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SYNTHESIS OF WATER SOLUBLE MOLECULAR RECEPTOR FROM CALIX[4]ARENE-BIS-CROWN-6

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Abstract: Hydrosoluble Calix[4]arenes-bis-crown-6 **2a**, **3a** and **3b** have been synthesised in two steps via formylation and chlorosulfonylation of **1**. Cs^+- Ligand interactions were studied in aqueous media by UV-Visible analysis and showed a good affinity between receptor **2a** and the caesium ion.

Calixarenes have aroused considerable interest as useful building blocks for the synthesis of receptors[1] for cationic, anionic, and neutral molecules. Some recent studies have been devoted more specificly to the highly selective recognition properties of calixcrowns of alkali and alkali-earth metal cations. This is due to the nature, the size and the position of grafted polyglycolic chains[2a-g]. For example, Vicens and co-workers[2e] have synthesised a series of calixarene bis-crowns in an 1,3-alternate conformation which constitutes a new family of lipophilic basket bowls for the selective complexation of caesium ions. Those receptors containing 6 oxygen atoms in the ether chain were widely studied for their abilities to extract selectively caesium from nuclear waste, by the supported liquid membrane (SLM's) technique[2e-f].

In a recent report[3], we have described the selective complexation-separation Cs^+/Na^+ by nanofiltration. This alternative method gave exellent results with calix[4]resorcinarene. In order to test the potential of calix[4]arene bis-crown ligands in this field, it would be desirable to have water soluble derivatives.

For this reason, we report here the synthesis and the preliminary caesium complexing results of water soluble calix[4]arene bis-crown-6.

The starting calixarene bis-crown-6 **1** was synthesised as described in the literature[2e] and each water soluble derivative **2a** and **3a-b** was obtained in two steps by either formylation or chlorosulfonylation[4].

As related in the literature[5a-b] about the exhaustive formylation of calix[4]arene, **1** was treated with excess of Cl_2CHOCH_3 and $TiCl_4$ to give the *distal* formylated calixarene **2** as a unique product in 88% yield.

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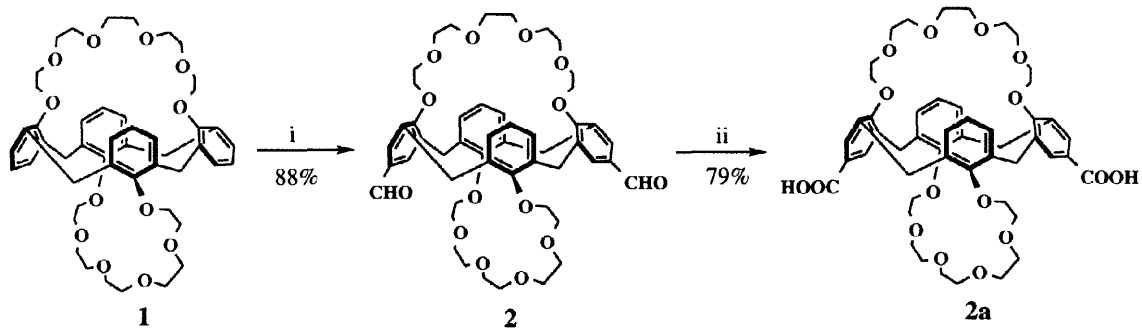
2 was subsequently converted into the bis acid analogue **2a** in 79% yield by oxidation with sulfamic acid and sodium chlorite.

The structure of **2** and the *distal* position of the fixed aldehyde functionality on **1** were characterised by the well defined ^{1}H-NMR spectrum which showed an AB system for the $ArCH_2Ar$ (3.83 - 3.96 ppm). Furthermore a singlet (7.68 ppm), doublet (7.12 ppm) and a multiplet (6.85 - 6.92 ppm) in the aromatic region were obtained corresponding to substituted and unsubstituted phenolic moieties. The ^{13}C-NMR confirmed the *C4v* symetry of this compound by showing only one absorption for the bridging methylene carbon at 37.81 ppm, which is typical for all *anti* oriented aromatic nuclei[6]. For derivative **2a**, the ^{1}H-NMR and ^{13}C-NMR spectra displayed similar resonance signals which were nevertheless broader than for **2**. Mass spectroscopy (FAB and electrospray) and microanalyses were in accordance with the expected structures.



