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Pierre Thuéry[a]; Martine Nierlich[a]; Véronique Lamare[b]; Jean-François Dozol[b]; Zouhair Asfari[c]; Jacques Vicens[c]
[a] CEA/Saclay, SCM (CNRS URA 331), Gif-sur-Yvette, France [b] CEA/Cadarache, SEP/LPTE, Saint-Paul-lez-Durance, France [c] ECPM, Laboratoire de Chimie des Interactions Moléculaires Spécifiques (CNRS URA 405),

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Potassium and Sodium Complexes of 1,3-calix[4]-*bis*-crown-6: Crystal and Molecular Structures, ^{1}H-NMR Investigation and Molecular Dynamics Simulation

PIERRE THUÉRY[a]*, MARTINE NIERLICH[a], VÉRONIQUE LAMARE[b], JEAN-FRANÇOIS DOZOL[b], ZOUHAIR ASFARI[c], and JACQUES VICENS[c]

[a]*CEA/Saclay, SCM (CNRS URA 331), Bât. 125, 91191 Gif-sur-Yvette, France*
[b]*CEA/Cadarache, SEP/LPTE, 13108 Saint-Paul-lez-Durance, France*
[c]*ECPM, Laboratoire de Chimie des Interactions Moléculaires Spécifiques (CNRS URA 405)*

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The crystal structures of two alkali metal complexes involving the ditopic receptor 1,3-calix[4]-*bis*-crown-6, **Bis-C6**, are reported. K**Bis-C6**(NO_3)·2CH_3CN (1) crystallizes in the monoclinic space group $C2/c$: a = 18.025(8), b = 17.672(9), c = 17.454(13) Å, β = 97.55(5)°, V = 5511(9) Å^3, Z = 4. Refinement led to a final conventional R value of 0.091 for 1563 reflections. The structure of (1) is isomorphous to those previously observed for the free ligand and some of its mono- and binuclear cesium complexes: the conformation of the ligand is the same in all cases, which results in nearly identical packings and cell parameters. The potassium ion is bonded to the six oxygen atoms of the crown-ether and two from nitrate ions. Na_2**Bis-C6**$(NO_3)_2(H_2O)_2$·CH_3CN (2) crystallizes in the monoclinic space group $P2_1/c$: a = 13.487(6), b = 16.758(9), c = 23.542(15) Å, β = 101.17(4)°, V = 5220(8) Å^3, Z = 4. Refinement led to a final conventional R factor of 0.14 for 2546 reflections. One sodium ion and one water molecule are included in each crown-ether moiety. The sodium ion is bonded to three oxygen atoms of the crown only, two from nitrate ions and the one of the water molecule, which also forms possible hydrogen bonds with two ether oxygen atoms. ^{1}H-NMR experiments show that 1:1 potassium or sodium complexes are formed in chloroform solution from picrate salts, they also confirm the bonding mode observed in the solid state, with no evidence of π-interactions between the cations and the aromatic rings. Molecular dynamics simulations were performed *in vacuo* and in an explicit water phase on **Bis-C6**/$NaNO_3$ mono- and binuclear complexes to study the influence of the nitrate counter-ion on the structural features of these complexes.

INTRODUCTION

The interest in the ditopic receptor 1,3-calix[4]-*bis*-crown-6, **Bis-C6**, represented in scheme 1, for cesium complexation has recently been demonstrated.[1–4] The high selectivity observed for

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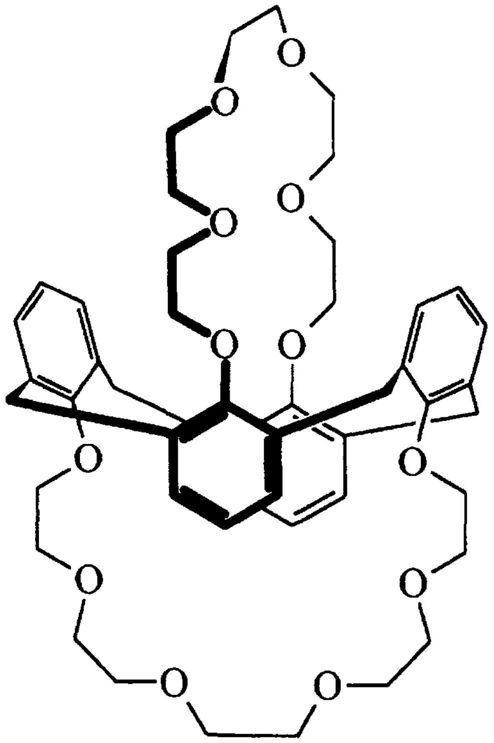
*Corresponding author



SCHEME 1 1,3-Calix[4]-*bis*-crown-6 (**Bis-C6**).

this ion in the presence of sodium, in a nitrate medium, makes **Bis-C6** a potentially useful molecule for removal of cesium ions at trace level concentration from medium-level radioactive waste by supported liquid membrane techniques.[1,2] The crystal structures determined so far[3,4] for free **Bis-C6** and some of its mono- and binuclear cesium complexes indicate that this selectivity could be due to the cation/ligand structural complementarity and the preorganization of **Bis-C6** for the complexation of $CsNO_3$ (where NO_3^- acts as a bidentate ion). In order to investigate further the complexing properties of this ligand towards alkali metal ions and the corresponding conformation modifications of the crown-ether chains, we have determined the crystal structures of its sodium and potassium complexes, with nitrate counter-ions, from single-crystal X-ray diffraction data. The complexing properties of simple crown-ethers towards alkali metal ions have been the subject of intensive work some years ago, primarily as models for the ion-carrier properties of antibiotics (see, for example.[5,6]) The ^1H-NMR investigation of the compounds under study is also reported as well as some molecular dynamics simulations. In recent years, there has been great interest in molecular modeling of calix[4]arenes and their cationic complexes in a solvent phase[7–9] and at a water-chloroform interface.[10,11] In a preceding paper, we have reported calculations on some sodium and cesium *bis*-crown complexes in water without counter-ion.[12] In this paper, we report a new set of simulations *in vacuo* and in water on mono- and binuclear sodium complexes in order to determine what are the most stable structures with the nitrate counter-ion.

