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Experimental and theoretical study of the first thiacalixcrowns and their alkali metal ion complexes

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The synthesis, crystal structure and extraction properties towards Na^+ and Cs^+ of thiacalix[4]-bis(crown-*n*) (with $n = 5$ and 6) are reported. Experimental investigations show that both ligands as well as unsubstituted thiacalix[4]arene are less efficient than their calixarene counterparts for the extraction of alkali metal ions. The structures and dynamic behavior of the hypothetical alkali metal ion complexes have been investigated by molecular modelling: the caesium cation is located close to the thiacalixarene cavity and does not interact strongly with the crown, which does not fulfil fully its role of ligand. The comparison of calixarene–crown with thiacalixarene–crown confirms that the size of the calixarene cavity in the 1,3-alternate conformation is a key parameter in the remarkable affinity of these molecules for caesium.

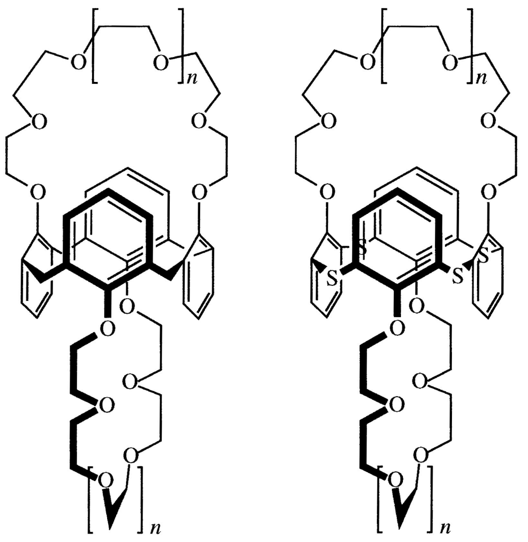
Introduction

Thiacalixarenes are macrocycles comprising phenolic units connected in the *ortho* position by sulfur bridges instead of the methylene bridges of calixarenes. The first syntheses of *p-tert*-butylthiacalix[4]arenes, in which one to four methylene bridges were replaced by sulfur bridges, were published in 1997[1] and recent publications report on the synthesis of new compounds based on the thiacalixarene platform, which is interesting because of the affinity of sulfur atoms for transition metals.[2] The size of the cavity is enlarged and the chemical reactivity (oxidation products) and chelating properties are modified upon replacement of carbon by sulfur bridges.[3]

NMR studies on thiacalix[4]arenes showed an increased conformational mobility, with respect to calix[4]arene, which becomes more pronounced as the number of sulfur bridges increases.[1] Three dominant conformations (cone, partial cone and 1,3-alternate) coexist at ambient temperature for the tetraethoxy derivative in $CDCl_3$[4] and a fast interconversion was evidenced by ROESY NMR spectra carried out on the *p-tert*-butyltetramethoxy derivative.[5] In the solid state, the conformation depends on the substituents: the thiacalix[4]arene adopts a cone conformation[1] whereas the tetraalkylated derivatives, with and without *p-tert*-butyl substituents, are in the 1,3-alternate conformation.[5,6] Several authors reported that the conformation of the tetraalkylated products depends on the base used during the synthesis: caesium carbonate gives the 1,3-alternate conformation whereas potassium carbonate leads to the partial cone and sodium carbonate to the cone conformation.[7–9]

Only *p-tert*-butylthiacalix[4]arene and some tetraester derivatives have been investigated with regard to the complexation of alkali cations. Iki *et al.* studied the extraction of the alkali metal cations by *p-tert*-butylthiacalix[4]arene[2] and its tetrakis[(ethoxycarbonyl)methoxy] *O*-derivative.[7] In the case of the parent compound (tetra-OH), the extraction is pH-dependent. The alkali cations are poorly extracted in chloroform, with a maximum of 32% for potassium at pH 5.5 and of 18% for lithium at pH 2.2. The complexation constants for alkali picrates in $CDCl_3$–CD_3CN were determined by NMR for the tetrakis[(ethoxycarbonyl)methoxy] *O*-derivatives with and without *p-tert*-butyl groups.[9] Only the 1,3-alternate de-*tert*-butylated compound is selective for caesium (selectivity order $Cs^+ > Rb^+ > K^+$) whereas the 1,3-alternate compound with *p-tert*-butyl substituents is selective for rubidium ($Rb^+ > K^+ > Cs^+$) in extraction as well as in complexation experiments.

Taking into account the selectivity observed for 1,3-alternate calix[4]crown-6s towards the caesium cation,[10,11] it appears interesting to evaluate the selectivity of thiacalix[4]arenes grafted with crown-ether loops towards alkali metal cations. In this paper, we report the syntheses and X-ray crystal structures of thiacalix[4]-bis(crown-5) and -bis(crown-6) (Scheme 1) and their extraction properties towards Na^+ and Cs^+. These experimental investigations are completed with molecular



$n = 0$: BC5
$n = 1$: BC6

$n = 0$: BC5S
$n = 1$: BC6S

Scheme 1 The thiacalixcrowns under study and their calixcrown counterparts.

