Synthesis and complexation properties of 1,3-alternate calix[4]arene-bis(crown-6) derivatives

Stéphane Pellet-Rostaing, Frédéric Chitry, Laurence Nicod and Marc Lemaire *

Laboratoire de Catalyse et Synthèse Organique, Université Claude Bernard Lyon I, CPE Lyon, 43 bd du 11 Novembre 1918, 69100, Villeurbanne, France. E-mail: marc.lemaire@univ-lyon1.fr; Fax: 33 (0) 4 72 43 14 08

Calix[4]arene-bis(crown-6) was converted into its di- and tetra-carboxy and hydroxy derivatives as water-soluble receptors. The complexation properties of these ionophores were studied for alkali cations in methanolic and aqueous media. Stability constants were calculated by UV–Vis spectroscopy. All ligands showed a more or less pronounced affinity for the larger cations. Cs^+/Na^+ selectivity is enhanced by the number and the nature of the substituents. Compound **7** represents the most selective ligand for the Cs^+ cation in methanol and in basic aqueous media. For selective Cs^+/Na^+ separation, the efficiency of the ligands was evaluated by means of a nanofiltration system.

Introduction

Nowadays, with the recent development of supramolecular chemistry, calixarenes represent a family of [1^n]cyclophane receptors which offer numerous possibilities for chemical modifications,[1,2] both at the phenolic OH groups (lower rim) and at the *para* position of the phenol rings (upper rim). These macrocyclic platforms have been used as building blocks for the synthesis of lipophilic[2] and water-soluble[3] cation hosts and carriers.

Of the many selective functionalisations possible, the introduction of polyether chains, first described by Ungaro and co-workers,[4a] has provided a new family of lipophilic basket bowls[4] known for their considerable interest as selective ion transport agents, notably in the treatment of nuclear waste.[5]

As reported in the literature,[6] the properties of selective recognition of calixcrowns for alkali cations depend on the nature, size and position of the grafted polyglycolic chains. In this field, Vicens and co-workers[6a] have described the synthesis of a series of calix[4]arene-bis(crown) compounds in an 1,3-alternate conformation, which constituted highly selective receptors for caesium ions. These ligands, containing 6 oxygen atoms in the ether chains (Fig. 1), were widely studied for their ability to extract caesium from nuclear waste with a high concentration of sodium salts by the supported liquid membrane technique (SLM).[4c,6a]

Since 1993, we have been developing the nanofiltration (NF) technique[7] in our laboratory. NF is a new pressure-driven membrane process for alkali and alkaline earth metal cation separation in aqueous media. Moreover, to increase ionic separation, nanofiltration can be associated with a preliminary selective complexation step. Such methods require the synthesis of water-soluble ligands that are selective for the target ion. In the separation of Cs^+ from Na^+, nanofiltration gave good results with calix[4]resorcinarene.[7a] Nevertheless, we estimated that the selective complexing properties of this ionophore toward Cs^+ could be enhanced using water-soluble cavitands.[8] In the same way, because some calix[4]arene-bis(crown) compounds were known to complex caesium cations selectively in organic media, we synthesized and evaluated new water-soluble calix[4]arene-bis(crown-6) compounds[9] by introducing two carboxy, four sulfonate and four sulfonamide groups at the *para* position of the phenolic moieties. Preliminary studies of the caesium–ligand interactions (cavitands and calixcrown) were carried out using UV–Vis spectroscopy in basic aqueous media and showed a good affinity for the target ions with some of these ligands. These analyses not only indicated the importance of the chosen ligand's structure but also proved that the grafted hydrophilic functionalities play a major role in the complexation and stabilization of the caesium ion both in the cavity of the hydrophobic aromatic annulus and in the crown ether chain.

Therefore, we decided to investigate the introduction of other functional groups in order to build water-soluble calix[4]arene-bis(crown-6) compounds and to increase their Cs^+ complexing behaviour in aqueous media.

We report in this paper the synthesis of several new water-soluble crown-6 derivatives of calix[4]arene incorporating proton-ionizable substituents, and a study of their affinity toward Cs^+, Rb^+, K^+ and Na^+ cations in methanol and in basic aqueous media. Finally, we have summarized the various aspects of the use of these ligands in a nanofiltration–complexation process.
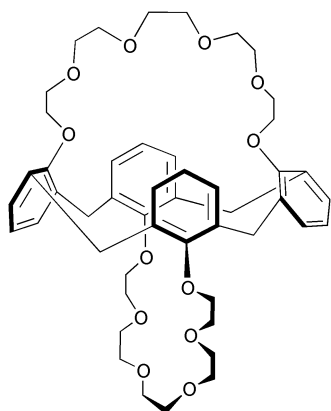
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**Fig. 1** Calix[4]arene-bis(crown-6).
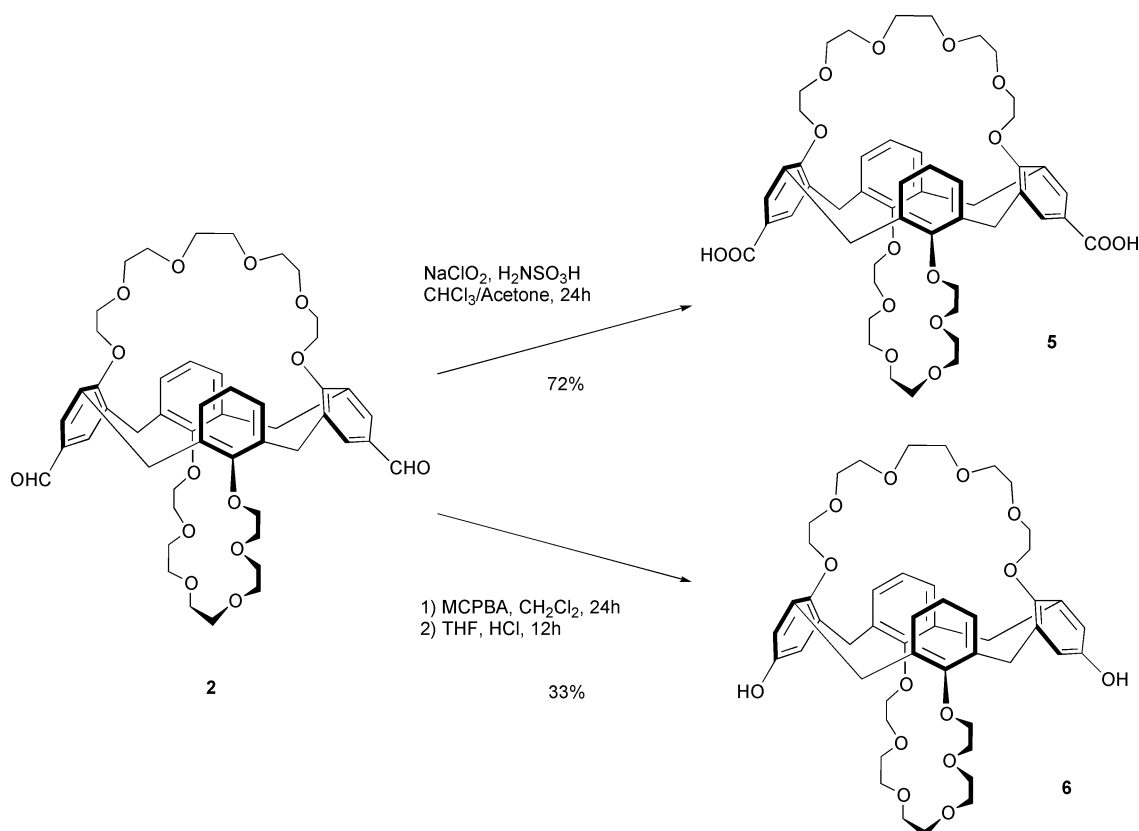
Scheme 1 Synthesis of the dicarboxy- and dihydroxy-calixarenes–bis(crown-6).

