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Sequestering agents for uranyl chelation: new calixarene ligands

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ABSTRACT

Synthesis of sulfocatecholamide (CAMS) and hydroxypyridinone (HOPO) calixarene ligands and determination of their binding abilities for the uranyl cation were described. Chelating properties were determined by UV spectrophotometry in aqueous media under various pH conditions and further studied by ^{1}H NMR analysis of the resonance signals of both aromatics' protons of the chelating groups. Each ligand shows a more or less pronounced affinity for uranium. HOPO calixarenes exhibit significant affinity towards uranyl ion at acidic and neutral pH while CAMS calixarene is more efficient at basic pH.

1. Introduction

Commonly used as nuclear fuel in fission reactors for civilian purpose, uranium can be introduced into the body in the case of internal contamination or in the event of a nuclear accident by ingestion, inhalation or through wounds. The hexavalent uranyl ion (UO_2^{2+}, U(VI)) was found to be the most stable form in vivo[1] and is complexed in the blood by chelating agents such as proteins or carbonates. Distribution of toxic species and retention in target organs such as kidneys, liver or marrow occurs[2] after chelation, potentially inducing cancer and chemical intoxication, especially in the case of heavy contamination.[3]

Elimination of toxic species from the body could be achieved by administrating non-toxic chelating agents, which must have high stability constant so that they can displace the natural complexes rapidly formed with components of blood. To lower uranyl concentrations and radiation doses, and subsequently tumour risks, the uranyl/ligand complex formed must also be soluble in physiological fluids and stable in a pH range of 2–9 to be subsequently eliminated from the body by crossing renal or hepatic barrier.

During the past 30 years, several effective uranyl ligands were synthesised, based on different complexing functions. Phosphorus containing molecules, especially bisphosphonates, were found to be very effective uranyl ligands,[4] but few significant decorporation work has been reported so far concerning the decorporation efficacy of ethane-1-hydroxy-1,1-bisphosphonate EHBP.[5] Decorporation with bidentate methylterphthalimide (MeTAM)-based chelating ligands was also studied and appeared not to be suitable for biological decorporation due to their high toxicity.[6]

Sulfocatechol Tiron proved to be effective for U(VI) complexation in vivo within the physiological pH range,[7] but a modest successful reduction of acute U(VI) toxicity and reduction of body U(VI) with this ligand was observed. Therefore, multidentate analogues containing sulfocatecholamide (CAMS) or structurally analogous hydroxyl-pyridone (HOPO) units would be effective for in vivo chelation of U(VI).[8]

Uranyl-sequestering agents based on 3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO) and sulfocatecholamide (CAMS) ligands resulted in two low-toxicity ligands 5-LICAM(S) and 5-LIO(Me-3,2-HOPO) (Fig. 1), both efficient chelating agents of circulating U(VI) in the body.[8b] However, these efficiencies were often observed when the ligands were administrated immediately (5–30 min) after contamination, which shows that the development of new ligands is still of interest.

Recently, we described the synthesis and the evaluation of several 5-CAMS analogues incorporating various diamine skeletons.[9] The chelating properties towards uranium were studied in aqueous media by UV–vis analysis and NMR spectroscopy and some of these showed pronounced affinity for the target ion (CYCAMS).

Owing to the development of supramolecular chemistry, a number of calixarene-based ligands have been extensively developed for their coordination properties.[10] Moreover, the chemistry of these macrocycles is presently well known and efficient.

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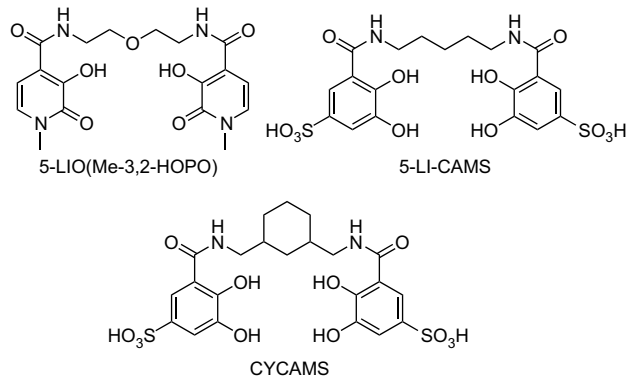


Figure 1. Low-toxicity uranyl complexants.

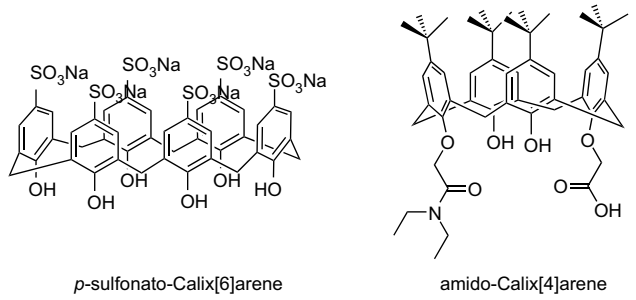


Figure 2. Calixarenes based uranophiles.