1 **2** **2a**

i) $TiCl_4$, Cl_2CHOCH_3, 40°C; ii) NH_2SO_3H, $NaClO_2$, r.t.

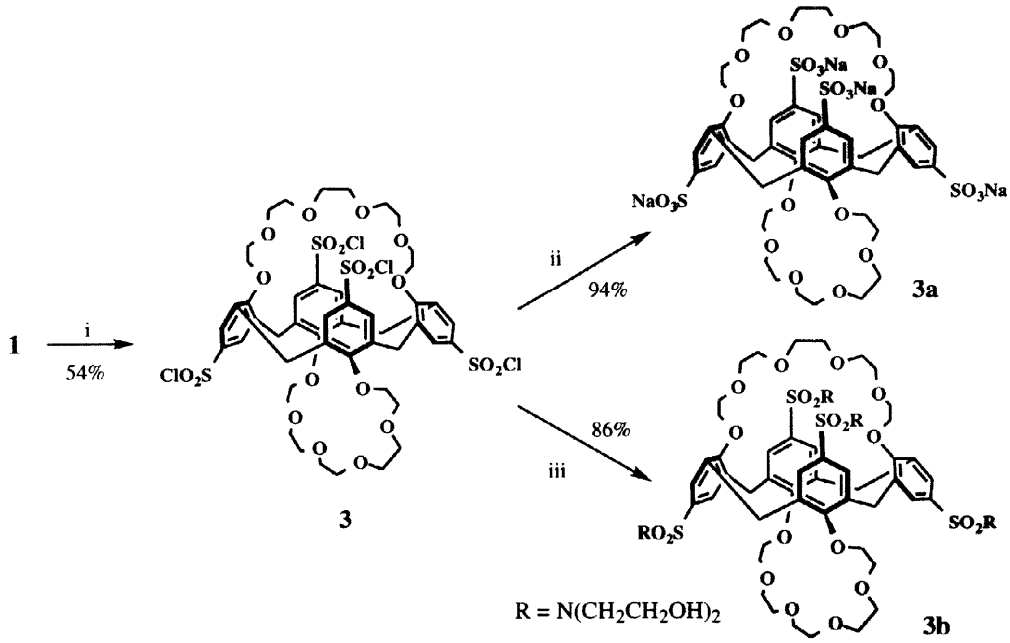
Calixarene bis-crown-6 **1** was also tetra-chlorosulfonylated to **3** by chlorosulfonic acid in $CHCl_3$ at -10°C (54% yield) according to the chlorosulfonylation of calixarene described in the literature[7]. **3** was subsequently converted to **3a** by hydrolysis of the chlorosulfonyl groups in pyridine/water, followed by neutralisation with $NaHCO_3$ (94% yield).

By the route used for the access to sulfonamide calixarenes[8], reaction of **3** with diethanolamine in DMSO gave quantitatively tetrasulfonamide **3b** (86% isolated).

The exhaustive "upper rim" functionnalisation of **1** conserved the magnetic equivalence of the bridged methylene and the aromatic protons which was characterised by two singlets in ^{1}H-NMR for the compounds **3**, **3a**, **3b**. Two triplets typical of the diethanolamine methylene protons were observed for **3b** at 3.25 and 3.89 ppm.

Because substituted calix[4]arene-bis-crowns-6 **2a** and **3a-b** were soluble in neutral or basic aqueous media, their caesium complexing properties could be studied by UV-Visible analyses in these conditions. Stability constants $K_{Cs/L}$ of caesium-ligand interactions (table 1) could be evaluated by using the Foster-Hammick-Wardley procedure[9]. Thus, absorption changes of UV ligand spectra were measured as Cs^+ was progressivly added to an aqueous solution containing a fixed amount of ligand. Interactions of **2a**, **3a** and **3b** with Cs^+ were respectively studied at 250, 235 and 268 nm. A hypochromic effect was observed for

2a and **3a**, whereas a hyperchromic one was detected for **3b.** However only **2a** and **3a** gave significantly results for allowing a $K_{Cs/L}$ and $\Delta G°$ calculation for a 1:1 ratio Cs/L.



i) $ClSO_3H$, $CHCl_3$, -10°C; ii) pyridine/H_2O, $NaHCO_3$, r.t.
iii) $HN(CH_2CH_2OH)_2$, DMSO, r.t.