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dynamics simulations to study the structure of their alkali metal ion complexes.

Experimental

Synthesis

Starting materials for syntheses. The solvents and all compounds were commercial reagents and were used without further purification.

Analytical procedures. The melting points (mp) were taken on a Büchi 500 apparatus in capillaries sealed under nitrogen. Silica gel columns were prepared with Kieselgel Merck (No. 11567). Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg. The ^{1}H NMR spectra were recorded at 200 MHz on a Bruker SY200 spectrometer. The FAB mass spectra were obtained on a VG-Analytical ZAB HF apparatus.

Preparation of thiacalix[4]-bis(crown-5), BC5S. This compound was synthesized according to a procedure previously described.[11] A 500 mL round-bottomed flask was equipped with a condenser and charged with acetonitrile (250 mL), thiacalix[4]arene (1.984 g, 4 mmol) and potassium carbonate (5.530 g, 40 mmol). The reaction mixture was stirred at room temperature for 2 h. Tetraethylene glycol ditosylate (2.010 g, 4 mmol) was then added, and the mixture was refluxed for 3 days. The same quantities of potassium carbonate and tetraethylene glycol ditosylate were added, and the reflux was continued for 4 additional days. After cooling down to room temperature, the solvents were removed *in vacuo* (40 °C bath). Dichloromethane (200 mL) was added and the suspension was neutralized with 1 M HCl. The organic layer was dried over sodium sulfate. The filtered solution was then concentrated. Chromatography on silica with a mixture 80 : 20 CH_2Cl_2–acetone as eluent yielded pure thiacalix[4]-bis(crown-5) (57% yield) as a white solid melting at >300 °C. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 8H, J_{H-H} = 7.5 Hz, *meta* Ar*H*), 6.93 (t, 4H, J_{H-H} = 7.5 Hz, *para* Ar*H*), 4.03 (t, 8H, J_{H-H} = 6.5 Hz, OCH_2CH_2O), 3.50 (s, 16H, OCH_2CH_2O), 3.18 (t, 8H, J_{H-H} = 6.5 Hz, OCH_2CH_2O); FAB positive, 813.2. Elemental analysis: calcd. for $C_{40}H_{44}O_{10}S_4$: C, 59.10; H, 5.46. Found: C, 59.26; H, 5.42%.

Preparation of thiacalix[4]-bis(crown-6), BC6S. The same procedure as for BC5S was followed. Thiacalix[4]arene (1.984 g, 4 mmol), potassium carbonate (5.53 g, 40 mmol), pentaethylene glycol ditosylate (2.186 g, 4 mmol), and acetonitrile (250 mL); melting point: 175–176 °C; yield 51%. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 8H, J_{H-H} = 7.5 Hz, *meta* Ar*H*), 6.92 (t, 4H, J_{H-H} = 7.5 Hz, *para* Ar*H*), 4.08 (t, 8H, J_{H-H} = 6.5 Hz, OCH_2CH_2O), 3.68 (s, 8H, OCH_2CH_2O), 3.60 (t, 8H, J_{H-H} = 6.5 Hz, OCH_2CH_2O), 3.45–3.35 (m, 16H, OCH_2CH_2O); FAB positive, 901.3. Elemental analysis: calcd. for $C_{44}H_{52}O_{12}S_4$: C, 58.65; H, 5.82. Found: C, 58.62; H, 5.87%.

Crystallography

Single crystals of compounds BC5S and BC6S were obtained by slow evaporation of chloroform solutions of the corresponding thiacalixcrowns. The data were collected on a Nonius Kappa-CCD area detector diffractometer[12] using graphite-monochromated Mo-Kα radiation (0.71073 Å). The crystals were introduced in Lindemann glass capillaries with a protecting "Paratone" oil (Exxon Chemical Ltd.) coating. A 180° φ-range was scanned with 2° steps. The data were processed with DENZO-SMN.[13] The structures were solved by direct methods with SHELXS-97[14] and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXL-97.[15] Absorption effects in BC6S were corrected empirically with the program DELABS from PLATON.[16] All hydrogen atoms in both compounds were introduced at calculated positions and treated as riding atoms with an isotropic displacement parameter equal to 1.2 times that of the parent atom. All non-hydrogen atoms were refined with anisotropic displacement parameters. Crystal data and structure refinement parameters are given in Table 1. The molecular plots were drawn with SHELXTL.[17] All calculations were performed on a Silicon Graphics R5000 workstation.

