was widely studied by neutral or acid organophosphorus extractants (*14–21*). A recent work of Taran et al. (*22*) reported that bis-phosphonates were powerful uranyl ligands. Several papers described the synthesis of phosphonatocalix[4]arenes (*23–31*). Some of them were also functionalised with an anchoring arm to be immobilised on solid supports (*7*, *8*, *13*). However, none of these phosphorus-containing calixarenes were used to extract the uranyl ion.

Consequently, the purpose of the present work was also to provide bifunctional ligands that could simultaneously bind uranium and be immobilised on solid supports.

In this work, the synthesis of two phosphorus-containing calix[4]arenes in the 1,3 alternate conformation bearing both phosphonic acid and *N*-hydroxysuccinimide ester entities is reported. Their incorporation into a macromolecular matrix is also demonstrated.

2. Results and discussion

2.1 Conception of uranyl cation immobilising agents: synthesis of several (phosphonic acid)calix[4]arenes

Phosphorus-containing calixarenes modified to provide an *N*-hydroxysuccinimide moiety able to react with NH_2 groups of a solid support were synthesised. As it is established that the 1,3-alternate conformation of calixarenes seems to be the most favourable for metal complexation (*32–34*), the synthesis was designed to produce the new calixarenes with this preferred conformation.

Calixarenes **6** and **9** were obtained via a five-step synthesis. The synthetic pathway is illustrated in Figure 1.

Calix[4]arene **1** was first *O*-alkylated in the presence of K_2CO_3 with 1 equiv. of methoxyethoxy-*p*-toluenesulphonate to obtain the monoalkoxycalix[4]arene **2** in a 68% yield. The cone conformation, stabilised by hydrogen

*Corresponding author. Email: asfariz@ecpm.u-strasbg.fr

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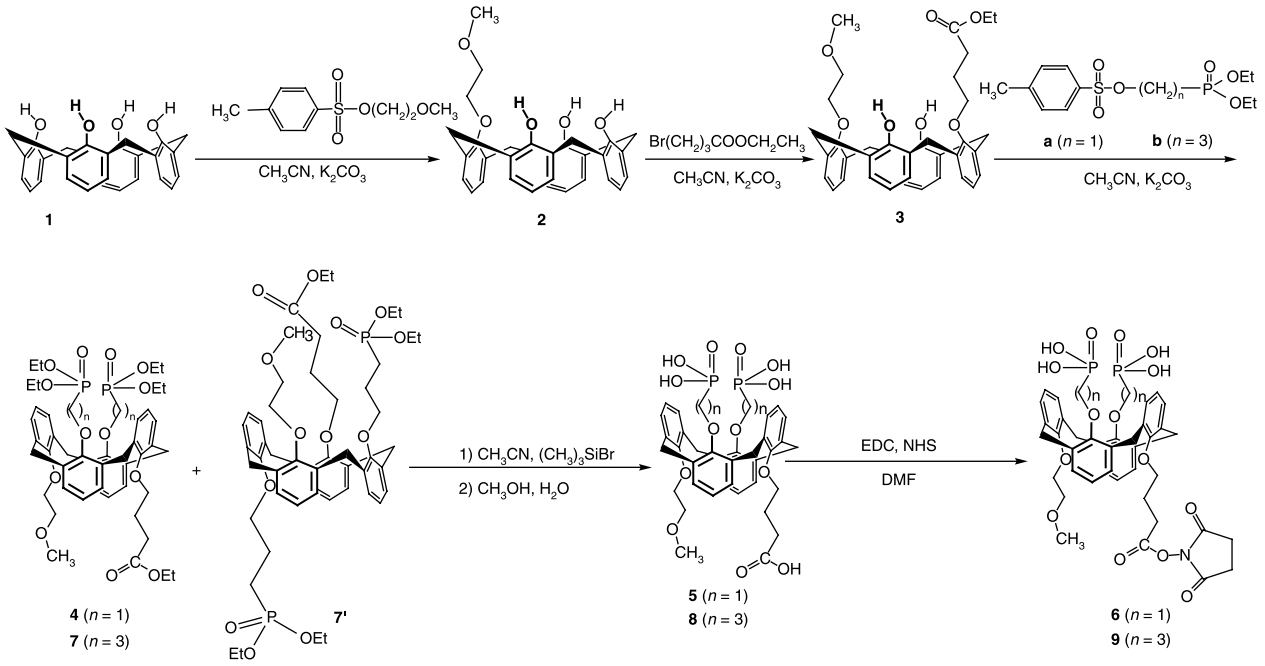