Synthesis of water-soluble calix[4]arene-bis(crown-6)

The calixarene-bis(crown-6) **1** was synthesised as described in the literature[6a] and each water-soluble derivative **5–8** was obtained in two steps by either formylation or bromination (Schemes 1 and 3). Compound **8** can be synthesised in three steps *via* a tetraformylated intermediate. The synthesis of ionophores **5** and **6** is depicted in Scheme 1.

As described previously,[9] treatment of **1** with an excess of Cl_2CHOCH_3 and $TiCl_4$ gave the distally formylated calixarene **2** which was converted into the diacid analogue **5** by oxidation with sulfamic acid and sodium chlorite. According to the procedure used by Ungaro and co-workers[10] for the introduction of an OH group at the upper rim of tetraalkoxycalix[4]arene, Bayer–Villiger oxidation of **2** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2, followed by acidic hydrolysis of the formate intermediate gave **6** in 33% yield. Compound **6** was fully characterised by ^{1}H NMR, electrospray spectrometry and elemental analysis. In $CDCl_3$, its ^{1}H NMR spectrum displayed relatively well defined resonance signals in the aromatic region corresponding to the typical signals of *para*-substituted (a singlet) and unsubstituted phenolic moieties (a doublet and a triplet). Subsequent treatment of **1** with Br_2 in acetic acid at 60 °C or in CH_2Cl_2 at 0 °C afforded *p*-bromocalix[4]arene-bis(crown-6) **3** with a 1,3-alternate structure in 70 and 90% yield, respectively. Bromination of **1** with NBS in butan-2-one decreased the yield of **3** to 41% (Scheme 2).

By means of the bromine–lithium exchange reaction of bromine-substituted calix[4]arenes,[11] compound **3** could be used to introduce a variety of hydrophilic substituents as OH or COOH groups. For example, Paek *et al.*[12] synthesized 5,17-dibromo-11,23-dihydroxycalix[4]arene hexyl ether with *n*-BuLi in THF at −78 °C and by reaction with $B(OMe)_3$ followed by H_2O_2–NaOH. Treatment of compound **3** with an excess of *n*-BuLi in dry THF at −78 °C for 90 min followed by quenching with $B(OMe)_3$, oxidation with 3 M NaOH–35% H_2O_2 and then acidic hydrolysis gave the expected tetraol **7** in 50% yield. When *t*-BuLi was used instead of *n*-BuLi, **7** was obtained in 65%
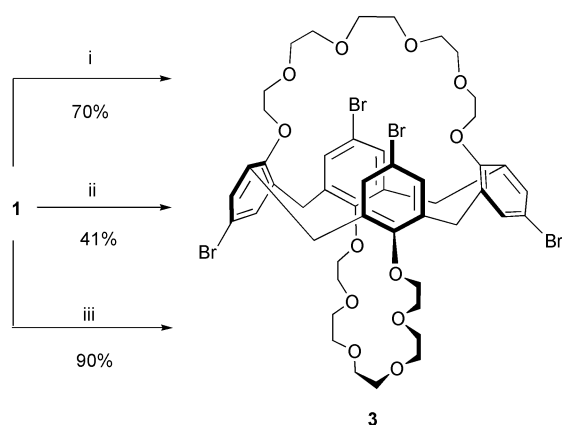
Scheme 2 *Reagents and conditions*: i) Br_2, AcOH, 60 °C; ii) NBS, butan-2-one, rt; iii) Br_2, CH_2Cl_2, 0 °C.

yield. As described by Larsen and Jørgensen[13] in their report on the selective introduction of COOH functionalities at the upper rim of tetrapropoxycalix[4]arene, quenching of the tetra-lithiated intermediate from **3** with DMF or CO_2 afforded the tetraformylated derivative **4** (46%) or directly the tetracarboxylated ligand **8** (45%). Derivative **4** was also converted into **8** in 66% yield by oxidation with sulfamic acid and sodium chlorite (Scheme 3).