Table 1 Crystal data and structure refinement details[a]

	1	**2**
Empirical formula	$C_{40}H_{44}O_{10}S_4$	$C_{44}H_{52}O_{12}S_4$
M/g mol^{-1}	812.99	901.10
T/K	100(2)	100(2)
Crystal system	Monoclinic	Tetragonal
Space group	*Cc*	$P4_12_12$
a/Å	15.6139(6)	14.798(2)
b/Å	16.7784(8)	14.798(2)
c/Å	29.5847(11)	40.113(8)
β/°	91.689(2)	
V/Å^3	7747.1(6)	8784(2)
Z	8	8
μ/mm^{-1}	0.304	0.278
Reflections collected	25086	42860
Independent reflections	13502	7935
Observed reflections [$I > 2\sigma(I)$]	9862	3482
R_{int}	0.061	0.084
R_1	0.057	0.092
wR_2	0.125	0.179

[a] CCDC 164775 (**1**) and 164776 (**2**). See http://www.rsc.org/suppdata/p2/b1/b104854f/ for crystallographic files in .cif or other electronic format.

Solvent extraction

All solvents and inorganic compounds were purchased from Aldrich Chemical and Prolabo, respectively. 2-Nitrophenyl hexyl ether (NPHE) was synthesized by ERAS Laboratories. Milli Q2 water was used to prepare the solutions.

Solvent extraction experiments were performed by contacting the aqueous solutions containing inactive salts (composition details in tables) spiked with ^{22}Na (2.6 y) and ^{137}Cs (30 y) with an organic phase containing the calixarene (10^{-2} M) in NPHE. The sodium and caesium distribution coefficients D_M were measured by gamma spectrometry on 2 ml aliquots as the ratio of cation γ activity in the organic phase to that in the aqueous phase. Measurement times were adapted to obtain a reproducibility within ±5%.

Molecular modelling

All calculations were carried out on an SG INDIGO 2 R8000 workstation with the AMBER 4.1 software,[18] using as a force field the all-atom parameters from PARM91.DAT file[19] and the representation of the potential energy given in eqn. (1), where r,

$$E_{pot} = \sum_{\text{bonds}} K_r(r - r_{eq})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}(1 + \cos(n\varphi - \eta)) + \sum_{i<j}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12} - \left(\frac{R^*}{R_{ij}}\right)^{6}\right)\right] + \sum_{i<j}\left[\frac{q_iq_j}{\varepsilon R_{ij}}\right] + \sum_{\text{H-bonds}}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12} - \left(\frac{R^*}{R_{ij}}\right)^{10}\right)\right] \quad (1)$$

θ and φ represent the bond length, bond angle and dihedral angle, respectively. R_{ij} is the distance between atoms i and j, q_i is the atomic charge on atom i and ε is the relative permittivity.

Non-standard parameters involving sulfur (atom type SC) are reported in Table 2. The force constants are derived from

Table 2 Non-standard parameters used in simulations

Bond	K_R/kcal mol^{-1} Å^{-2}	R_0/Å	
CA–SC	222	1.785	
Angle	K_θ/kcal mol^{-1} rad^{-2}	θ_0/°	
CA–SC–CA	62	100	
CA–CA–SC	70	120	
Dihedral	$1/2\,V_n$/kcal mol^{-1}	γ/°	n
CA–CA–SC–CA	1.0	0	3
Van der Waals	R^*/Å	ε/kcal mol^{-1}	
SC	2.00	0.2	

Table 3 Atomic charges used in simulations

Atom name	Atom type	Charges for BC6[24a]	Charges for BC6S
O1	OS	−0.36	−0.346
C1	CA	0.157	0.156
C2,C6	CA	−0.14	−0.142
C3,C5	CA	−0.013	−0.013
H3–H5	HC	0.076	0.097
C4	CA	−0.087	−0.078
H4	HC	0.08	0.09
C (bridge)	CT	0.164	
S (bridge)	SC		0.093
C (crown)	CT	0.2	0.202
O (crown)	OS	−0.4	−0.404
H (crown)	HC	0.0	0.0

the S atom type of PARM91.DAT, the equilibrium CA–SC distances and CA–SC–CA angles are adjusted from the X-ray data that were available before the thiacalixcrowns were obtained.[8,20]

The thiacalixcrowns BC5 and BC6 are built from their calixcrown counterparts by replacing methylene groups by sulfur atoms. A first minimization is performed without point charges on a caesium complex geometry to adjust the modified bonds. Point charges are calculated on the thiacalixcrown with the MNDO semiempirical method without geometry optimization. These charges are then averaged on equivalent atoms and scaled up with a 1.33 factor to obtain a charge on crown oxygen atoms close to the −0.4 value used for BC6 (Table 3).[21] The alkali metal ion complexes were generated from the caesium complex geometry by changing the parameters of the cation described by the Aqvist set modified for the AMBER force field available in PARM91.DAT. The 1–4 non-bonded contributions were scaled down by a factor of 0.5.