Synthetic modifications can be realised on the lower and/or the upper rim with various functional chelating groups. The easy accessibility and the selective functionalisations at the phenolic hydroxy groups of calix[4]arenes have made this member of the series increasingly attractive for chemists involved in host/guest chemistry.[11] Since sulfonato-calix[*n*]arenes (*n*=4,6,8) have been reported[12] as selective uranophiles (Fig. 2), the importance of structural rigidity and pre-organisation of these macrocycles was proved with the very high stability of the complexes with UO_2^{2+} of the calixarene-based ligand for the uranyl ion relative to other metal ions.[13] Calix[4]arene systems containing amides,[14] hydroxamates,[15] CMPO[16] or HOPO[17] have also been designed expressively for the selective coordination of uranyl ions.

Surprisingly, to the best of our knowledge, combination of the architecture of calix[*n*]arenes with the chelating behaviour of sulfocatechol amides has not been reported in the literature so far. We present here the synthesis and the chelating properties of new calixarene derivatives containing HOPO or CAMS function.

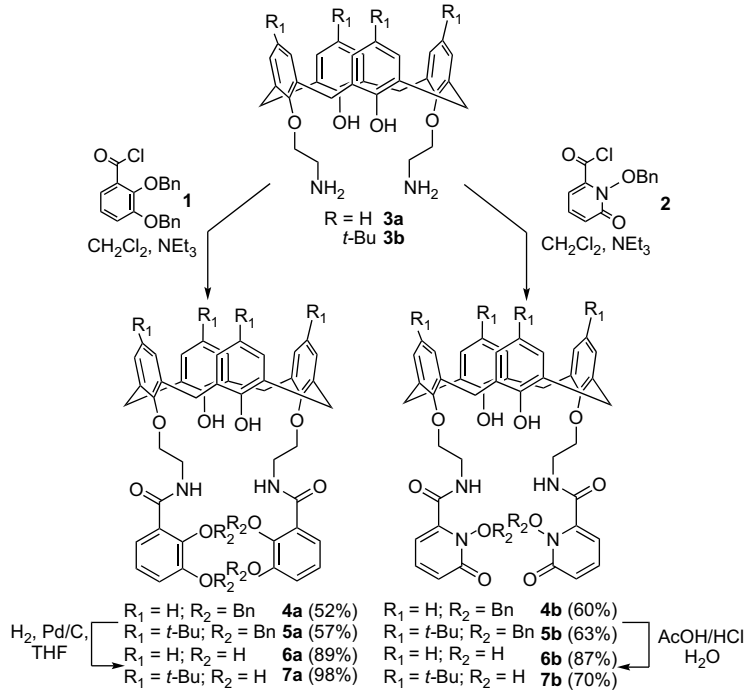
The first step in this project involves the condensation of protected chelating groups on bis-ethoxyamino calix[4]arenes **3a**,**b** (Scheme 1). After deprotection of the hydroxyl groups of the chelating units CAM and HOPO, sulfonation afforded the target compounds. The second step concerns the comparative evaluation of the complexation constants with uranyl ions in water with 5-LICAM(S) as a reference, using SCP method developed by Taran and co-workers.[4a]

2. Results and discussion

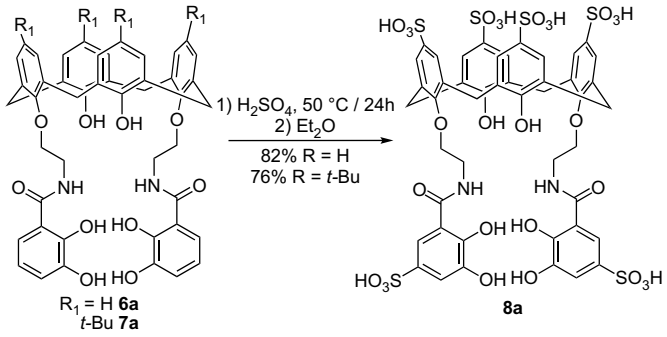
2.1. Synthesis

Acid chloride derivatives **1** and **2** were obtained by the reaction of oxalyl chloride with *O*-benzyl catechol[18] and *N*-benzyl HOPO[19] carboxylic acids preliminarily synthesised following the previously described procedures in dichloromoethane with a catalytic amount of DMF in quantitative yield. Bis-catecholamide analogues **4a**,**b** and **5a**,**b** were obtained by condensation of the acid chloride derivatives **1** and **2** with calixarenes **3a** and **3b** prepared according to a described procedure[20] in the presence of Et_3N (Scheme 1). Deprotection of the hydroxyl groups was achieved using HCl in acetic acid for the HOPO pendant arms to give **6b** and **7b** in 87% and 70% yields, respectively. Hydrogenolysis of the catechol **4a** and **5a** led to **6a** and **7a** in 89% and 98% yields.

Sulfonation in hot sulfuric acid of **6a** or **7a** followed by precipitation in diethylether gave the desired pure 1,3-CalixCAMS **8a** in good yield (Scheme 2). In parallel, sulfonation of 1,3-CalixHOPO **6b** or **7b** failed, leading to partial and total removal of HOPO groups



Scheme 1. Synthesis of 1,3-CalixCAM and CalixHOPO.