Exhaustive substitution of **1** in the fixed 1,3-alternate cone structure simplified the characterisation of the reaction products by NMR which showed very simple patterns. Thus, one singlet for the aromatic rings and another for the bridged methylene allowed characterisation of each macrocyclic frame by ^{1}H NMR. Lipophilic derivatives **3** and **4** exhibited well defined ^{1}H NMR spectra which showed respectively one singlet at 7.23 and 7.70 ppm for the aromatic protons and one singlet at 3.78 and 3.96 ppm for Ar*CH₂*Ar. ^{13}C NMR spectroscopy confirmed the symmetrical 1,3-alternate structure[14] of these compounds, since only one signal assigned to the bridging
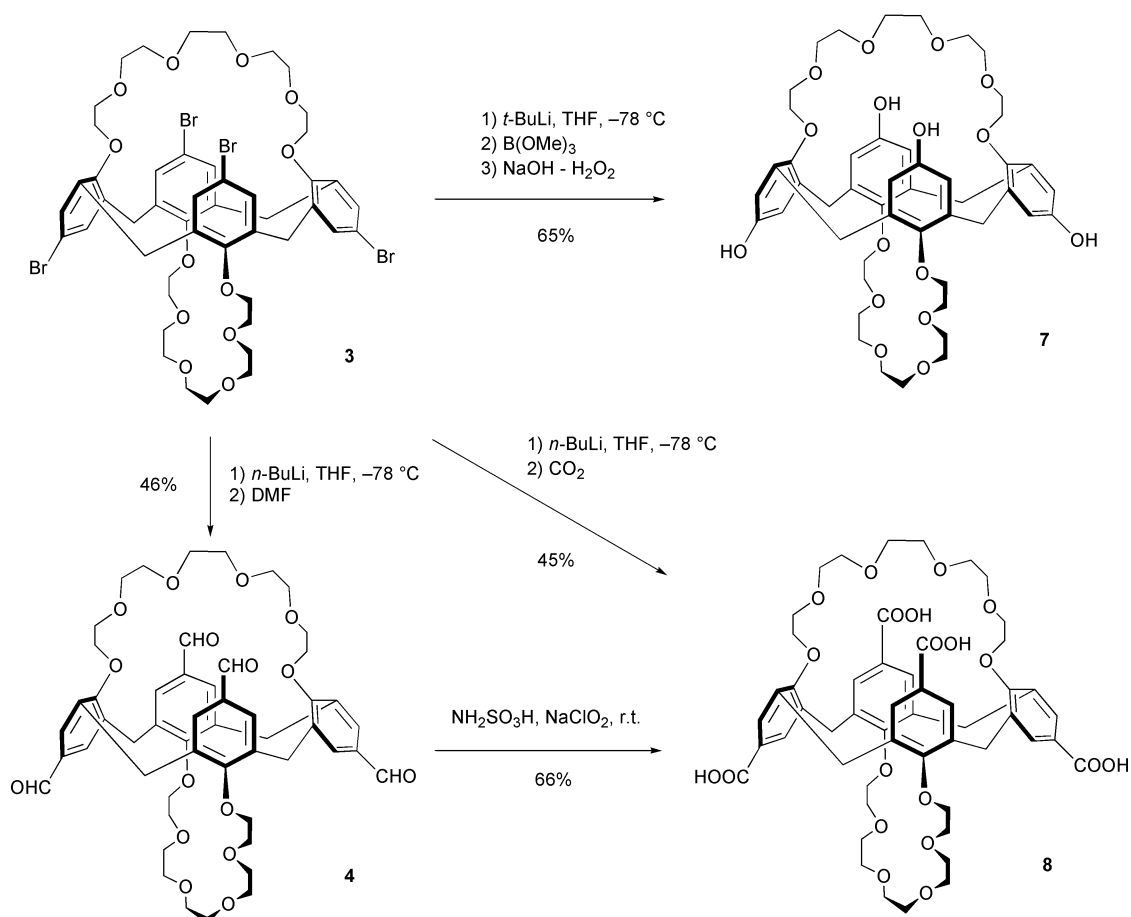
Scheme 3 Synthesis of the tetracarboxy- and tetrahydroxy-calixarene-bis(crown-6) derivatives.

methylene carbons was present at 37.29 ppm for **3** and at 37.51 ppm for **4**. In the same way, only one resonance at 132.0 and 132.1 ppm corresponding to the residual aromatic C–H was observed for **3** and **4**. For the hydrophilic derivatives **7** and **8**, the ^{1}H and ^{13}C NMR spectra displayed similar resonance signals which were nevertheless broader than those for **3** and **4**. In the case of **7**, the singlet corresponding to the bridging methylene resonance signal overlapped with the broad multiplet of the oxymethylene protons at 3.51–3.72 ppm in CD$_3$OD or at 3.26–3.49 ppm in D$_2$O–NaOD. In DMSO-d_6, the spectrum revealed a better defined pattern in the methylenic region with, in particular, a singlet at 3.6 ppm corresponding to ArCH_2Ar. The aromatic region was characterised by two singlets at 6.40 for ArH and at 8.65 ppm for OH.

The results of mass spectrometry and elemental analysis were in accordance with the hosts' expected structures.

Complexation studies

UV–Vis studies

The molecular recognition properties of the water-soluble calix[4]arenes-bis(crown) compounds **5**–**8** toward alkali ions were studied by UV–Vis spectroscopy analysis, first in methanol, then in a basic aqueous medium (NaOH 0.1 M). The stability constants β of the metal–ligand complexes were determined by this absorption method, in which β is the constant ratio ([ML$^+$]/[M$^+$][L]) corresponding to the equilibrium M$^+$ + L $\leftrightarrow$ ML$^+$ (M$^+$ is Na$^+$, K$^+$, Rb$^+$ or Cs$^+$ and L is the ligand). The absorption changes in the UV spectra of the ligands were recorded as alkali ions were progressively added to the medium containing a fixed amount of receptor. These modifications allowed the calculation of β_{MCl} stability constants, according to the Foster–Hammick–Wardley method.[15]

Table 1 Determination of the formation constants of alkali–ligand **7** complexes by UV spectroscopy

log β'_{Cs-L}	log β'_{Rb-L}	log β'_{K-L}	log β'_{Na-L}
5.79 ± 0.01	5.45 ± 0.02	4.4 ± 0.1	3.5 ± 0.2

Methanolic medium. Only ligand **7** was tested by UV–Vis analysis in methanol. Addition of CsCl to the ligand solution induced a bathochromic effect, whereas RbCl, KCl and NaCl additions induced a hypsochromic effect on the band of the ligand **7** at 284 nm. A single isosbestic point appeared for each alkali ion tested, which proved the formation of a 1 : 1 metal–ligand complex. The metal–ligand complex formation constant was evaluated by the straight curve of the plot of ΔAbs/[MCl] *vs.* ΔAbs. The association constant β = [ML]/([L][M]) could be calculated from the slope. Association constants, without units, β' = β × [MeOH] are given in Table 1.