The thiacalixcrowns and their alkali complexes were submitted to minimization *in vacuo* with 50 steepest descent iterations followed by conjugate gradient iterations till convergence with an rms of 0.01 kcal mol^{-1} Å^{-1} on the energy gradient. Then MD simulations were performed at constant temperature (300 K) and energy for 500 ps for the alkali complexes and 1 ns for the free thiacalixcrowns with a 1.0 fs time step, with relative permittivity set at 1.0 and a sharp 10 Å residue-based cut-off. One conformation was saved after each picosecond calculation and the trajectories, constituted by the collection of these conformations, were visualized with MD/DRAW[22] and analyzed with MDS.[23] The first ten picoseconds, corresponding to the thermal equilibration of the system, were not taken into account in the structural and energetic analysis.

In water, the molecular dynamics simulations used a time step of 2.0 fs, and a 12 Å cut-off. The SHAKE procedure was used to constrain bonds involving hydrogen atoms. We used PBC and an isothermal/isobaric ensemble of 300 K and 1 atm through coupling to temperature and pressure baths. All the starting structures were complexes minimized at the end of the MD run *in vacuo*, and immersed in a TIP3P cubic box, with water molecules removed within 2 Å of the solute. These systems were energy-minimized and submitted to molecular dynamics simulations. The simulation length was at least 100 ps for the alkali complexes and 400 ps for free thiacalixcrowns.

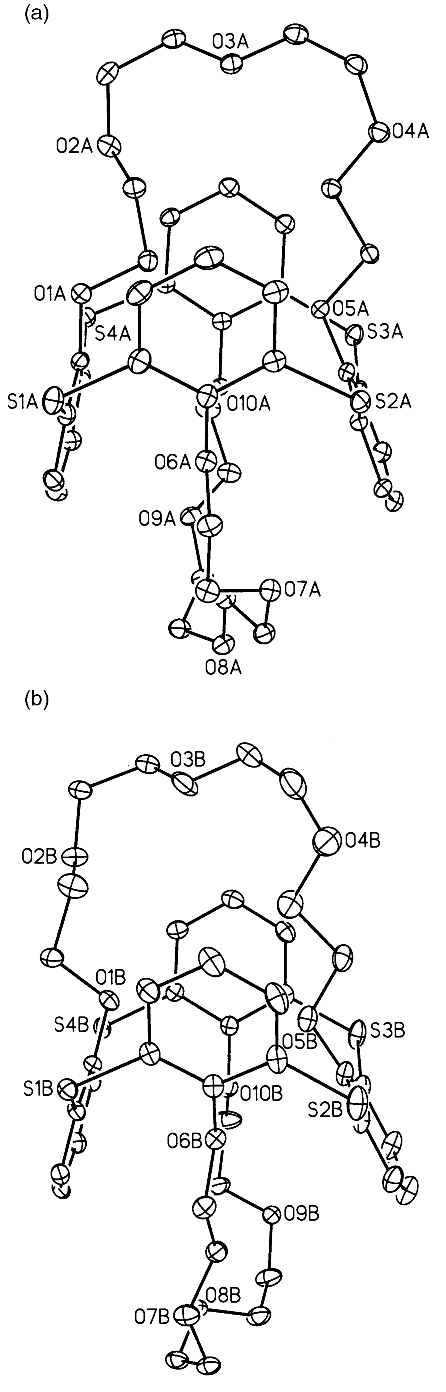


Fig. 1 View of thiacalix[4]-bis(crown-5), BC5S (molecules A and B). Hydrogen atoms omitted for clarity.

Results and discussion

Crystal structures

Thiacalix[4]-bis(crown-5), BC5S, crystallizes with two independent molecules in the asymmetric unit, denoted A and B and represented in Fig. 1. The calixarene platform, in the 1,3-alternate conformation, is nearly identical in both molecules. The four sulfur atoms define a plane with an rms deviation of 0.090 and 0.025 Å in A and B, respectively. The dihedral angles between the four aromatic rings and this mean plane are 80.9(1), 76.8(1), 67.5(1) and 73.6(1)° in A and 76.4(1), 69.5(1), 61.3(1) and 69.4(1)° in B, showing that the rings are somewhat more "vertical" in A. This slight difference in calixarene geom-

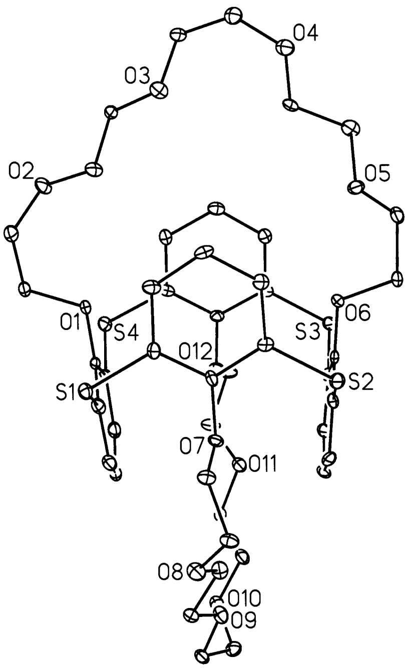


Fig. 2 View of thiacalix[4]-bis(crown-6), BC6S. Hydrogen atoms omitted for clarity.