Figure 1. Synthetic pathway for (phosphonic acid)calix[4]arenes possessing an anchoring arm.

bonds, was revealed by the presence of two AB systems at 4.49 and 3.48 ppm ($J = 13.0$ Hz) and at 4.31 and 3.46 ppm ($J = 13.0$ Hz), in the ^{1}H NMR spectrum, attributed to the methylenic protons ArC*H*$_2$Ar. The calixarene derivative **2** was then functionalised by reacting 1 equiv. of ethyl-4-bromobutyrate to obtain compound **3** in a 56% yield. The cone conformation was proved to be maintained by the ^{1}H NMR spectrum of compound **3**, which revealed two AB systems at 4.42 and 3.38 ppm ($J = 13.0$ Hz) and at 4.28 and 3.38 ppm ($J = 13.0$ Hz), attributed to the methylenic protons ArC*H*$_2$Ar.

The introduction of the phosphorus-containing functions was performed by *O*-alkylation with 2.1 equiv. of diethylphosphonoylmethoxy-*p*-toluenesulphonate (**a**) or diethylphosphonoylpropoxy-*p*-toluenesulphonate (**b**) in the presence of K_2CO_3 to yield calixarene **4** and a mixture of compounds **7** and **7′**, respectively. The 1,3-alternate conformation of compound **4** was confirmed by the presence in the ^{1}H NMR spectrum of a singlet for the methylenic protons ArCH_2Ar at 3.49 ppm and by the ^{31}P NMR spectrum that showed a singlet at 21.8 ppm. Compounds **7** and **7′** were further separated by gel chromatography and were shown to be the expected diethylphosphonate calix[4]arene in two different conformations. Compound **7** was proved to be in the 1,3-alternate conformation, confirmed by the absence of any AB system in the ^{1}H NMR spectrum for the methylenic protons ArCH_2Ar and the presence of a singlet at 33.5 ppm in the ^{31}P NMR spectrum indicating the presence of two equivalent phosphorous atoms. Compound **7′** was shown to be in the partial cone conformation. The ^{1}H NMR spectrum revealed an AB system at 4.05 and 3.09 ppm ($J = 13.0$ Hz), corresponding to four methylenic protons ArCH_2Ar. The singlet corresponding to the other four methylenic protons ArCH_2Ar was located in the multiplet at 3.92–3.57 ppm. The ^{31}P NMR spectrum confirmed this conformation, revealing two singlets at 34.1 and 33.1 ppm for the two different phosphorous atoms.

Calixarenes **5** and **8** were obtained by transesterification using trimethylbromosilane and subsequent hydrolysis of the trimethylsilylesters in a nearly quantitative yield. Finally, the activation of the carboxylic groups was performed using 2 equiv. of NHS and 2 equiv. of EDC to obtain calixarenes **6** and **9** with a 64 and 45% yield, respectively. For all these compounds, the absence of any AB system in the ^{1}H NMR spectra confirmed that the 1,3-alternate conformation was maintained.

2.2 Immobilisation of calixarenes 6 and 9 on a gel column

Immobilisation was performed by incubating the Ultralink hydrazide gel (15 μmol NH_2 functions per gram) with calixarene quantities corresponding to 20% of the total amount of NH_2 groups.

Since the calixarenes synthesised in this paper are based on a succinimide ester that is commonly used for reactive amine crosslinking, the ester hydrolysis is a limiting factor. Two buffers were tested for the coupling: a HEPES buffer (pH 8.0) and a borate buffer (pH 9.2). A higher pH was shown to favour the nucleophilic attack

Table 1. Successive couplings of calixarene **6** on the same gel.