Ligand	[ ] (mol.L^{-1})	pH	λ (nm)	$K_{Cs/L}$ (no unit)	ΔG° (kJ.mol^{-1})
2a	2.5 10^{-5}	11	250	340,000	- 31.5
3a	4 10^{-5}	11	235	30,000	- 25.5
3b	1.6 10^{-5}	7	268	-	-

table 1

Further research on the complexation properties of **2a** is under current investigation by the nanofiltration-complexation technique[3] and will be presented in due course.

Acknowledgment

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4 **2**: To a solution of 1,1'-dichloromethylether (15.6 g, 135.6 mmol) in 50 ml of $CHCl_3$ at 40°C were added dropwise **1** (1.5 g, 1.81 mmol) in 50 ml of $CHCl_3$ and tin chloride (12.87 g, 67.8 mmol) in 50 ml of $CHCl_3$. The reaction mixture was stirred for 1h. and after cooling, treated with cold water (300 ml). The organic layer was separated, washed with water (3 x 200 ml) until pH 7, with satured NaCl solution and dried over $MgSO_4$. The solvent was evapored to dryness and **2** was obtained as a colourless foam (1,41 g, 88%). A sample was recristallised in CH_2Cl_2-heptane for analyses. M. P.: 121°C; IR (KBr): 1688 (C=O); ^{1}H-NMR ($CDCl_3$): 3.17-3.70 (m, 40 H, OCH_2CH_2O); 3.83-3.96 ('q', AB, J_{AB}= 9.03, 4 $ArCH_2Ar$); 6.85-6.92 (m, 2ArH); 7.12 (d, J=7.4, 4 ArH); 9.93 (s, 2 CHO); ^{13}C-NMR ($CDCl_3$): 37.81 ($ArCH_2Ar$), 69.33, 69.61, 70.31, 70.80, 70.94 (OCH_2CH_2O); 122.9, 129.8, 130.2, 131.6, 132.3 (ArH); 133.0, 133.6, 134.1, 134.8, 135.2, 156.5, 162.3 (ArC), 191.7 (CHO); m/z (FAB$^+$ in NBA): 885.5 ([M + H]$^+$); $C_{50}H_{60}O_{14}$, 0.15CH_2Cl_2, 0.45 C_7H_{16} (942.86): *calc.* C 67.90, H 7.11, O 23.76; *found* C 68.14, H 6.83, O 23.76.

2a: **2** (0.5 g, 0.565 mmol) was dissolved in 80 ml of $CHCl_3$/acetone (1:1). $NaClO_2$ (0.171 g, 1.89 mmol) and NH_2SO_3H (0.215 g, 2.21 mmol) was added and the mixture was stirred for 24h. at r.t.. After evaporation of solvents, the residue was triturated in HCl 10% (100 ml). The resulting brownish precipitate was filtrered, washed with water nd recristallised in MeOH-H_2O to give pur **2a** as a light yellow powder (0.409 g, 79%). M.P.: 204-206°C; UV (H_2O/NaOH): 250 (17600), 275 (16000); IR (KBr): 3421, 1706 (COOH); ^{1}H-NMR (CD_3OD): 3.17-3.65 (m, 40H, OCH_2CH_2O); 3.80-4.10 (br 'q', AB, 4 $ArCH_2Ar$); 6.86-6.90 (br m, 2 ArH); 7.10 (br s, 4 ArH); 7.81 (br s, 4 ArH); ^{13}C-NMR (CD_3OD): 38.51 ($ArCH_2Ar$); 69.71, 69.92, 70.94, 71.41, 71.60 (OCH_2CH_2O); 125.4, 129.9, 130.6, 131.6, 132.6 (ArH); 133.7, 133.9, 134.4, 135.6, 136.4, 155.8, 161.4 (ArC); 169.7 (COOH); m/z (ES$^-$): 915.2 ([M - H]$^-$) (FAB$^+$, KOH): 993.4 ([M + 2K - H]$^+$); 955.4 ([M + K]$^+$); $C_{50}H_{60}O_{16}$, 0.75 $CHCl_3$, 0.5 H_2O (1015.55): *calc.* C 60.02, H 6.13, O 25.99; *found* C 59.97, H 6.20, O 26.09.