Scheme 2. Sulfonation of CAM analogues.

from the calixarene ring. Each component was fully characterised by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Cone conformation of the macrocycles was confirmed by ^{1}H NMR that displays two doublets at 3.25–3.48/4.50–4.17 ppm corresponding to the resonance signals of H_{ax} and H_{eq} of the methylene bridges and ^{13}C NMR with signals at 31.0–32.1 ppm corresponding to the resonance signals of the methylene bridges.[21]

2.2. Constant stability determination

The complexation behaviour of water-soluble calixarenes **6b**, **7b** and **8a** towards the uranyl cation was studied by the spectrophotometric method developed by Taran co-workers,[4a] based on competitive uranium binding by using sulfochlorophenol SCP as a chromogenic chelate. This latter was found highly suitable for a rapid screening of putative uranium ligand library and compared with 5-LICAMS, synthesised as previously described by Raymond and co-workers (Table 1).[6] Globally, the CAMS macrocycles exhibit high K_{cond} enhancement in basic conditions in accordance with previous findings.[22] At pH=7.4, none of the synthesised calixarene displaced SCP/uranyl complexation equilibrium better than the 5-LICAMS with log $K_{pH=7.4}$=17.0. Except for the 1,3-CalixCAMS **8a**, which was not able to displace more than 20% of the SCP/UO_2 complex,[4a] 1,3-calixHOPO and 5-LICAMS exhibited similar log K_{cond} close to 11. At pH 9, **8a** exhibited a larger complexation efficiency (log K_{cond}=20.2) towards UO_2^{2+}. As far as we know, such very large stability constant has never been observed with CAMS ligands.

The ability of compound **8a** to complex UO_2^{2+} was also studied by ^{1}H NMR spectroscopy. Due to their low solubility in D_2O, such studies couldn't be achieved with compounds **6b** and **7b**.

Figure 3 shows the NMR spectra of **8a** with variable amounts of uranyl nitrate hexahydrate in the presence of a binary mixture of D_2O/NaOD at room temperature with sodium nitrate (0.05 mol L^{-1}). After each addition of $UO_2(NO_3)_2\cdot 6H_2O$, the pH of the deuterated solution was adjusted 12 by addition of NaOD.

Resonance signals of the catechol protons H_1 and H_2 of compound **8a** (Fig. 3) in D_2O/NaOD were, respectively, identified as two doublets at 7.62 and 6.97 ppm (J=1.9 Hz), while resonance signals of the aromatic protons H_3 and H_4 of the phenolic ring were located as two singlets at 7.42 and 7.68 ppm. Addition of increasing amounts of $UO_2(NO_3)_2\cdot 6H_2O$ (Fig. 3) led to appreciable changes with downfield shifts of the H_1/H_2 aromatic proton resonances of the catechol moiety and upfield shifts of the H_3/H_4 aromatic proton resonance signals of the calixarene ring.

Thus, upon addition of $UO_2(NO_3)_2\cdot 6H_2O$ in a deuterated solution containing **8a**, two new doublets appear, respectively, at 7.72 and 7.13 ppm (Δ_δ=0.10 and 0.16 ppm) corresponding to the resonance signals of the catechol protons of the uranyl complexes. Similarly, the changes in the level of the signals of the phenolic protons of the calixarene ring were also indicative due to the proximity of the uranyl cation nearby the altered protons. Thus, two new broad singlets appear, respectively, at 7.28 ppm and 7.54 ppm (Δ_δ=−0.14 ppm). Finally, the 1:1 stoichiometry of the uranyl complexes was confirmed by the total disappearance of the four resonance signals of the free ligand without appearance of new resonance signals.

Table 1
K_{cond} of ligand-UO_2^{2+} at several pH values (±0.1)

pH	log K_{cond} U-L/(pH)		
	5.5	7.4	9.0
5-LICAMS	11.1	17.0	19.4
8a	10	16.3	**20.2**
6b	11	16	18.1
7b	**11.2**	15.5	17.9

3. Conclusion

The dipodal bis-catecholamide **8a** and bis-HOPO uranophiles **6b**, **7b** were obtained by an efficient synthetic route from diaminocalixarenes **3a**,**b**. Their binding abilities for UO_2^{2+} were determined by UV spectrophotometry in aqueous media under acidic, neutral and basic pH conditions. Globally, the binding properties were found similar to those observed with 5-LICAMS, a well known ligand that displays in vivo uranyl removal capabilities. At pH=9.0, the CalixCAMS **8a** showed a higher constant of 20.2 never observed with CAMS ligands.

4. Experimental part

4.1. General

All the organic reagents used were pure commercial products from Aldrich, Acros, Fluka, Avocado, Lancaster & Maybridge. Diaminocalixarenes **3a** and **3b** in cone conformation,[20] (2,3)dibenzyloxybenzoic acid[18] and 1-hydroxy-6-oxo-1,6-dihydropyridine-2-carboxylic acid (1,2-HOPO)[19a] were synthesised as previously described.