Experiment number	Addition of calixarene **6** (μmol)	Calixarene **6** found in the eluate (μmol)	% Calixarene **6** coupled to the gel
1	2.99	1.99	33.5
2	2.99	1.97	34.1
3	6.00	6.15	–

to the detriment of the ester hydrolysis, and pH 9.2 was thus used in further experiments.

The repeatability of the coupling was then evaluated on two different gels using compound **6**. An average value of (32 ± 2)% (% mol) of coupled calixarene **6** was found.

The same experiment conducted with calixarene **9** led to 28.5% (% mol), which seems to indicate that the alkyl chain length has no influence on the coupling.

Improvement of the coupling extent was investigated by performing successive calixarene **6** additions and incubations. Results are reported in Table 1 and show that a maximum of 2 μmol calixarene **6**/g gel is obtained.

2.3 *Immobilisation of uranyl ions on a gel column*

Assessment of the complexation efficiency on a modified gel was performed. About 1 g of the Ultralink hydrazide gel coupled with 2 μmol calixarene **6**/g was incubated overnight in the presence of 5 equiv. of uranyl acetate. A similar experiment was also conducted with the same quantity of a non-coupled gel. The uranyl cation content in the eluates was quantified and found to be 7.5 μmol for the eluates of the gel bound with calixarene **6** and 9.9 μmol for the blank. Consequently, (2.4 ± 0.1) μmol uranyl cation/g were immobilised on the modified gel, which correspond to a 100% immobilisation (referring to the calixarene). For the non-coupled gel, the immobilised concentration was found to be as low as (0.1 ± 0.1) μmol uranyl cation/g. It seems then that the immobilisation of the uranyl cation occurs through the formation of a 1:1 (uranyl:calixarene) complex. The total release of the uranyl cation from the blank gel shows the absence of non-specific interactions and reinforces this assumption.

3. Conclusion

The synthesis of new phosphorous-containing calix[4]-arenes bearing phosphonic acid functions on one side and NHS-activated carboxylic functions on the other side was achieved. With the aim of providing solid supports, the coupling of these compounds to a solid support was performed. A coupling extent of 2 μmol calixarene **6**/g gel was obtained. Under the used conditions, a quantitative immobilisation of uranyl cations was shown to occur through the formation of an 1:1 UO_2^{2+}:calixarene **6** complex.

Further studies will be performed to improve the coupling extent of calixarene **6** on such support. However, the use of these heterofunctional macrocycles for many other usages into supramolecular devices could be further envisioned.

4. Experimental

4.1 *Synthesis*

All reagents and solvents were commercial and were used without further purification. Reagents for the synthesis were all Sigma-Aldrich and Prolabo products. Calix[4]arene was prepared according to the literature (*35*). Chromatography used SiO_2 columns with Kieselgel Merck (art. 11567). The melting points were taken on a Büchi 535 apparatus in capillaries sealed under nitrogen. The ^1H and ^{31}P NMR spectra were, respectively, recorded at 300 and 400 MHz on a Bruker Avance spectrometer. For ^1H NMR spectra, $CHCl_3$ ($\delta = 7.26$ ppm) was used as the internal standard in $CDCl_3$ and CHD_2OD ($\delta = 3.31$ ppm) was used as the internal standard in CD_3OD. For ^{31}P NMR spectra, 85% H_3PO_4 was used as an external reference. MALDI-TOF mass spectra were obtained with a Bruker Autoflex II equipped with a N_2 laser ($\lambda = 337$ nm) using α-cyano-4-hydroxycinnamic acid as matrix. Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg.

4.1.1 *Synthesis of 1,3-[di-(oxamethyl-phosphonic acid)], 2-(*N*-succinimide-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]-arene (**6**)*

*4.1.1.1 Mono-methoxyethoxy-calix[4]arene (**2**).* A suspension of calix[4]arene **1** (12.73 g, 30.0 mmol) and K_2CO_3 (2.16 g, 15.6 mmol) in acetonitrile (500 ml) was stirred for 30 min at room temperature under a nitrogen atmosphere. Methoxyethyl *p*-toluenesulphonate (6.91 g, 12.0 mmol) was then added and the mixture was stirred and refluxed for 4 days. After removal of the solvent, 400 ml of CH_2Cl_2 and 400 ml of water were added and the mixture was stirred and acidified with 1 M HCl. The organic layer was recovered and dried over anhydrous Na_2SO_4. After removal of the solvent, compound **2** was purified by column chromatography (SiO_2, eluent: CH_2Cl_2) and obtained as a white powder.