3: To a solution of **1** (2.6 g, 3.14 mmol) in $CHCl_3$ (40 ml) was added dropwise HSO_3Cl (8.34 ml, 126 mmol) at -10 °C. When the addition was complete, the reaction mixture was stirred for 3h. at r.t.. The solution was poured into an ice-water solution (100 ml) and to the resulting suspension was added $CHCl_3$ (150 ml). The organic layer was separated and supplementar material was extracted from aqueous layer with $CHCl_3$ (2 x 100 ml). The organic layers were rassembled, dried over $MgSO_4$ and concentrated. By addition of isopropanol (150 ml), pur **3** was collected by filtration as a white powder (2.08 g, 54%). M.P.: >260°C; IR (KBr): 1372 (SO_2Cl); ^{1}H-NMR ($CDCl_3$): 3.07 (t, J=6.3, 8H, OCH_2CH_2O); 3.45-3.69 (m, 32 H, OCH_2CH_2O); 4.09 (s, 8H, $ArCH_2Ar$); 7.85 (s, 8 ArH); ^{13}C-NMR ($CDCl_3$): 37.58 ($ArCH_2Ar$); 68.82, 70.32, 70.51, 70.94 (OCH_2CH_2O); 128.5 (ArH); 134.3, 138.8, 161.7 (ArC); m/z (FAB+, NBA + LiCl): 1229.1 ([M + Li]$^+$); $C_{48}H_{56}O_{20}S_4Cl_4$, 2 H_2O (1259.02): *calc.* C 45.79, H 4.80, O 27.96; *found* C 45.58, H 4.81, O 28.42.

3a: **3** (1.6 g, 1.31 mmol) was dissolved at room temperature in pyridine (8 ml), then water (1 ml) was added and the reaction mixture stirred for 2h.. The solvent was evaporated and water (1 ml) was added. The brownish solution was titrated to neutrality with a solution of 10% $NaHCO_3$ and acetone was added. The resulting precipitate was filtered and **3a** (1.54 g, 94%) was obtained after recristallisation in acetone-water as a white powder. M.P.: >260°C; UV (H_2O): 235 (23200), 267 (2000); IR (KBr): 1050, 1190 (Ar-SO_3^-); ^{1}H-NMR (D_2O): 3.09 (t, J=6.6, 8H, OCH_2CH_2O); 3.52-3.73 (m, 32H, OCH_2CH_2O); 4.13 (s, 4 $ArCH_2Ar$), 7.64 (s, 8 ArH); ^{13}C-NMR (D_2O): 37.49 ($ArCH_2Ar$); 68.81, 68.91, 69.36, 70.29 (OCH_2CH_2O); 126.9 (ArH); 134.3, 138.1, 159.1 (ArC); m/z (FAB$^+$): 1273.4 ([M + Na]$^+$); 1237.5 ([M + H]$^+$); $C_{48}H_{56}O_{24}S_4Na_4$, 8 H_2O (1379.99): *calc.* C 41.70, H 5.25; *found* C 41.69, H 4.99.

3b: To a solution of **3** (2 g, 1.63 mmol) in DMSO (30 ml) was added diethanolamine (1.72 g, 16.3 mmol) and the mixture was stirred at r.t. for 24h.. After addition of isopropanol (150 ml), the resulting viscous material was triturated and the solvent was removed by suction. This treatement was repeated twice and **3b** (2.1 g, 86%) was obtained as a colourless hygroscopic foam. A small sample of **3b** was recristallised in MeOH-isopropanol for analyses. M.P.: 155°C; IR (KBr): 3500 (OH) ; ^{1}H-NMR (D_2O): 3.09 (t, J=6.8, 8H, OCH_2CH_2O); 3.25 (t, J=5.2, 16H, NCH_2); 3.53-3.74 (m, 32H, OCH_2CH_2O); 3.89 (t, J=5.2, 16H, CH_2OH); 4.29 (s, 4 $ArCH_2Ar$); 7.64 (s, 8 ArH); ^{13}C-NMR (D_2O): 37.56 ($ArCH_2Ar$); 49.39, 57.04 (NCH_2CH_2OH); 68.92, 69.75, 70.59 (OCH_2CH_2O); 126.8 (ArH); 134.4, 138.1, 159.2 (ArC); $C_{64}H_{96}O_{28}N_4S_4$, 9 H_2O, 0.5 DMSO (1698.87): *calc* C 45.95, H 6.94, O 35.31, N 3.29; *found* C 45.95, H 6.81, O 35.08, N 3.18.

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