Table 4 Distribution coefficients D_M of Cs$^+$ and Na$^+$ in an acidic medium[a]

	BC6	BC6S	BC5	BC5S
D_{Cs}	19.5	1.5	0.4	2.5×10^{-2}
D_{Na}	1.3×10^{-2}	$<10^{-3}$	2×10^{-3}	$<10^{-3}$

[a] Aqueous phase: alkali metal ion nitrate 5×10^{-4} M in HNO_3 (1 M). Organic phase: calixarene (10^{-2} M) in NPHE.

Table 5 Distribution coefficients D_{Cs} of Cs$^+$ in concentrated sodium nitrate solution[a]

	BC6	BC6S	BC5	BC5S
D_{Cs}	6	1.21	$< 10^{-3}$	5.2×10^{-2}

[a] Aqueous phase: $CsNO_3$ (10^{-6} M) in $NaNO_3$ (4 M) + HNO_3 (1 M). Organic phase: calixarene (10^{-2} M) in NPHE.

etry is seemingly related to the different crown conformations present in the two molecules. It was previously shown that, in the absence of any interaction with solvent or cations, the crown ethers in calixcrown molecules are highly flexible and can adopt a large range of conformations.[24] This is the case in BC5S, since the four sequences of O–C–C–O torsion angles in the crowns of molecules A and B are all different: $g^-g^-g^+a$ and $g^+ag^-g^+$ in A, $g^+g^-g^+a$ and $ag^+g^+g^-$ in B (*a* = *anti*, *g* = *gauche*), with in all cases two or three C–O–C–C torsion angles converted from their ideal *anti* conformation to a *gauche* one. As a consequence, not all the oxygen atom lone pairs are directed towards the centre of the crown. The distances and angles involving sulfur atoms are in the usual range,[6,8,20,25,26] with ⟨S–C⟩ 1.771(8) Å and ⟨C–S–C⟩ 107(2)° [mean values including both molecules; mean literature values 1.782(7) Å, 102(3)°]. The size of the calixarene cavity is given by ⟨S · · · S⟩ (adjacent) 5.57(2) and ⟨S · · · S⟩ (non adjacent) 7.9(2) Å. The distances between the oxygen atoms and the centroid defined by the five oxygen atoms of each crown are in the range 2.313–3.407 Å, with a mean value of 2.9(3) Å, which is definitely too small for Cs$^+$ to be complexed within the crown ether chain.[21]

The molecular structure of thiacalix[4]-bis(crown-6), BC6S, is represented in Fig. 2. The asymmetric unit contains one molecule, without any crystallographically-imposed symmetry. The geometry around sulfur atoms does not deviate significantly from usual [⟨S–C⟩ 1.79(1) Å and ⟨C–S–C⟩ 99.8(3)°]. However, the calixarene platform presents a particularly unusual feature for a calixcrown including a crown-6 unit, which is the tilting of the aromatic rings, bringing the first oxygen atoms of the chains out of the basal square of the calixarene. The four sulfur atoms define a mean plane with an rms deviation of 0.058 Å, and the dihedral angles between the four aromatic rings and this mean plane are 96.7(2), 98.5(2), 96.1(2) and 95.7(2)°. Such a geometry has already been encountered for calix[4]-bis(crown-7) and for some other calixcrowns including longer chains.[24b] It is accompanied in **2** by an unprecedented crown conformation (the same for both crowns), characterized by the sequence of O–C–C–O torsion angles $g^+ag^+ag^+$ (with one *gauche* C–O–C–C torsion angle). This conformation results in some oxygen atom lone pairs being directed towards the exterior of the crown and also in a nearly "vertical" position of the crowns with respect to the calixarene: the six oxygen atoms of each crown define a mean plane with an rms deviation of 0.21 Å and the dihedral angles between these mean planes and that defined by the sulfur atoms are 84.61(8) and 87.93(8)°. In the case of calixcrown compounds with methylene bridges, such a geometry of the calixarene platform has been supposed to arise from the necessity to minimize the strains in the case of the longer chains (crown-7 or spacer-containing crown-6).[24b] In the present case, both the peculiar calixarene geometry and crown conformation may be assumed to be necessary to accommodate the crown-6 moieties to a calixarene platform wider than usual (⟨S · · · S⟩ (adjacent) 5.531(8) and ⟨S · · · S⟩ (non adjacent) 7.82(1) Å, to be compared to ≈5.1 and ≈7.1 Å in calixcrowns). The distances between the oxygen atoms and the centroid defined by the six oxygen atoms of each crown are in the range 2.492–4.063 Å, with a mean value of 3.6(6) Å (the lower values correspond to oxygen atoms whose lone pairs point towards the centre of the crown). Typical mean values for calixcrowns calculated from crystal structures are 3.2(5) Å for a "free" crown (in which all the oxygen lone pairs do not point towards the interior of the crown), 3.3(4) Å for a crown bound to a solvent molecule such as acetonitrile by weak C–H · · · O hydrogen bonds and 3.1(4) Å for a crown complexing a caesium cation {in the last two cases, the mean distance between the complexed species, –CH_3 or Cs$^+$, and the six oxygen atoms, is larger [3.5(1) and 3.3(1) Å, respectively] owing to the displacement of the former out of the oxygen atoms mean plane}. In agreement with the results of the modelling calculations (*vide infra*), the crystal structure of BC6S shows that the enlargement of the crown subsequent to that of the calixarene platform results in a crown ether cavity too large for efficiently complexing Cs$^+$.