Yield: 9.91 g (68%); mp 224–225°C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.86 (s, 1H, ArO*H*), 9.24 (s, 2H, ArO*H*), 7.12–7.00 (m, 8H, ArH_{meta}), 6.89 (t, 1H, $J = 7.5$ Hz, ArH_{para}), 6.72–6.65 (m, 3H, ArH_{para}), 4.49 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.35–4.32 (m, 2H, CH_2CH$_2$OCH$_3$), 4.31 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.04–4.01 (m, 2H, CH$_2$CH_2OCH$_3$), 3.62 (s, 3H, OCH_3), 3.48 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 3.46 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar). Anal. calcd for $C_{31}H_{30}O_5$ (%): C, 77.16; H, 6.27. Found: C, 77.43; H, 6.00.

*4.1.1.2 1-(Ethyl-4-oxabutyrate), 3-(methoxyethoxy)-calix[4]arene (**3**).* Mono-methoxyethoxy-calix[4]arene **2** (4.83 g, 10.0 mmol) and K_2CO_3 (0.72 g, 5.2 mmol) were suspended in acetonitrile (200 ml) and stirred for 1 h at room temperature under a nitrogen atmosphere. $Br(CH_2)_3C(O)OCH_2CH_3$ (2.34 g, 12.0 mmol) was then added and the resulting solution was refluxed for 4 days. After evaporation of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2 (300 ml) and water (300 ml) and the resulting mixture was acidified then separated in order to recover the organic layer which was dried over anhydrous Na_2SO_4. After evaporation of the solvent, compound **3** was purified by column chromatography (SiO_2, eluent: CH_2Cl_2/acetone 98/2, v/v) and obtained as a white powder.

Yield: 3.36 g (56%); mp 165–166°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 2H, ArO*H*), 7.06 (d, 4H, $J = 7.5$ Hz, ArH_{meta}), 6.90 (d, 4H, $J = 7.5$ Hz, ArH_{meta}), 6.76–6.71 (m, 2H, ArH_{para}), 6.65 (t, 2H, $J = 7.5$ Hz, ArH_{para}), 4.42 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.28 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 4.23–4.16 (m, 4H, COOCH_2CH$_3$+CH_2CH$_2$OCH$_3$), 4.07 (t, 2H, $J = 6.1$ Hz, CH_2CH$_2$CH$_2$COOEt), 3.95–3.92 (m, 2H, CH$_2$CH_2OCH$_3$), 3.56 (s, 3H, CH$_2$OCH_3), 3.38 (d, 4H, $J = 13.0$ Hz, ArCH_2Ar), 2.90 (t, 2H, $J = 7.4$ Hz, CH_2COOEt), 2.41–2.32 (m, 2H, CH$_2$CH_2CH$_2$COOEt), 1.29 (t, 3H, $J = 7.2$ Hz, COOCH$_2$CH_3). Anal. calcd for $C_{37}H_{40}O_7$ (%): C, 74.47; H, 6.76. Found: C, 74.68; H, 6.52.

*4.1.1.3 Diethylphosphonoylmethoxy-p-toluenesulphonate (**a**).* A solution of triethylamine (10.12 g, 100.0 mmol) in CH_2Cl_2 (50 ml) was added dropwise to a stirred mixture of diethyl(hydroxy-methyl)phosphonate (8.41 g, 50.0 mmol) and *p*-toluenesulphonyl chloride (10.01 g, 52.5 mmol) in CH_2Cl_2 (450 ml) at *ca.* 0°C. The resulting mixture was cooled to room temperature and stirred for 15 h. It was then extracted with 300 ml of acidified aqueous solution and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel. CH_2Cl_2 was used as the first mobile phase then CH_2Cl_2/acetone (98/2, v/v). Compound **a** was recovered as a viscous liquid.