Ligand **7** proved to be more selective toward larger ions such as Cs$^+$ and Rb$^+$. The following selectivities were obtained: $S_{Cs/Rb}$ = 2, $S_{Cs/K}$ = 25 and $S_{Cs/Na}$ = 200.

Basic aqueous medium. After the UV–Vis studies in methanol, we decided to assess the complexation ability of ligands **5**–**8** toward Cs$^+$, Rb$^+$ and K$^+$ ions in an aqueous medium. In fact, it was hoped that the interactions of the calix[4]crowns with alkali ions would be higher in aqueous media than in methanol, because of the possibility of carboxy and hydroxy group deprotonation in a basic medium, which could lead to higher selectivities between the alkali ions. Unfortunately the ligand–Na$^+$ interactions could not be evaluated because NaOH was used to obtain the aqueous basic medium, and therefore NaOH was a source of high amounts of Na$^+$ ions (about 10^{-2} M) compared to the other metal concentrations (roughly

Table 2 Logarithms of the stability constants ($\log \beta \pm \sigma_{n-1}$) of the alkali–ligand complexes by UV spectroscopy for ligands **5**–**8** in an aqueous medium at 20 °C

Ligands	5	6	7	8
[NaOH]/mol l^{-1}	0.01	0.001	0.01	0.01
λ/nm	245	303	304	245
Cs$^+$	4.88 ± 0.02	5.39 ± 0.01	5.63 ± 0.01	4.78 ± 0.04
Rb$^+$	4.34 ± 0.04	4.40 ± 0.06	5.27 ± 0.02	4.36 ± 0.06
K$^+$	N.d.^{a}	N.d.^{a}	4.60 ± 0.06	N.d.^{a}

^{a} N.d. = not determined.
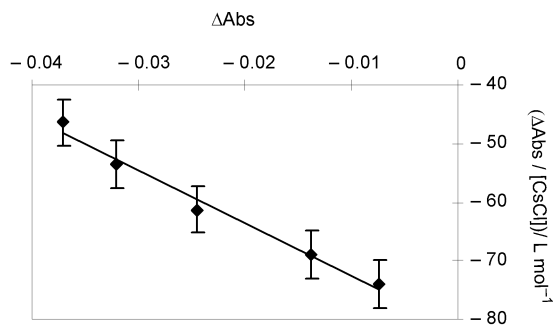
Fig. 2 Plot of ΔAbs/[CsCl] = f(ΔAbs) with ligand **8** in NaOH 0.1 M at rt.

Fig. 3 Changes in the absorption spectrum of a solution of ligand **7** (bold line) with CsCl addition in water ([**7**] = 10^{-4} mol l^{-1}; pH = 12).

10^{-4} M) used for UV–Vis analysis. The complexation constants given in Table 2 are relative constants, because they depend on the amount of Na$^+$ in the medium. Moreover, they allow a comparison of the complexing ability of calixarenes toward other alkali ions such as Cs$^+$, Rb$^+$ and K$^+$.

Carboxy derivatives **5** and **8** induced a hypochromic effect of the absorption band at 245 nm owing the interaction of the ligands with caesium and rubidium cations. Despite the absence of any isosbestic point, the 1 : 1 M$^+$–ligand ratio was evaluated by the straight curve of the plot of ΔAbs/[MCl] *versus* ΔAbs in accordance with the Forster–Hammick–Wardley procedure (Fig. 2). These ligands gave respectively 4.88 and 4.78 for $\log \beta'_{\text{Cs-L}}$, and 4.34 and 4.36 for $\log \beta'_{\text{Rb-L}}$. Both compounds showed approximately the same affinity for the cations but the number of grafted carboxy groups seemed to increase the hindrance with the larger caesium ions. No significant spectral modifications were noticed after addition of KCl to the aqueous medium. Therefore, no $\beta'_{\text{K-L}}$ values were calculated.

Interactions of CsCl and RbCl with compounds **6** and **7** resulted in significant hyperchromic and bathochromic shifts of the UV absorption band at the studied wavelengths of 303 and 304 nm respectively. The UV spectral changes observed in the complexation of Cs$^+$ by **7** are shown in Fig. 3 as an example. Variations of absorption resulted in a single isosbestic point for each ligand at 295 and 296 nm which proved the formation of 1 : 1 complexes with Cs$^+$ and Rb$^+$ in the aqueous medium. Ligand **7** with four hydroxy side arms exhibited much higher complexation efficiency towards the metal cations ($\log \beta'_{\text{Cs-7}} = 5.63$, $\log \beta'_{\text{Rb-7}} = 5.27$) than **6** with only two hydroxy substituents ($\log \beta'_{\text{Cs-6}} = 5.39$, $\log \beta'_{\text{Rb-6}} = 4.40$). By comparison with the carboxylated analogues **5** and **8**, these results suggested both the importance of the number of grafted substituents on the phenolic ring and the influence of the nature of these functionalities on the complex's stability in aqueous media. On the other hand, the presence of two and four OH groups resulted in a sufficiently polar and rigid macrocyclic cavity to maximise the cation–ligand interactions in basic aqueous media with a higher selectivity for the tetrahydroxy derivative **7**.