The solvents were purchased from Carlo Erba, Acros, Pro-Labo, Fulka & Aldrich. Anhydrous solvents came from Acros, anhydrous THF and dry CH_2Cl_2 were distilled. Flash chromatography was carried out on Merck Silica Si60 (40–63 μm). ^{1}H, ^{13}C NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C) or AC-300 FT (300.13 MHz for ^{1}H, 75.46 MHz for ^{13}C) spectrometer; δ values are given in parts per million and J in hertz. Elemental analyses (C, H, N, S, O, F) were obtained from the Service Central d'Analyse of the CNRS (Solaize). High resolution mass spectra: HR LSIMS (Liquid Secondary Ionisation Mass Spectrometry: Thioglycerol), HR CIMS (Isobutan) and HR EIMS were carried out on a Finnegan MAT 95xL by the UCBL Centre de Spectroscopie de Masse.

4.2. Synthesis of calixarene 4a

Oxalyl chloride (0.8 ml, 9.3 mmol) was added dropwise to a solution of 2.04 g 2,3-bis(benzyloxy)benzoic acid (6.1 mmol) in CH_2Cl_2 (30 ml). After adding a drop of DMF, the mixture was stirred until the end of HCl release. After evaporation of solvents and residual oxalyl chloride, the residue was dissolved in 30 ml of dry CH_2Cl_2 and added dropwise to a solution of 1.53 g of 25,27-(2-aminoethoxy)-26,28-dihydroxycalix[4]arene (3 mmol) and 1.3 ml of triethylamine (9.2 mmol) in 40 ml of dry CH_2Cl_2. After 18 h under stirring, the mixture was washed with HCl 1 N (100 ml), water (2×50 ml), brine (100 ml), then dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane 1:2) to give **4a** (1.78 g, 52%) as white powder. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 8.19 (br s, 2H, N*H*), 7.54 (m, 2H,

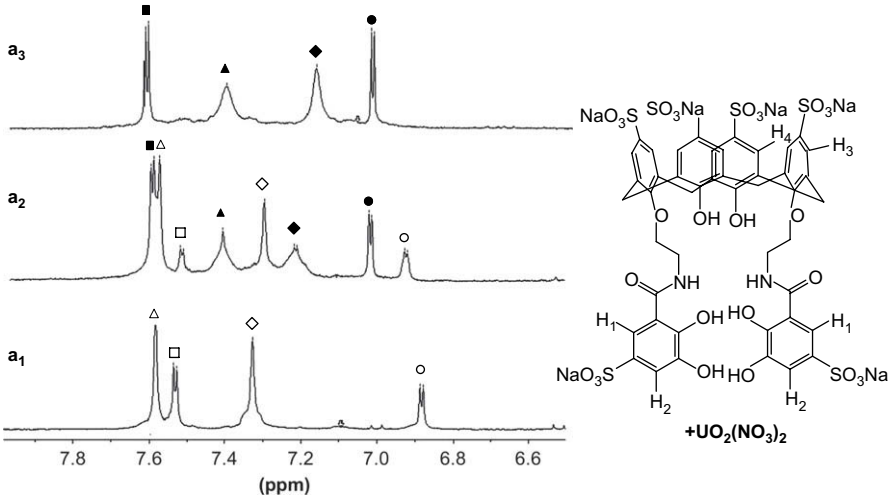


Figure 3. ^{1}H NMR aromatic shifts upon addition of $UO_2(NO_3)_2{\cdot}6H_2O$ in D_2O+NaOD at pH 12 (a_1: 0 equiv; a_2: 0.5 equiv; a_3: 1 equiv) at 298 K (○: H_1, □: H_2, ◇: H_3, △: H_4 of the free 1,3-CalixCAMS and ●: H_1, ■: H_2, ◆: H_3, ▲: H_4 of 1,3-CalixCAMS/UO_2^{2+}).

Ar–*H*), 7.25–7.37 (m, 20H, Ar–*H*), 6.97–7.09 (m, 8H, Ar–*H*), 6.78 (d, *J*=7.5 Hz, 4H, Ar–*H*), 6.64 (t, *J*=4.7 Hz, 4H, Ar–*H*), 5.07 (s, 4H, O–C*H*$_2$–Ar), 4.99 (s, 4H, O–C*H*$_2$–Ar), 4.13 (AB d, 4H, ^2J(H,H)=13.3 Hz, Ar–C*H*$_2$–Ar ax), 3.90 (t, 4H, *J*=5.6 Hz, O–C*H*$_2$–CH$_2$–NH), 3.49 (m, 4H, O–CH$_2$–C*H*$_2$–NH), 3.22 (AB d, 4H, ^2J(H,H)=13.3 Hz, Ar–C*H*$_2$–Ar eq). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 166.8 (C=O), 153.3 (ArC), 152.3 (ArC), 151.7 (ArC), 147.3 (ArC), 137.3 (ArC), 137.1 (ArC), 133.4 (ArC), 129.5 (ArC), 129.4 (ArCH), 129.3 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.6 (ArCH), 128.4 (ArC), 126.0 (ArCH), 124.7 (ArCH), 123.2 (ArCH), 119.7 (ArCH), 117.6 (ArCH), 77.0 (CH_2), 74.9 (CH_2), 71.8 (CH_2), 39.9 (CH_2), 31.8 (CH_2). HR ESIMS calculated for $C_{74}H_{66}N_2O_{10}Na^+$=1165.4615; found=1165.4620. Anal. Calcd (%) for $C_{74}H_{66}N_2O_{10}$: C, 77.74; H, 5.82; N, 2.45; O, 13.99. Found: C, 77.92; H, 5.96, N 2.13.