Yield: 12.93 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, 2H, $J = 8.1$ Hz, Ar*H*), 7.36 (d, 2H, $J = 8.1$ Hz, Ar*H*), 4.19–4.09 (m, 6H, SO$_3$CH_2P + POOCH_2CH$_3$), 2.45 (s, 3H, CH_3Ar), 1.31 (t, 6H, $J = 7.1$ Hz, POOCH$_2$CH_3).

*4.1.1.4 1,3-[Di-(oxamethyl-diethylphosphonate)], 2-(ethyl-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]arene (**4**).* A suspension of 1-(ethyl-4-oxabutyrate), 3-(methoxyethoxy)-calix[4]arene **3** (1.79 g, 3.0 mmol) and K_2CO_3 (4.15 g, 30.0 mmol) in acetonitrile (100 ml) was stirred for 2 h at room temperature under nitrogen atmosphere. Diethylphosphonoylmethoxy-*p*-toluenesulphonate **a** (2.03g, 6.3mmol) was then added and the mixture was refluxed for 10 days. After filtration of the mixture, the solvent was removed under *vacuum* and the residue was taken up in CH_2Cl_2 (200 ml). About 200 ml of water was added and the mixture was acidified with 1 M HCl. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography (SiO_2, eluent: CH_2Cl_2/acetone 90/10, v/v). Compound **4** was obtained as a pure yellow viscous liquid.

Yield: 1.69 g (63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.25–7.21 (m, 4H, ArH_{meta}), 7.11–7.08 (m, 2H, ArH_{meta}), 6.99–6.96 (m, 2H, ArH_{meta}), 6.68–6.57 (m, 4H, ArH_{para}), 4.29–4.17 (m, 6H, ArOCH_2 + COOCH_2CH$_3$), 4.07 (d, 4H, $J = 9.2$ Hz, ArOCH_2P), 3.91–3.88 (m, 2H, CH_2OCH$_3$), 3.77–3.64 (m, 8H, POOCH_2), 3.59 (s, 3H, CH$_2$OCH_3), 3.49 (s, 8H, ArCH_2Ar), 2.53 (t, 2H, $J = 7.2$ Hz, CH_2COOEt), 2.20 (q, 2H, $J = 7.2$ Hz, CH$_2$ CH_2CH$_2$COOEt), 1.42 (t, 12H, $J = 7.1$ Hz, POOCH$_2$ CH_3), 1.24 (t, 3H, $J = 7.1$ Hz, COOCH$_2$CH_3). ^{31}P NMR (400 MHz, $CDCl_3$) δ (ppm): 21.8. Anal. calcd for $C_{47}H_{62}O_{13}P_2$ (%): C, 62.94; H, 6.97. Found: C, 62.76; H, 7.14.

*4.1.1.5 1,3-[Di-(oxamethyl-phosphonic acid)], 2-(4-oxabutyric acid), 4-(methoxyethoxy)-calix[4]arene (**5**).* Bromotrimethylsilane (5.64 g, 36.83 mmol) was added to a solution of compound **4** (1.10 g, 1.23 mmol) in 20 ml acetonitrile. The reaction mixture was stirred for 24 h at room temperature under nitrogen atmosphere. It was then evaporated under reduced pressure and a mixture of 10 ml of methanol/water (50/50, v/v) was added to the residue. The resulting solution was stirred at room temperature overnight. After removal of methanol and water, the residue was evaporated twice with 10 ml of dry toluene and filtered to obtain compound **5** as a pink solid.