With K$^+$, only **7** showed a moderate affinity ($\log \beta'_{\text{K-7}} = 4.60$), this interaction being too weak with **6** to allow a precise determination of the complexation constant.
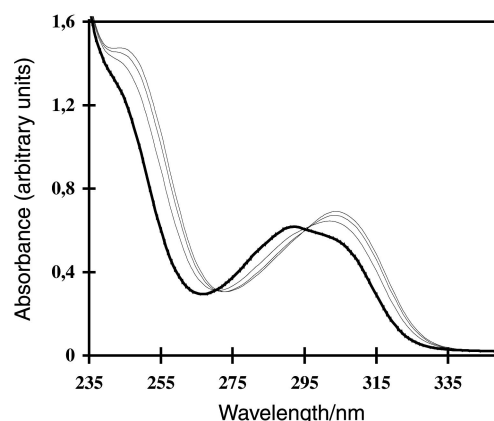
NMR study

To confirm the 1 : 1 stoichiometry of the caesium complex of ligand **7** and to locate the position of the cation inside the macrocycle, a ^{1}H NMR study was performed with the 1 : 1 complex of **7**–Cs$^+$Cl$^-$ at room temperature. Addition of caesium chloride to a solution of the ligand in CD$_3$OD or D$_2$O–NaOD led to an appreciable downfield shift of the aromatic protons' resonance, which was characterised by a relatively sharp singlet. In CD$_3$OD, the signal moved from 6.52 ppm for the free ligand to 6.67 ppm for the 1 : 1 Cs$^+$ complex, corresponding to a downfield shift of 0.15 ppm, higher than that observed in D$_2$O–NaOD ($\Delta\delta = -0.09$ ppm) from 6.19 (free ligand) to 6.28 ppm (complex). The presence of only one singlet in the aromatic region seemed to indicate either a rapid cation–ligand exchange or a symmetrical position in the aromatic ring of the ligand, as suggested by Arnaud-Neu *et al.*[16] for the calixcrown **1**–Cs$^+$I$^-$ complex studied in deuterated acetonitrile. Furthermore, when the ligand–caesium ratio decreased from 1 : 1 to 1 : 5, no spectral change was observed assuming a 1 : 1 stoichiometry for the cation complex in polar solvents (methanol or water) as predicted by Wipff[17] for the caesium complex with **1**.

Caesium–sodium separation by nanofiltration–complexation

The hydrophilic calixcrown derivatives were subsequently used as specific ligands for caesium in a nanofiltration–complexation process. Nanofiltration–complexation tests were carried out to measure the ligand's ability to improve the separation of caesium from sodium by the nanofiltration process. Over a range of molecular weights from 300 to 1000 g mol^{-1}, nanofiltration membrane "cutoffs" are located between ultrafiltration and reverse osmosis. The Nanomax 50 membrane allowed only 10% retention of Na$^+$ and Cs$^+$ ions. Thus, selective complexation of caesium with a ligand of larger size and mass than the target should increase the retention of the latter, preventing
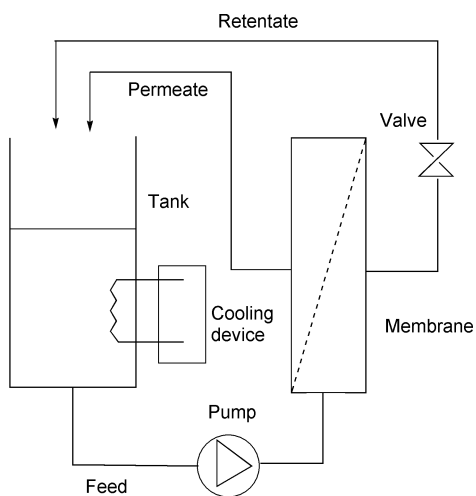
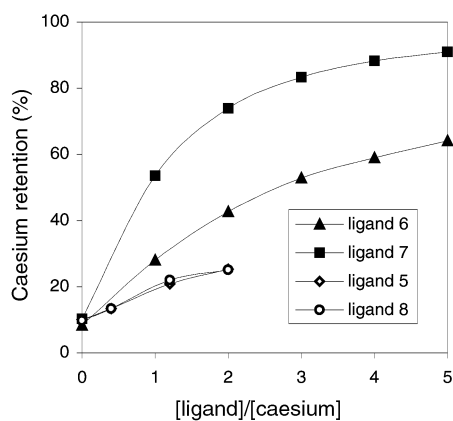**Fig. 4** Schematic diagram of the nanofiltration loop.

Fig. 5 Caesium retention = f([ligand]/[caesium]) ([caesium] = 15 mg l^{-1}, [NaNO$_3$] = 0.1 mol l^{-1}, T = 293 K, ΔP = 0.06 MPa).

Fig. 6 Caesium retention as a function of [NaNO$_3$] ([caesium] = 15 mg l^{-1}; T = 293K; pH = 12; [ligand]/[caesium] = 5; ΔP = 0.6 MPa).

Table 3 Caesium retention as a function of sodium nitrate concentration (%)[a]

[NaNO$_3$]/mol l^{-1}	Caesium retention (%)	Permeate flow/l h^{-1} m^{-2} bar^{-1}
0.1	98.5	4
1	96.1	3.6
2	93.6	3.2
3	90.6	2.8

[a] [Caesium] = 12.5 mg l^{-1}; [7]/[CsNO$_3$] = 40; pH = 12; T = 293 K; ΔP = 0.6 MPa.

Table 4 Complexation constants of ligands **6** and **7** with caesium and sodium

Ligand	$K_{Cs–L}$/l mol^{-1}	$K_{Na–L}$/l mol^{-1}	$S = K_{Cs–L}/K_{Na–L}$
6	3900	2	1950
7	23000	3.5	6570

this ion from passing through the membrane. A schematic representation of the nanofiltration (NF) loop used in our experiments is given in Fig. 4. By totally recycling the permeate and the retentate, the feed remains at constant composition during the experiment.

At first, the selective caesium affinity of the ligands was studied in an aqueous medium containing low levels of sodium nitrate. Several known amounts of a selected ligand were progressively added to a solution containing fixed concentrations of caesium (15 mg l^{-1}) and sodium nitrates (0.1 mol l^{-1}), which was filtered on an NF membrane. Samples of permeate and retentate were taken half an hour after each ligand addition.