Solvent extraction

The extraction of caesium and sodium ions by the thiacalixarenes BC5S and BC6S was studied in an acidic medium under standard conditions, to allow an easy comparison with experiments on calixcrowns BC5 and BC6 reported elsewhere.[11] Distribution coefficients for caesium and sodium cations, reported in Table 4, show that the thiacalixcrowns BC5S and BC6S extract caesium approximately 15 times less efficiently than the corresponding calixcrowns. The decrease in extraction ability is also discernible for sodium, and to better quantify it, experiments in the presence of a large excess of sodium nitrate were performed (Table 5).

A weak decrease of the distribution coefficient of caesium ions in concentrated sodium nitrate solution can be observed, which indicates that the Cs$^+$/Na$^+$ selectivity is more significant for thiacalixcrowns than for calixcrowns. The distribution coefficients for the potassium and rubidium cations were not determined. However, all the complexation attempts to analyse

Table 6 Distribution coefficient of Cs^+ in concentrated soda[a]

D_{Cs}	C[4]/10^{-2} M	C[4]/5 × 10^{-3} M	*p-tert*-butyl-S[4]/5 × 10^{-3} M
Aqueous phase 1	2.53	1.6	0.17
Aqueous phase 2	6.96	4.28	0.5

[a] Aqueous phase 1: $CsNO_3$ (10^{-5} M) in $NaNO_3$ (2 M) + NaOH (2 M). Aqueous phase 2: $CsNO_3$ (10^{-5} M) in NaOH (4 M).

Table 7 Structural data on free macrocycles from MD simulations of 1 ns in the gas phase

	BC5[24a]	BC6[24a]	BC5S	BC6S	X-Ray BC5S	X-Ray BC6S
⟨*d*S–S⟩ or ⟨*d*CH_2–CH_2⟩/Å	5.13	5.09	5.61	5.57	5.57 (2)	5.531 (8)
⟨C–S–C angle⟩/°			103.5 (2)	101.2 (1)	107 (2)	99.8 (3)
⟨*d*S–C⟩/Å			1.79 (0)	1.79 (0)	1.771 (8)	1.79 (1)

the complexes by NMR spectroscopy or by X-ray diffraction failed, confirming the lack of affinity of these compounds for the alkali cations. The extraction results show that the BC5S derivative is a less efficient extractant of caesium than BC6S.

In order to complete these observations, a direct comparison of the caesium extraction by the parent calix[4]arene C[4] and *p-tert*-butylthiacalix[4]arene (*p-tert*-butyl-S[4]) was undertaken in an alkaline medium so as to deprotonate the hydroxy functions and to facilitate the extraction process (Table 6). The low solubility of thiacalix[4]arene in most organic solvents led to the choice of the more soluble *p-tert*-butylthiacalix[4]arene, and the liquid–liquid extraction experiments in NPHE were carried out with a concentration of 5 × 10^{-3} M. The results obtained are in agreement with those observed with the thiacalixcrowns, and confirm the low intrinsic affinity of thiacalixarenes for the alkali cations, compared to that of calixarenes.[27]

Molecular modelling

Molecular dynamics simulations in the gas phase and in an explicit aqueous phase have been performed. The comparison of X-ray data on both BC5S and BC6S and the average structural data calculated on 1 ns of MD simulation in the gas phase on free thiacalixcrowns (Table 7) shows that the parametrization of the bonded interactions implying sulfur, although not perfect, did not justify a finer evaluation in the frame of this study.