Yield: 0.91 g (98%); mp 158–159°C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.17 (d, 4H, $J = 7.5$ Hz, ArH_{meta}), 7.05–7.02 (m, 2H, ArH_{meta}), 6.95–6.92 (m, 2H, ArH_{meta}), 6.62–6.53 (m, 4H, ArH_{para}), 3.76–3.50 (m, 18H, ArOCH_2CH$_2$ + ArCH_2Ar + ArOCH_2P + CH_2OCH$_3$), 3.22 (s, 3H, CH$_2$OCH_3), 2.47–2.39 (m, 2H, CH_2COOH), 2.03–1.92 (m, 2H, CH_2CH$_2$COOH). ^{31}P NMR (400 MHz, CD_3OD) δ (ppm): 19.9. Anal. calcd for $C_{37}H_{42}O_{13}P_2$ (%): C, 58.73; H, 5.59. Found: C, 58.47; H, 5.44. Mass spectrum (MALDI-TOF): $m/z = 755.2$ $[M-H]^-$.

*4.1.1.6 1,3-[Di-(oxamethyl-phosphonic acid)], 2-(N-succinimide-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]arene (**6**).* Compound **5** (1.14 g, 1.5 mmol), EDC [1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide (0.58 g, 3.0 mmol) and NHS (*N*-hydroxysuccinimide) (0.35 g, 3.0 mmol) were dissolved in DMF (90 ml) and the mixture was stirred overnight at room temperature and then for 3 h

at 55°C. After removal of the solvent, the residue was treated with acetonitrile to obtain compound **6** as white solid.

Yield: 0.82 g (64%); mp 109–111°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.24 (d, 4H, $J = 7.4$ Hz, ArH_{meta}), 7.02–6.99 (m, 2H, ArH_{meta}), 6.93–6.90 (m, 2H, ArH_{meta}), 6.57–6.52 (m, 4H, ArH_{para}), 3.75–3.55 (m, 12H, ArOCH_2CH$_2$ + ArCH_2Ar), 3.37 (s, 3H, CH$_2$OCH_3), 3.03–2.89 (m, 6H, ArOCH_2P + CH_2OCH$_3$), 2.71 (s, 4H, NHS), 1.99–1.95 (m, 2H, CH_2COONHS), 1.76–1.71 (m, 2H, CH_2CH$_2$COONHS). ^{31}P NMR (400 MHz, DMSO-d_6) δ (ppm): 16.4. Anal. calcd for $C_{41}H_{45}NO_{15}P_2$ (%): C, 57.68; H, 5.31; N, 1.64. Found: C, 57.39; H, 5.45; N, 1.81. Mass spectrum (MALDI-TOF): $m/z = 855.1$ [MH$^+$].

*4.1.2 Synthesis of 1,3-[di-(oxapropyl-phosphonic acid)], 2-(*N*-succinimide-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]-arene (**9**)*

*4.1.2.1 Diethylphosphonoylpropoxy-p-toluenesulphonate (**b**).* Diethyl 3-bromopropylphosphonate (5.18 g, 20.0 mmol) and silver *p*-toluenesulphonate (11.16 g, 40.0 mmol) were dissolved in 200 ml acetonitrile and stirred at room temperature for 3 days. The solution was then filtered and the solvent was evaporated to dryness under reduced pressure. The residue was then taken up in CH_2Cl_2 (400 ml) and water (400 ml). The organic layer was recovered and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column (SiO_2, eluent: CH_2Cl_2/acetone 80/20, v/v). Compound **b** was recovered as a viscous liquid.

Yield: 1.75 g (25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (d, 2H, $J = 8.2$ Hz, Ar*H*), 7.34 (d, 2H, $J = 8.2$ Hz, Ar*H*), 4.12–3.99 (m, 6H, CH$_3$ArSO$_3$CH_2 + POOCH_2CH$_3$), 2.44 (s, 3H, CH_3Ar), 2.01–1.87 (m, 2H, SO$_3$CH$_2$CH$_2$CH_2P), 1.81–1.69 (m, 2H, SO$_3$CH$_2$CH_2CH$_2$P), 1.29 (t, 6H, $J = 7.1$ Hz, POOCH$_2$CH_3).

*4.1.2.2 1,3-[Di-(oxapropyl-diethylphosphonate)], 2-(ethyl-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]arene (**7** and **7′**).* The synthesis was performed as for compound **4**.