4.3. Synthesis of calixarene 5a

Oxalyl chloride (0.8 ml, 9.3 mmol) was added dropwise to a solution of 2.14 g 2,3-bis(benzyloxy)benzoic acid (6.4 mmol) in CH_2Cl_2 (50 ml). After adding a drop of DMF, the mixture was stirred until the end of HCl release. After evaporation of solvents and residual oxalyl chloride, the residue was dissolved in 30 ml of dry CH_2Cl_2 and added dropwise to a solution of 2.2 g 5,11,17,23-tetra-*tert*-butyl-25,27-(2-aminoethoxy)-26,28-dihydroxy calix[4]arene (3 mmol) and 1.3 ml of triethylamine (9.2 mmol) in 50 ml of dry CH_2Cl_2.

After 18 h under stirring, the mixture was washed with HCl 1 N (100 ml), water (2×50 ml), brine (100 ml), then dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane 1:2) to give **5a** (2.34 g, 57%) as white foam. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 8.20 (br s, 2H, N*H*), 7.59 (m, 2H, Ar–*H*), 7.30–7.41 (m, 20H, Ar–*H*), 7.15 (s, 2H, Ar–*H*), 7.03–7.08 (m, 8H, Ar–*H*), 6.78 (s, 4H, Ar–*H* subst. rings), 5.13 (s, 4H, O–C*H*$_2$–Ar), 5.04 (s, 4H, O–C*H*$_2$–Ar), 4.18 (AB d, 4H, ^2J(H,H)=13.0 Hz, Ar–C*H*$_2$–Ar ax), 3.93 (t, 4H, *J*=4.9 Hz, O–C*H*$_2$–CH$_2$–NH), 3.65–3.71 (m, 4H, O–CH$_2$–C*H*$_2$–NH), 3.22 (AB d, 4H, ^2J(H,H)=13.0 Hz, Ar–C*H*$_2$–Ar eq), 1.31 (s, 18H, (C*H*$_3$)$_3$C unsubst. rings), 0.98 (s, 18H, (C*H*$_3$)$_3$C subst. rings). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 166.5 (C=O), 150.2 (ArC), 150.7 (ArC), 149.9 (ArC), 147.4 (ArC), 142.0 (ArC), 137.2 (ArC), 137.1 (ArC), 132.8 (ArC), 129.4 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.5 (ArCH), 128.1 (ArCH), 126.0 (ArCH), 125.6 (ArCH), 124.6 (ArCH), 123.4 (ArCH), 117.9 (ArCH), 76.8 (CH_2), 75.0 (CH_2), 72.0 (CH_2), 39.9 (CH_2), 34.4 (Cq), 34.2 (Cq), 32.2 (CH_2), 32.1 (CH_3), 31.5 (CH_3). HR ESIMS calculated for $C_{90}H_{98}N_2O_{10}Na^+$=1389.7119; found=1389.7122. Anal. Calcd (%) for $C_{90}H_{98}N_2O_{10}$: C, 79.03; H, 7.22; N, 2.05; O, 11.70. Found: C, 78.59; H, 7.49, N 1.88.

4.4. Synthesis of calixarene 4b

Oxalyl chloride (0.35 ml, 4.08 mmol) was added dropwise to a solution of 0.54 g 1-(benzyloxy)-2-oxo-1,2-dihydropyridine-6-carboxylic acid (2.2 mmol) in CH_2Cl_2 (20 ml). After adding a drop of DMF, the mixture was stirred until the end of HCl release. After evaporation of solvents and residual oxalyl chloride, the residue was dissolved in 20 ml of dry CH_2Cl_2 and added dropwise to a solution of 0.55 g 25,27-(2-aminoethoxy)-26,28-dihydroxycalix[4]-arene (1.07 mmol) and 0.5 ml of triethylamine (3.6 mmol) in 30 ml of dry CH_2Cl_2. After 18 h under stirring, the mixture was washed with HCl 1 N (20 ml), water (2×50 ml), brine (100 ml), then dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc) to give **4b** (0.625 g, *Y*=60%) as white powder. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 8.50 (br s, 2H, N*H*), 7.76 (s, 2H, Ar–O*H*), 7.52 (m, 4H, Ar–*H*), 7.35 (m, 6H, Ar–*H*), 6.82–6.99 (m, 10H, Ar–*H*), 6.73–6.80 (m, 4H, Ar–*H*), 6.49 (m, 2H, Ar–*H*), 6.19 (m, 2H, Ar–*H*), 5.32 (s, 4H, O–C*H*$_2$–Ar), 4.06 (m, 8H, O–C*H*$_2$–CH$_2$–NH and Ar–C*H*$_2$–Ar ax), 3.73 (m, 4H, O–CH$_2$–C*H*$_2$–NH$_2$), 3.29 (AB d, 4H, ^2J(H,H)=13.4 Hz, Ar–C*H*$_2$–Ar eq). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 161.3 (C=O), 158.9 (C=O), 152.4 (ArC), 150.1 (ArC), 143.7 (ArC), 138.7 (ArC), 138.1 (ArCH), 133.8 (ArC), 133.2 (ArC), 130.7 (ArCH), 129.8 (ArCH), 129.7 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.0 (ArC), 126.4 (ArCH), 123.8 (ArCH), 123.2 (ArCH), 120.4 (ArCH), 105.1 (ArCH), 79.8 (CH_2), 74.9 (CH_2), 39.9 (CH_2), 31.7 (CH_2). HR ESIMS calculated for $C_{58}H_{52}N_4O_{10}Na^+$=987.3581; found=987.3585. Anal. Cald (%) for $C_{58}H_{52}N_4O_{10}$: C, 72.18; H, 5.43; N, 5.81; O, 16.58. Found: C, 72.05; H, 5.67; N, 5.70.