In the absence of ligand, the performances of the nanofiltration membrane used (Nanomax 50 membrane) were not sufficient (Fig. 5). Phenolic groups are known to be efficient for Cs$^+$ complexation[18] and both hydroxylated derivatives **6** and **7** showed good affinity toward caesium, much higher than with carboxylic analogues **5** and **8**, the retention rates of which varied identically up to 25% with a [ligand]/[caesium] molar ratio of 2. Including four hydroxy substituents, ligand **7** exhibited higher caesium retention than **6**, which contains two phenolic groups. With a [ligand]/[caesium] ratio equal to 5, caesium retention was 91% for **7** and 64% for **6**.

Since the purpose of this work was to improve the separation of traces of caesium contained in high concentration sodium salt media, a second experiment was performed to evaluate the Cs$^+$/Na$^+$ selectivity of ligands **6** and **7** by addition of known amounts of sodium nitrate to a solution containing a fixed proportion of [ligand]/[caesium] of 5, which was then filtered on the NF membrane.
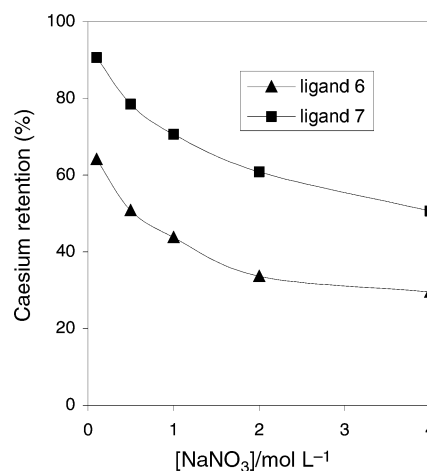
When NaNO$_3$ was added, the Cs$^+$/Na$^+$ selectivity of these ligands decreased identically (Fig. 6). In fact, in a 4 mol l^{-1} NaNO$_3$ basic aqueous medium with [ligand]/[caesium] = 5, the caesium retention by the NF membrane was still as high as 50% with **7** and 28% with **6**. Finally, results of further experiments revealed that achieving 90% caesium retention in a 3 mol l^{-1} sodium nitrate aqueous medium was possible with ligand **7**. With a basic aqueous solution containing 12.5 mg l^{-1} of caesium, 3.4 g l^{-1} of ligand was required to reach 90% caesium retention (Table 3).

Both of the NF–complexation tests carried out with ligands **6** and **7** allowed the calculation of distinct caesium–ligand and sodium–ligand constants (Table 4). These constants were found to be realistic because the theoretical caesium retention calculated from these $K_{Cs–L}$ and $K_{Na–L}$ values was in good agreement with the experimental caesium retention.

With a selectivity $S = K_{Cs–L}/K_{Na–L}$ = 6570, tetrahydroxycalix-[4]arene-bis(crown-6) **7** is three times more selective than **6** (S = 1950). Ligand **7** is a high-performance receptor for possible Cs$^+$/Na$^+$ separation by NF–complexation in aqueous media.

Conclusion

The newly synthesised host molecules **5–8** were obtained by different synthetic routes *via* their brominated or formylated intermediates. Their binding efficiencies for alkali metal cations were determined by UV spectrophotometry in aqueous media.

The results have shown that the efficiency of these hydrosoluble calix[4]crown-6 compounds depends on the nature and the number of grafted hydrophilic groups. Each ligand shows a more or less pronounced affinity for the studied alkali metal cations, decreasing in all cases from the larger (Cs^+) to the smaller (K^+). The best receptor for Cs^+ is ligand **7**, which achieves the best compromise between preorganization, steric hindrance and cooperative effect of the cation–arene and cation–phenolate interactions. Results concerning Cs^+/Na^+ separation by nanofiltration combined with these organic compounds fit well with UV–Vis analysis, *i.e.* the stability sequence and selectivity followed the same order **7 > 6 > 5 = 8** for Cs^+ ion. Tetrahydroxylated calix[4]arene-bis(crown-6) **7** is a high performance ligand for possible Cs^+/Na^+ separation by nanofiltration–complexation in aqueous media. It allows efficient separation of traces of caesium from a highly salted medium (caesium retention of 90% was reached from 3 mol l^{-1} $NaNO_3$). Finally, the removal of 99% of the caesium traces and not more than 10% of the initial sodium salt should then be possible by combining the two stages of such a process.

Experimental

General

Mps were determined with a Büchi melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR: Bruker AC200 or AM300 (chemical shifts in ppm, *J* in Hz). Mass spectrometry: electrospray technique, positive and negative mode. Elemental analysis was performed at Service Central d'Analyse, CNRS, Vernaison (France).

Preparation of calixarenes 3–8

The solvents were commercial reagents and used without further purification. Vicens' procedure was used to prepare calixarene-bis(crown-6).[6a] The synthesis of compounds **2** and **5** has been described in a previous paper on water-soluble calixarene-bis(crown-6) derivatives.[9]

5,11,17,23-Tetrabromocalix[4]arene-bis(crown-6) (3). *With Br$_2$ in AcOH.* Compound **1** (5 g, 6.031 mmol) was dissolved in 100 ml of glacial AcOH at room temperature. Br$_2$ (9.65 g, 60.03 mmol) in AcOH (30 ml) was added dropwise under vigorous stirring. The resulting suspension was heated at 60 °C during 3 h. The reaction mixture was cooled again at room temperature and stirred overnight. The resulting precipitate was filtered off, washed with AcOH and H$_2$O, and dissolved in CH$_2$Cl$_2$. The organic layer was washed successively with Na$_2$S$_2$O$_5$ 10% (2 × 300 ml), H$_2$O (2 × 300 ml), saturated NaCl and dried over MgSO$_4$. The solvent was evaporated to dryness and **3** was obtained without further purification as a white foam (4.8 g, 70%).