Calix[4]arene derivative **3**. 1.43 g, 2.4 mmol; K_2CO_3: 3.32 g, 24.0 mmol; acetonitrile: 100 ml; diethylphosphonoyl propoxy-*p*-toluenesulphonate **b**: 1.77 g, 5.0 mmol; CH_2Cl_2: 200 ml; H_2O: 200 ml. Column chromatography (SiO_2, eluent: CH_2Cl_2/acetone 80/20, v/v). Compounds **7** and **7′** were obtained as yellow viscous liquids.

Compound **7** (1,3-alternate), yield: 0.53 g (23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.09–7.06 (m, 2H, ArH_{meta}), 7.02–7.00 (m, 6H, ArH_{meta}), 6.75–6.70 (m, 4H, ArH_{para}), 4.21–4.09 (m, 10H, ArOCH_2 + COOCH_2CH$_3$), 3.75–3.55 (m, 16H, POOCH_2CH$_3$ + ArCH_2Ar), 3.37–3.35 (m, 2H, CH$_2$CH_2OCH$_3$), 3.34 (s, 3H, CH$_2$CH$_2$OCH_3), 2.26 (t, 2H, $J = 7.5$ Hz, CH$_2$CH$_2$CH_2COOEt), 1.92–1.66 (m, 10H, CH$_2$CH_2CH_2POOEt + CH$_2$CH_2CH$_2$COOEt), 1.37 (t, 12H, $J = 7.1$ Hz, POOCH$_2$CH_3), 1.30 (t, 3H, $J = 7.1$ Hz, COOCH$_2$CH_3). ^{31}P NMR (400 MHz, $CDCl_3$) δ (ppm): 33.5. Anal. calcd for $C_{51}H_{70}O_{13}P_2$ (%): C, 64.27; H, 7.40. Found: C, 64.17; H, 7.29. Mass spectrum (MALDI-TOF): $m/z = 975.4$ [MNa$^+$].

Compound **7′** (partial cone), yield: 0.43 g (19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35–7.33 (m, 1H, ArH_{meta}), 7.25–7.22 (m, 1H, ArH_{meta}), 7.10–7.07 (m, 2H, ArH_{meta}), 7.01–6.88 (m, 4H, ArH_{meta}), 6.49–6.42 (m, 2H, ArH_{para}), 6.32–6.26 (m, 2H, ArH_{para}), 4.21–4.10 (m, 10H, ArOCH_2+COOCH_2CH$_3$), 4.05 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 3.92–3.57 (m, 12H, POOCH_2CH$_3$ + ArCH_2Ar), 3.45 (s, 3H, CH$_2$CH$_2$OCH_3), 3.09 (d, 2H, $J = 13.0$ Hz, ArCH_2Ar), 2.61–2.43 (m, 2H, CH$_2$CH_2OCH$_3$), 2.23–2.14 (m, 4H, CH_2POOEt + CH_2COOEt), 1.96–1.84 (m, 2H, CH_2POOEt), 1.76–1.53 (m, 6H, CH$_2$CH_2CH$_2$POOEt + CH$_2$CH_2CH$_2$COOEt), 1.43–1.34 (m, 12H, POOCH$_2$CH_3), 1.26 (t, 3H, $J = 7.1$ Hz, COOCH$_2$CH_3). ^{31}P NMR (400 MHz, $CDCl_3$) δ (ppm): 34.1 and 33.1. Anal. calcd for $C_{51}H_{70}O_{13}P_2$ (%): C, 64.27; H, 7.40. Found: C, 64.17; H, 7.29.

*4.1.2.3 1,3-[Di-(oxapropyl-phosphonic acid)], 2-(4-oxa butyric acid), 4-(methoxyethoxy)-calix[4]arene (**8**).* The synthesis was performed as for compound **5**.