4.5. Synthesis of calixarene 5b

Oxalyl chloride (0.7 ml, 8.15 mmol) was added dropwise to a solution of 1.44 g 1-(benzyloxy)-2-oxo-1,2-dihydropyridine-6-carboxylic acid (5.87 mmol) in CH_2Cl_2 (50 ml). After adding a drop of DMF, the mixture was stirred until the end of HCl release. After evaporation of solvents and residual oxalyl chloride, the residue was dissolved in 30 ml of dry CH_2Cl_2 and added dropwise to a solution of 2.1 g 5,11,17,23-tetra-*tert*-butyl-25,27-(2-aminoethoxy)-26,28-dihydroxycalix[4]arene (2.85 mmol) and 1 ml of triethylamine (7.2 mmol) in 50 ml of dry CH_2Cl_2. After 18 h under stirring, the mixture was washed with HCl 1 N (100 ml), water (2×50 ml), brine (100 ml), then dried over $MgSO_4$ and evaporated to dryness. The

residue was purified by silica gel column chromatography (EtOAc/cyclohexane 3:1) to give **5b** (2.27 g, 63%) as white foam. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 8.64 (br s, 2H, N*H*), 7.52 (m, 4H, Ar–*H*), 7.35 (m, 6H, Ar–*H*), 6.96 (m, 6H, Ar–*H*), 6.79 (s, 4H, Ar–*H*), 6.48 (m, 2H, Ar–*H*), 6.21 (m, 2H, Ar–*H*), 5.34 (s, 4H, O–C*H*$_2$–Ar), 4.26 (m, 8H, O–C*H*$_2$–CH$_2$–NH and Ar–C*H*$_2$–Ar ax), 3.70 (m, 4H, O–CH$_2$–C*H*$_2$–NH$_2$), 3.28 (AB d, 4H, ^2J(H,H)=13.2 Hz, Ar–C*H*$_2$–Ar eq), 1.25 (s, 18H, (C*H*$_3$)$_3$C unsubst. rings), 0.98 (s, 18H, (C*H*$_3$)$_3$C subst. rings). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 161.4 (C=O), 158.9 (C=O), 149.7 (ArC), 149.0 (ArC), 148.1 (ArC), 143.7 (ArC), 143.0 (ArC), 138.1 (ArCH), 134.0 (ArC), 132.7 (ArC), 130.7 (ArCH), 129.8 (ArCH), 129.0 (ArCH), 127.7 (ArC), 126.3 (ArCH), 125.8 (ArCH), 123.7 (ArCH), 105.7 (ArCH), 80.0 (CH$_2$), 74.8 (CH$_2$), 40.0 (CH$_2$), 34.4 (Cq), 34.2 (Cq), 32.2 (CH$_2$), 32.0 (CH$_3$), 31.4 (CH$_3$). HR ESIMS calculated for $C_{74}H_{84}N_4O_{10}Na^+$=1211.6085; found=1211.6084. Anal. Calcd (%) for $C_{74}H_{84}N_4O_{10}$: C, 74.72; H, 7.12; N, 4.71; O, 13.45. Found: C, 74.76; H, 7.25; N, 4.54.

4.6. Synthesis of 1,3-CalixCAM 6a

25,27-(2-(2,3-Bis(benzyloxy)-1-carboxamido)ethyl)-26,28-dihydroxycalix[4]arene (0.47 g, 0.41 mmol) and 70 mg of Pd/C (5%) in 20 ml of THF was stirred under 1 atm of H_2. After 96 h, the mixture was filtered on Celite, evaporated to dryness to give **6a** (315 mg, 97%) as grey foam. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 12.53 (br s, Ar–O*H*), 8.31 (br s, 2H, N*H*), 8.23 (br s, 2H, Ar–O*H*), 7.19 (m, 2H, Ar–*H*), 6.68–7.04 (m, 14H, Ar–*H*), 6.38 (m, 2H, Ar–*H*), 4.01–4.12 (m, 8H, O–C*H*$_2$–CH$_2$–NH and Ar–C*H*$_2$–Ar ax), 3.36–3.43 (m, 8H, O–CH$_2$–C*H*$_2$–NH$_2$ and Ar–C*H*$_2$–Ar eq). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 171.0 (C=O), 152.2 (ArC), 150.5 (ArC), 146.5 (ArC), 133.5 (ArC), 129.9 (ArCH), 129.5 (ArCH), 128.2 (ArC), 127.0 (ArCH), 125.9 (ArCH), 121.1 (ArCH), 119.1 (ArCH), 118.6 (ArCH), 117.4 (ArCH), 114.5 (ArC), 75.0 (CH$_2$), 39.9 (CH$_2$), 32.1 (CH$_2$). HR ESIMS calculated for $C_{46}H_{42}N_2O_{10}Na^+$=805.2737; found=805.2736. Anal. Calcd (%) for $C_{46}H_{42}N_2O_{10}\cdot 4^*H_2O$: C, 64.63; H, 5.90; N, 3.28; O, 26.20. Found: C, 64.92; H, 5.83, N 3.05.