With Br$_2$ in CH$_2$Cl$_2$. Compound **1** (2.5 g, 3.016 mmol) was stirred in CH$_2$Cl$_2$ (200 ml) at 0 °C. Br$_2$ (7.24 g, 45.2 mmol) in CH$_2$Cl$_2$ was added. After 4 h, the formed precipitate was dissolved by addition of CH$_2$Cl$_2$ (100 ml) and more Br$_2$ (4.8 g) was added. The solution was stirred overnight at 0 °C. The light suspension was then dissolved in CH$_2$Cl$_2$ (100 ml) and the organic solution was washed with sodium metabisulfite 10%, H$_2$O and saturated NaCl, then dried over MgSO$_4$. Evaporation of CH$_2$Cl$_2$ afforded pure **3** (3.08 g, 90%).

With NBS. A mixture of **1** (1 g, 1.21 mmol) and NBS (2.15 g, 12.06 mmol) in butan-2-one (25 ml) was stirred during 24 h. The organic solution was washed with sodium metabisulfite 10%, H$_2$O and saturated NaCl, then dried over MgSO$_4$ and evaporated to dryness. The residue was dissolved in CH$_2$Cl$_2$ and purified by silica gel column chromatography (CH$_2$Cl$_2$–MeOH, 98 : 2) to give **3** (0.56 g, 41%).

Mp >250 °C; δ_H (CDCl$_3$): 3.21 (t, *J* = 6.5, 8H, OCH$_2$CH$_2$O), 3.56–3.72 (m, 32H, OCH$_2$CH$_2$O), 3.78 (s, 8H, ArCH$_2$Ar), 7.23

(s, 8H, ArH); δ_C (CDCl$_3$): 37.29 (ArCH$_2$Ar), 69.25, 69.43, 70.54, 71.08 (OCH$_2$CH$_2$O), 115.4, 135.4, 155.5 (ArC), 132.0 (ArCH); ES-MS (ES$^+$): 1167.1 ([M + Na]$^+$). Anal. calc. for C$_{48}$H$_{56}$O$_{12}$Br$_4$·0.25CH$_2$Cl$_2$: C, 49.74; H, 5.01; O, 16.47, found: C, 49.51; H, 5.05; O, 16.18%.

5,11,17,23-Tetraformylcalix[4]arene-bis(crown-6) (4). To a solution of **3** (1 g, 0.874 mmol) in dry THF (300 ml) cooled to −78 °C under Ar were added 16.4 ml of BuLi (1.6 M in hexane, 26.2 mmol). After 2 h, dry DMF (10 ml) was added and the reaction mixture was allowed to warm to ambient temperature. After 5 h, the solution was concentrated, acidified with 1 M aqueous HCl (30 ml) and extracted with chloroform. The organic extract was washed with H$_2$O and evaporated. The residue was triturated in water and the resulting white precipitate was filtered off and purified by chromatography (SiO$_2$, CH$_2$Cl$_2$–MeOH, 95 : 5) to give pure **4** (0.38 g, 46%). Mp 174–175 °C; δ_H (CDCl$_3$): 3.31 (t, *J* = 5.7, 8H, OCH$_2$CH$_2$O), 3.42–3.64 (m, 24H, OCH$_2$CH$_2$O), 3.70 (t, *J* = 5.7, 8H, ArCH$_2$Ar), 7.70 (s, 8 ArH), 9.91 (s, 4H, CHO); δ_C (CDCl$_3$): 37.51 (ArCH$_2$Ar), 69.31, 69.56, 70.45, 70.50, 70.79, 71.18 (OCH$_2$-CH$_2$O), 132.1 (ArCH), 131.5, 134.1, 161.7 (ArC), 191.6 (CHO); ES-MS (ES$^+$): 963.5 ([M + Na]$^+$); 493.2 ([M + 2Na]$^{2+/2}$). Anal. calc. for C$_{52}$H$_{60}$O$_{16}$·0.15CH$_2$Cl$_2$: C, 65.65; H, 6.37; O, 26.84, found: C, 65.47; H, 6.52; O, 26.56%.

5,17-Dihydroxycalix[4]arene-bis(crown-6) (6). To a solution of **2** (2 g, 2.26 mmol) dissolved in CH$_2$Cl$_2$ (100 ml) at rt under Ar was added dropwise a solution of *m*-chloroperbenzoic acid (MCPBA 60%, 5.2 g, 18.1 mmol) in CH$_2$Cl$_2$. After being stirred for 24 h, the reaction mixture was washed with sodium metabisulfite 10% (100 ml) and water (2 × 200 ml). The organic extract was dried over MgSO$_4$ and evaporated to dryness. The residue was triturated in Et$_2$O and filtered. The resulting white powder was dissolved in dry THF with concentrated HCl (10 ml). After 36 h under stirring, the solvents were evapored. The crude product was then stirred in propan-2-ol and filtered from the insoluble impurities. The filtrate was concentrated and a precipitate was obtained by addition of Et$_2$O. After filtration, **6** (0.7 g, 33%) was obtained without further purification as a pale yellow powder. Mp 104 –106 °C; δ_H (CDCl$_3$): 3.41–3.74 (m, 48H, OCH$_2$CH$_2$O and ArCH$_2$Ar), 6.69 (br d, 4H, ArH), 6.85 (s, 4H, ArH), 7.10 (br t, 2H, ArH); ES-MS (ES$^-$): 859.4 ([M − H]$^-$); ES-MS (ES$^+$): 899.3 ([M + K]$^+$), 883.3 ([M + Na]$^+$, 861.3 ([M + H]$^+$). Anal. calc. for C$_{48}$H$_{60}$O$_{14}$·HCl·3H$_2$O: C, 60.57; H, 6.88; O, 28.56, found: C, 60.59; H, 6.38; O, 28.36%.