Calix[4]arene derivative **7**. 0.29 g, 0.3 mmol; bromotrimethylsilane: 1.38 g, 9.0 mmol; acetonitrile: 10 ml; methanol/water (50/50, v/v): 5 ml. Pink solid, yield: 0.24 g (98%), mp > 290°C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.15–7.03 (m, 8H, ArH_{meta}), 6.92–6.77 (m, 4H, ArH_{para}), 3.84–3.49 (m, 18H, ArOCH_2 + ArCH_2Ar + CH$_2$CH_2OCH$_3$), 3.31 (s, 3H, CH$_2$OCH_3), 2.12–1.98 (m, 2H, CH_2COOH), 1.72–1.45 (m, 10H, CH$_2$CH_2CH_2POOH + CH$_2$CH_2CH$_2$COOH). ^{31}P NMR (400 MHz, CD_3OD) δ (ppm): 33.5. Anal. calcd for $C_{41}H_{50}O_{13}P_2$ (%): C, 60.59; H, 6.20. Found: C, 60.46; H, 6.13.

*4.1.2.4 1,3-[Di-(oxapropyl-phosphonic acid)], 2-(N-succi nimide-4-oxabutyrate), 4-(methoxyethoxy)-calix[4]arene (**9**).* The synthesis was performed as for compound **6**.

Calix[4]arene derivative **8**. 0.22 g, 0.27 mmol; EDC: 0.10 g, 0.54 mmol; NHS: 0.06 g, 0.54 mmol; DMF: 16 ml. Brown solid, yield: 0.11 g (45%), mp >290°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.13–6.94 (m, 8H, ArH_{meta}), 6.79–6.69 (m, 4H, ArH_{para}), 3.66–3.46 (m, 18H, ArOCH_2 + ArCH_2Ar + ArOCH$_2$CH_2OCH$_3$), 3.36 (s, 3H, CH$_2$OCH_3), 2.71 (s, 4H, NHS), 1.99–1.88 (m, 2H, CH_2COONHS), 1.57–1.21 (m, 10H, CH$_2$CH_2CH_2POOH + CH$_2$CH_2CH$_2$COONHS). ^{31}P NMR (400 MHz, DMSO-d_6) δ (ppm): 32.1. Anal. calcd for $C_{45}H_{53}NO_{15}P_2$ (%): C, 59.40; H, 5.87; N, 1.54. Found: C, 59.18; H, 5.60; N, 1.60. Mass spectrum not available due to the poor solubility in solvents compatible with mass spectrometry.

4.2 Coupling on the solid support

A column was packed with 1 g Ultralink hydrazide gel according to the protocol described by the manufacturer and conditioned with a 50 mM sodium borate buffer at pH 9. About 40 mg/ml solutions of compounds **6** and **9** were prepared in DMSO. Five successive additions of these solutions were performed in order to obtain a final concentration of 3 μmol/g calixarene and the coupling was performed during 2.5 h under agitation.

The column was then washed with 2× 2 ml coupling buffer and 2 ml coupling buffer containing 1 M NaCl and the eluates were analysed using a fluorimeter CARY-Eclipse (Varian) at $\lambda_{exc} = 268$ nm and $\lambda_{em} = 310$ nm. λ_{exc} and λ_{em} were previously determined from a calixarene solution and the calixarene amount in the eluates was quantified from a calibration curve (0; 1.86; 3.70; and 7.36×10^{-4} M).

The calixarene content was determined from the mass balance, by difference between the initial number of moles of calixarene and that found in the eluate fractions.

4.3 Uranyl cation binding

Aliquots of gels (1 g) coupled with 2 μmol calixarene **6**/g were washed with 4× 2 ml of 50 mM sodium acetate buffer (pH 4.0). About 5× 20 μl of a 0.1 M uranyl acetate solution (i.e. 10 μM) were then added to the column and contacted overnight under agitation at room temperature. The supernatant was recovered and the column was then rinsed using 3× 2 ml of 50 mM acetate buffer (pH 4) and 3× 2 ml of 50 mM HEPES buffer (pH 7.4).

UV spectra of uranyl solutions, recorded on a CARY 50 (Varian), showed a maximum peak between 222 and 234 nm, correlated to the uranyl concentrations in the solutions. A calibration curve (0, 1.5, 3 and 6×10^{-4} M) was used to quantify the uranyl amount in both supernatant and eluates. The amount of gel sorbed uranyl cation was determined by difference between its initial quantity and that measured in the liquid fractions.

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