4.7. Synthesis of 1,3-CalixHOPO 6b

25,27-(2-(1-Benzyloxy-2-oxo-1,2-dihydropyridine-6- carboxamido)ethyl)-26,28-dihydroxycalix[4]arene (0.85 mg, 0.888 mmol) was added in 30 ml 32% HCl in 60 ml acetic acid. After 96 h under stirring, the mixture was evaporated, 100 ml were added. The mixture was washed with CH_2Cl_2 (3×50 ml). The combined organic layers were washed with water (3×50 ml), brine (50 ml), then dried over $MgSO_4$ and evaporated to dryness to give **6b** (603 mg, 87%) as yellow foam. ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C) δ (ppm): 9.13 (br s, 2H, Ar–O*H*), 8.06 (s, 2H, N*H*), 7.26 (m, 2H, Ar–*H*), 7.11 (d, *J*=7.5 Hz, 4H, Ar–H), 7.06 (d, *J*=7.5 Hz, 4H, Ar–H), 6.77 (m, 2H, Ar–*H*), 6.48–6.56 (m, 4H, Ar–*H*), 6.42 (d, *J*=6.9 Hz, 2H, Ar–*H*), 4.17 (AB d, 4H, ^2J(H,H)=13.0 Hz, Ar–C*H*$_2$–Ar ax), 4.06 (m, 4H, O–C*H*$_2$–CH$_2$–NH), 3.80 (d, *J*=5.4 Hz, 4H O–CH$_2$–C*H*$_2$–NH), 3.25 (AB d, 4H, ^2J(H,H)=13.0 Hz, Ar–C*H*$_2$–Ar eq).

^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 160.6 (C=O), 158.0 (C=O), 153.0 (ArC), 151.5 (ArC), 138.5 (ArC), 135.4 (ArCH), 133.2 (ArC), 129.6 (ArCH), 129.1 (ArCH), 128.3 (ArC), 126.1 (ArCH), 120.0 (ArCH), 117.9 (ArCH), 111.8 (ArCH), 74.8 (CH$_2$), 40.4 (CH$_2$), 31.7 (CH$_2$). HR ESIMS calculated for $C_{44}H_{40}N_4O_{10}Na^+$=807.2642; found=807.2644. Anal. Calcd (%) for $C_{44}H_{40}N_4O_{10}$: C, 67.34; H, 5.14; N, 7.14; O, 20.39. Found: C, 67.38; H, 5.38; N, 6.85.

4.8. Synthesis of 1,3-CalixCAM 7a

5,11,17,23-Tetra-*tert*-butyl-25,27-(2-(2,3-bis(benzyloxy)-1- carboxamido)ethyl)-26,28-dihydroxycalix[4]arene (1.027 g, 0.75 mmol) and 200 mg of Pd/C (5%) in 25 ml of THF was stirred under 1 atm of H_2. After 96 h, the mixture was filtered on Celite, evaporated to dryness to give **7a** (735 mg, 98%) as grey foam. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 8.31 (br s, 2H, N*H*), 7.26 (m, 2H, Ar–*H*), 6.87–7.03 (m, 10H, Ar–*H*), 6.41 (m, 2H, Ar–*H*), 4.09 (AB d, 4H, ^2J(H,H)=12.8 Hz, Ar–C*H*$_2$–Ar ax), 3.97 (m, 4H, O–C*H*$_2$–CH$_2$–NH), 3.59 (m, 4H, O–CH$_2$–C*H*$_2$–NH$_2$), 3.36 (AB d, 4H, ^2J(H,H)=12.8 Hz, Ar–C*H*$_2$–Ar eq), 1.17 (s, 18H, (C*H*$_3$)$_3$C unsubst. rings), 1.01 (s, 18H, (C*H*$_3$)$_3$C subst. rings). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 171.1 (C=O), 150.1 (ArC), 149.7 (ArC), 148.8 (ArC), 146.5 (ArC), 143.6 (ArC), 136.3 (ArC), 133.3 (ArC), 129.4 (ArCH), 128.6 (ArCH), 127.9 (ArC), 126.7 (ArCH), 126.3 (ArCH), 126.0 (ArCH), 118.8 (ArCH), 117.7 (ArCH), 114.5 (ArC), 75.0 (CH$_2$), 39.9 (CH$_2$), 34.7 (Cq), 34.4 (Cq), 32.8 (CH$_2$), 32.2 (CH$_3$), 31.6 (CH$_3$). HR ESIMS calculated for $C_{62}H_{74}N_2O_{10}Na^+$=1029.5241; found=1029.5242. Anal. Calcd (%) for $C_{62}H_{74}N_2O_{10}$: C, 73.93; H, 7.41; N, 2.78; O, 15.88. Found: C, 73.92; H, 7.66, N 2.54.