The direct comparison of the structural parameters of the calixcrowns BC5 and BC6 and their thiacalixcrown counterparts shows that the size of the cavity defined by the sulfur bridges is definitely larger than that in calixarenes (average $S\cdots S$ distance larger than $CH_2\cdots CH_2$ by 0.48 Å). Consequently, the crown basis is considerably widened. The alkali cation complexes behave differently to those observed with BC6 and BC5. In the absence of nitrate counter-ion or water in the simulations, the sodium and potassium cations for BC5S and potassium and rubidium cations for BC6S go from one crown to the other through the aromatic cavity during the 500 ps of MD at 300 K. This mobility makes difficult the usual reasoning on the structural parameters referring to the position of the cation in the complexing crown (average cation–oxygen distance and position of the cation compared to the centre of mass of the complexing crown). The discussion will thus relate to more adequate parameters such as the distance from the cation to the mass centre of the sulfur or methylene bridges *d*M^+–CMP, and the crown size, monitored by the ⟨*d*C–O_C⟩ parameter, average distance from the crown oxygen atoms to their mass centre.

The widening of the cavity has a significant influence on the average size of the free crown. Indeed, the average ⟨*d*C–O_C⟩ distance (Fig. 3) is definitely larger for free BC6S (3.61 ± 0.64 Å in the gas phase, comparing well with X-ray data) than for BC6, whose crown is already considered to be at the "upper limit" size for caesium complexation.[21] For the caesium complexes of calixcrown-6s and 21-crown-7 derivatives showing a good complementarity for this cation, the computed ⟨*d*C–O_C⟩ parameter ranges from 3.0 to 3.2 Å.[28] This value is reached for BC6S, but BC5S is out of range with a crown definitely too small for this cation. This observation is confirmed by the examination of the position of the cation compared to the calixarene cavity (Fig. 4). Indeed, in the BC6 complexes, the cation is located in the crown, the largest cations being closer to the centre of mass of the oxygen atoms and farther from the calixarene cavity. The crown plays its role of ligand fully and the complexing properties can be related to the arrangement of the oxygen atoms around the cation. In the BC5 complexes, the crown is too small for the largest cations. These simulations refer to the structure of modelled complexes built without managing their actual formation, and the caesium and rubidium cations adopt a

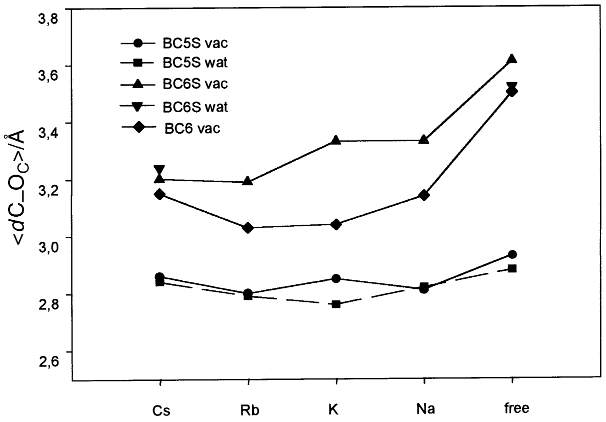


Fig. 3 Average crown size for free and complexed BC5S, BC6S and BC6 during MD simulations in gaseous and aqueous phases (fluctuations around the averages between 0.4 and 0.5 Å).

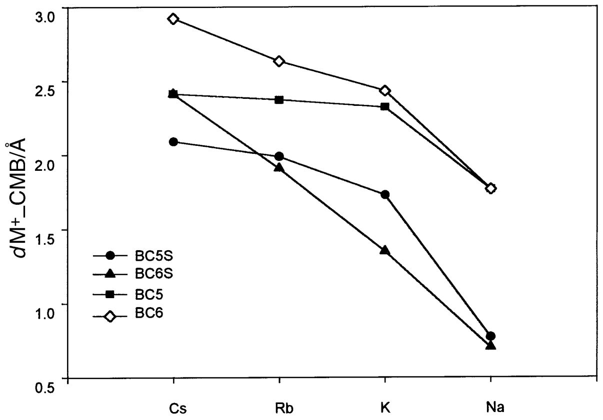
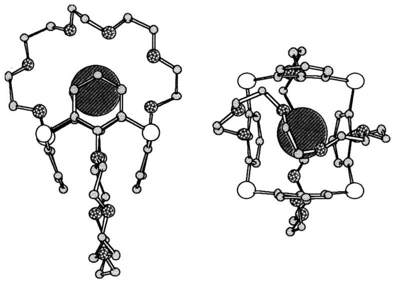
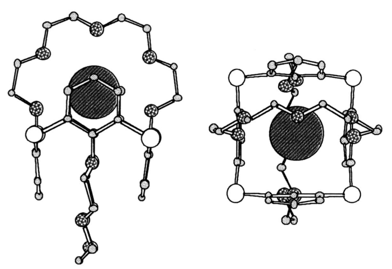


Fig. 4 Average distance between the cation and the centre of mass of the sulfur or methylene bridges (CMB) during MD simulations in the gas phase (fluctuations around the averages between 0.2 and 0.5 Å).