5,11,17,23-Tetrahydroxycalix[4]arene-bis(crown-6) (7). To a solution of **3** (5 g, 4.37 mmol) in dry THF (600 ml) cooled to −78 °C under Ar was added *t*-BuLi (77 ml of a 1.7 M solution in pentane, 131 mmol). After 1 h, B(OMe)$_3$ (29.5 g, 284 mmol) was added and the solution was allowed to warm to rt. After being stirred for 5 h, the reaction mixture was cooled again to −78 °C and 3 M NaOH–H$_2$O$_2$ 35% (125 ml) was added dropwise. The mixture was again warmed to rt and stirred overnight. Na$_2$S$_2$O$_3$·5H$_2$O was carefully added to the solution (cooled to 0 °C) until saturation. After evaporation of THF, water (300 ml) was added and the mixture was acidified with 2 M HCl until 6 < pH < 7. The resulting precipitate was filtered off, rinsed with H$_2$O and dissolved in MeOH. Insoluble impurities were removed by filtration. The filtrate was evaporated to dryness and the residue dissolved in THF. Precipitation with Et$_2$O and fitration afforded pure **7** (2.04 g, 65%) as a white powder. Mp 116–118 °C. δ_H (DMSO-d_6): 3.02 (br t, 8H, OCH$_2$CH$_2$O), 3.25 (br t, 8H, OCH$_2$CH$_2$O), 3.39–3.54 (m, 24H, OCH$_2$CH$_2$O), 3.6 (s, 8H, ArCH$_2$Ar), 6.40 (s, 8H, ArH), 8.65 (s, 4H, OH); δ_C (CD$_3$OD): 39.43 (ArCH$_2$Ar), 71.02, 71.91, 72.13 (OCH$_2$-CH$_2$O), 117.5 (ArCH), 136.4, 151.3, 153.2 (ArC); ES-MS:

(ES⁻): 891.4 ([M − H]⁻); ES-MS: (ES⁺): 931.4 ([M + K]⁺), 915.4 ([M + Na]⁺), 894.4 ([M + H]⁺). Anal. calc. for $C_{48}H_{60}$-$O_{16}\cdot 0.25H_2O\cdot 0.25CH_2Cl_2$ C, 61.97; H, 6.59; O, 27.66; found: C, 62.10; H, 6.59; O, 27.50%.

5,11,17,23-Tetracarboxycalix[4]arene-bis(crown-6)   (8).
Method A. Compound **4** (0.5 g, 0.531 mmol) was dissolved in 80 ml of $CHCl_3$–acetone (1 : 1). $NaClO_2$ (0.764 g, 8.5 mmol) and NH_2SO_3H (0.930 g, 9.56 mmol) in H_2O (10 ml) were added and the mixture was stirred for 4 days at rt until the complete removal of the mono-, di- and tri-carboxy derivatives (TLC, SiO_2, CH_2Cl_2–MeOH, 92 : 8). After evaporation of the organic solvents, the aqueous solution was acidified with 1 M HCl and the resulting white precipitate was filtered, washed with H_2O and dried *in vacuo* to give pure **8** (0.354 g, 66%).

Method B. To a stirred solution of **3** (1.2 g, 1.05 mmol) dissolved in dry THF (60 ml) at −78 °C under Ar were added *n*-BuLi (13.1 ml, 1.6 M in hexane, 20 mmol). The resulting red solution was stirred at −78 °C for 30 min and quenched with a large excess of CO_2 (g). HCl (10 ml, 6 M) was added to the reaction mixture and the THF was evaporated. The resulting precipitate was filtered, washed with H_2O and dried *in vacuo* at 50 °C overnight. Precipitation in cooled $CHCl_3$ and filtration afforded pure **8** as a white powder (0.476 g, 45%). Mp >250 °C; δ_H (DMSO-d_6): 2.88–2.92 (br t, 8H, OCH_2CH_2O), 3.35–3.49 (br m, 32H, OCH_2CH_2O), 3.99 (s, 58H, $ArCH_2Ar$), 7.73 (s, 8H, ArH), 12.56 (s, 4H, COOH); δ_C (DMSO-d_6): 36.73 ($ArCH_2Ar$), 68.03, 68.84, 69.63, 70.05 (OCH_2CH_2O), 130.5 (ArCH), 124.8, 133.4, 159.9 (ArC), 167.2 (COOH); ES-MS (ES⁻): 1003.5 ([M − H]⁻). Anal. calc. for $C_{52}H_{60}O_{20}\cdot 0.5H_2O\cdot 0.75CHCl_3$: C, 57.51; H, 5.63; O, 29.72; found: C, 57.68; H, 5.96; O, 29.85%.

Stability constant measurements

UV–Vis studies were carried out in methanol and in an aqueous medium containing 0.1 M NaOH at 25 °C. The spectral changes of the calixarene solutions (2–3 ml) upon stepwise addition of alkali metal salt into the measurement cell were recorded from 200 to 350 nm with an HP 8453 spectrophotometer using a 1 cm path length quartz vessel. Chloride salts (KCl, RbCl, CsCl, Acros, p.a.) were preferred to nitrate salts to prevent overlapping of the ligand spectrum by the broad NO_3^- band.

Nanofiltration tests

Apparatus. A SEPA CF Membrane Cell (OSMONICS) was used with a Nanomax 50 plane membrane (Millipore), which presents a surface area of 0.015 m², designed for tangential filtration. The retention (%) of a substance *i* was calculated as $R_i = 100 \times (1 − C_{ip}/C_{ir})$ where C_{ip} is the concentration of *i* in the retentate and C_{ir} the concentration in the retentate. For all the NF results, sodium retention remained under 10% because the Nanomax membrane was chosen to be very permeable to monovalent ions. Tests were carried out using a transmembrane pressure of 0.06 MPa and a temperature of 293 K.

Chemicals and reagents. The metallic salts used for the NF tests were the nitrates $NaNO_3$ (99%, Aldrich) and $CsNO_3$ (99.99%, Aldrich). Ligands were synthesised as described above.

Analytical. Caesium concentrations were determined by atomic absorption spectroscopy (AAS) in an air–acetylene flame with a PU 9100X PHILIPS atomic absorption spectrometer. Each result is assumed to have a 5% standard deviation. Standards for AAS analysis were made from pure Cs^+ (caesium standards for ICP-AES analysis) and dissolved in the corresponding $NaNO_3$ and NaOH aqueous matrix.

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