4.9. Synthesis of 1,3-CalixHOPO 7b

5,11,17,23-Tetra-*tert*-butyl-25,27-(2-(1-benzyloxy-2-oxo-1,2-dihydropyridine-6-carboxamido)ethyl)-26,28-dihydroxycalix[4]arene (884 mg, 0.876 mmol) was added in 25 ml 32% HCl in 65 ml acetic acid. After a week under stirring, the mixture was evaporated, 100 ml were added. The mixture was washed with CH_2Cl_2 (3×50 ml). The combined organic layers were washed with water (3×50 ml), brine (50 ml), then dried over $MgSO_4$ and evaporated to dryness to give **7b** (617 mg, 70%) as orange powder. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ (ppm): 6.89–7.23 (m, 3H, Ar*H*), 7.01 (s, 4H, Ar–*H*), 6.75 (s, 4H, Ar–*H*), 4.06–4.21 (m, 12H, O–C*H*$_2$–C*H*$_2$–NH and Ar–C*H*$_2$–Ar ax), 3.29 (AB d, 4H, ^2J(H,H)=13.2 Hz, Ar–C*H*$_2$–Ar eq), 1.28 (s, 18H, (C*H*$_3$)$_3$C unsubst. rings), 0.93 (s, 18H, (C*H*$_3$)$_3$C subst. rings). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ (ppm): 160.2 (C=O), 157.3 (C=O), 150.2 (ArC), 149.6 (ArC), 147.9 (ArC), 142.6 (ArC), 135.1 (ArCH), 132.7 (ArC), 128.2 (ArC), 126.2 (ArCH), 126.1 (ArCH), 125.6 (ArCH), 117.3 (ArCH), 112.2 (ArCH), 74.5 (CH$_2$), 40.4 (CH$_2$), 34.3 (Cq), 34.2 (Cq), 32.1 (CH$_2$), 32.0 (CH$_3$), 31.4 (CH$_3$). HR ESIMS calculated for $C_{60}H_{72}N_4O_{10}Na^+$=1031.5146; found=1031.5145. Anal. Calcd (%) for $C_{60}H_{72}N_4O_{10}$: C, 71.40; H, 7.19; N, 5.55; O, 15.85. Found: C, 71.61; H, 7.32; N, 5.21.

4.10. Synthesis of 1,3-CalixCAMS 8a

25,27-(2-(*N*-(2,3-Bis(hydroxy)-1-benzamido))ethyl)-26,28-dihydroxycalix[4]arene (106 mg, 0.135 mmol) in H_2SO_4 (2 ml) was stirred at 50 °C for 16 h. The mixture was then allowed to cool to room temperature, poured in Et_2O (50 ml). The resulting precipitate was filtered off under argon and dried under vacuum to give **8a** as a hygroscopic brown powder (140 mg, 82%). ^{1}H NMR (D_2O, 300 MHz, 25 °C) δ (ppm): 7.26 (d, *J*=1.9 Hz, 2H, Ar–*H*), 7.49 (s, 4H, Ar–*H*), 7.24 (s, 4H, Ar–*H*), 7.14 (d, *J*=1.9 Hz, 2H, Ar–*H*), 4.23 (t, *J*=4.2 Hz, 4H, O–C*H*$_2$–CH$_2$–N), 4.13 (t, *J*=4.2 Hz, 4H, O–CH$_2$–C*H*$_2$–N), 4.05 (AB d, 4H, ^2J(H,H)=13.8 Hz, Ar–C*H*$_2$–Ar ax), 3.48 (AB d, 4H, ^2J(H,H)=13.8 Hz, Ar–C*H*$_2$–Ar eq). ^{13}C NMR (D_2O, 75 MHz, 25 °C) δ (ppm): 169.8 (C=O), 155.2 (ArC), 153.9 (ArC), 148.8 (ArC), 145.1 (ArC), 139.8 (ArC), 134.2 (ArC), 133.7 (ArC), 133.5 (ArC), 127.4 (ArC), 127.0 (ArCH), 126.9 (ArCH), 126.7 (ArCH), 117.8 (ArC), 117.2 (ArCH), 115.3 (ArCH), 74.4 (CH$_2$), 40.1 (CH$_2$), 31.0 (CH$_2$). HR ESIMS calculated for $C_{46}H_{42}N_2O_{28}S_6Na^+$=1285.0141; found=1285.0136. Anal. Calcd (%) for $C_{46}H_{42}N_2O_{28}S_6\cdot 6^*H_2O$: C, 40.29; H, 3.97; N, 2.04; O, 39.67; S, 14.03. Found: C, 39.98; H, 4.12; N, 1.79.

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