BC6S:Cs



BC5S:Cs

Fig. 5 Minimized structures of the BC6S and BC5S caesium complexes simulated in the gas phase (front and top views).

forced position that does not go closer than 2 Å (± 0.2 Å, with very weak fluctuations) from the calixarene cavity. Thiacalixcrowns having a broader cavity than calixcrowns, these cations naturally find their equilibrium position closer to the centre of the cavity, but also further from the centre of the crown. In the case of the BC6S caesium complex, the oxygen atoms of the crown remain in the first coordination sphere because of the great flexibility of the crown, but the caesium–oxygen distances are far from the 3.2 Å optimum. Thus, the four oxygen atoms of the crown are at an average distance ranging from 3.5 to 3.7 Å from caesium, whereas the two oxygen atoms connected to the calixarene platform are at an average distance of 3.1 Å. As soon as the size of the cation decreases, the crown is no longer adaptable and the cations move from one crown to the other, except for the sodium ion which remains in the thiacalixarene cavity without particular interaction with the crowns. This is illustrated by the spectacular fall of the dM^+–CMB parameter observed in the BC6S complexes with respect to the size of the cation.

The BC6S crown is thus much too large for the caesium cation due to the widening of the cavity. One could think that by decreasing the crown size, that is to say with compound BC5S, a correct balance could be found (Fig. 5). Thus, for the BC5S complexes, the structural parameters dM^+–CMB and $\langle dM^+–O_C\rangle$ are correct for caesium and particularly for rubidium ions, although the crown is much too rigid and small. The cation is deeply included in the cavity and shielded from the surrounding medium so that in simulations in the aqueous phase, the average number of water molecules in contact with caesium and rubidium are 0.44 and 0.70, respectively, to be compared with 0.5 and 1.0 in the case of BC5. The energy analysis (Table 8) confirms the small influence of the size of the cation on the energy of compound BC5S, and the weak interaction between the cations and BC6S. The comparison of the structural parameters obtained from molecular dynamics simulations of the alkali complexes of thiacalixcrowns and of their calixcrown counterparts, shows that the cations are located much lower in the cavity of thiacalixarene and interact less strongly with the crown. The latter does not correctly fulfil its role of ligand, even with the caesium cation. On the basis of the structural analysis of the complexes, compound BC5S seems better adapted than BC6S to complex caesium, although none of these compounds is fully satisfactory.

Table 8 Energy data from MD simulations in the gas phase

		E/kcal mol^{-1}				
		Free	Cs	Rb	K	Na
$E(\text{intra}_{\text{ligand}})^a$	BC5S	140	143	143	143	148
	BC6S	146	163	161	157	159
$E(\text{inter}_{\text{ligand/cation}})^b$	BC5S		−60	−69	−72	−81
	BC6S		−60	−64	−64	−70

[a] Fluctuation: ± 6 kcal mol^{-1}. [b] Fluctuation: ± 4 kcal mol^{-1}.

However, the extraction results show that the BC5S derivative extracts caesium ions less efficiently than BC6S. The very poor affinity of BC5S towards the four cations investigated does not follow the molecular dynamics observations based on the structural complementarity of the simulated complexes. One can conclude that the larger space provided by the thiacalixarene cavity does not compensate for its lack of chemical affinity and the inadequate size of the crown. The thiacalix[4]arene cavity thus appears badly preorganized to support an efficient crown ether bridge. Bad preorganization of the cavity has already been invoked to explain the weak performances of the calix[4]-mono(crown-6) in the cone conformation which do not extract the alkali cations, although the crown itself shows good complementarity for caesium ions.[29]

Conclusion

This study was performed at both experimental and theoretical levels to evaluate the affinity of new compounds of the thiacalixarene family with respect to alkali metal ions and their potential for the extraction of caesium ions from radioactive wastes. The experimental investigations confirmed that thiacalixcrowns are less interesting than calixcrowns for the extraction of these ions. In agreement with crystal structures, molecular dynamics simulations showed that the thiacalix[4]arene cavity side was approximately 0.5 Å larger than that of calix[4]arene. Molecular modelling simulations have given some insight into the structure of the hypothetical alkali complexes. They have shown that the cations are located close to the thiacalixarene cavity, with the possibility of migration through the latter, and that the crown does not correctly fulfil its role of ligand. The comparison of calixcrown with thiacalixcrown, both in the 1,3-alternate conformation, evidences the importance of the size of the calixarene cavity and confirms that it is a key parameter in the remarkable affinity of these molecules for caesium ions, because of the preorganization of the crown it induces.

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