EXPERIMENTAL

Synthesis

The ligand calix[4]-*bis*-crown-6 or **Bis-C6** was prepared as described elsewhere.[1] The reaction at room temperature between KNO_3 (0.35 mmole) and **Bis-C6** (0.25 mmole) in acetonitrile (2 mL), followed by filtration of unreacted KNO_3 and slow evaporation of the solution, yields colourless single crystals of (**1**) suitable for X-ray crystallography.

Single-crystals of (**2**) were obtained from the reaction at 60°C during 24 hours, under ambient atmosphere, between $NaNO_3$ (large excess: 40 mmoles) and **Bis-C6** (0.25 mmole) in an equimolar acetonitrile/chloroform solution (10 mL), followed by filtration of unreacted $NaNO_3$ and slow evaporation of the solution. In spite of repeated attempts, we did not manage to obtain high quality crystals. It must be noted that no reaction occurs at room temperature, at variance with the cesium and potassium cases.

Crystal Data

The diffraction experiments were performed with an Enraf-Nonius CAD4 diffractometer using Mo*K*α radiation. Crystals of both compounds were introduced in glass capillaries. The lattice parameters were determined from the least-squares refinement of the setting angles of 25 reflections ($8 < \theta < 12°$). The data were collected in the range $1 < \theta < 20°$ (very few reflections being measured above 20°), in the ω/θ scan mode, at 295 K for (**1**) and 243 K for (**2**). The intensity decay was estimated from three standard reflections, measured every 60 mn (not significant for both compounds). The data were corrected for Lorentz-polarization effects. No absorption corrections were made.

Both structures were solved by direct methods with SHELXS-86[13] and refined by full-matrix least-squares on *F*. Hydrogen atoms were located at their ideal positions (C-H 0.95 Å, *B* 6 Å^2) and constrained to ride on their parent carbon atom. Analytical scattering factors for neutral atoms[14] were corrected for the anomalous dispersion terms $\Delta f'$ and $\Delta f''$. All calculations have been performed on a Vax 4000-200 computer, with the Enraf-Nonius MolEN system.[15]

K**Bis-C6**$(NO_3)2CH_3CN$ (**1**)

$KC_{52}N_3O_{15}H_{66}$, formula weight: 1012.22. Monoclinic, space group $C2/c$, $a = 18.025(8)$, $b = 17.672(9)$, $c = 17.454(13)$ Å, $\beta = 97.55(5)°$, $V = 5511(9)$ Å^3, $Z = 4$, $D_x = 1.220$, $\mu = 1.57$ cm^{-1}. Crystal size: 0.85 × 0.65 × 0.65 mm^3. 1563 observations with $I > 3\sigma(I)$, out of 2564 unique reflections measured, were used. 203 parameters were refined (anisotropic displacement parameters for potassium and oxygen atoms). An occupation factor of 0.5, corresponding to the 1:1 potassium/ligand stoichiometry, was given to the KNO_3 moiety, so as to be in agreement with the stoichiometry used during the synthesis and to obtain physically acceptable displacement parameters. The resulting *R* factor is about 0.02 higher when the 2:1 stoichiometry is assumed. However, some deviation from the 1:1 stoichiometry cannot be excluded. The final *R* values were $R = 0.091$ and $R_w = 0.12$ ($w = 1/\sigma^2(F)$) and the maximum residual density 0.59 eÅ^{-3}.

Na_2**Bis-C6**$(NO_3)_2(H_2O)_2.CH_3CN$ (**2**)

$Na_2C_{50}N_3O_{20}H_{67}$, formula weight: 1076.08. Monoclinic, space group $P2_1/c$, $a = 13.487(6)$, $b = 16.758(9)$, $c = 23.542(15)$ Å, $\beta = 101.17(4)°$, $V = 5220(8)$ Å^3, $Z = 4$, $D_x = 1.369$, $\mu = 1.12$ cm^{-1}. Crystal size: 0.90 × 0.60 × 0.60 mm^3. 2546 observations with $I > 2\ \sigma(I)$, out of 4848 unique reflections measured, were used. 399 parameters were refined (anisotropic displacement parameters for sodium and oxygen atoms). The solvent molecule was found, then fixed in the refinements. The final *R* values were $R = 0.14$ and $R_w = 0.17$ ($w = 1/\sigma^2(F)$) and the maximum residual density 0.92 eÅ^{-3}. In spite of the low temperature used for data recording, the poor quality of the crystals and the high thermal motion of some parts of the molecule (the nitrate ions in particular, that were not resolved at ambient temperature) did not give a perfectly satisfying structure determination. However, the main characteristics of the structure are well established: in particular, the 2:1 sodium/ligand stoichiometry is confirmed by the higher *R* factors when occupation factors of 0.5 are assigned to the $NaNO_3$ groups ($R = 0.18$).

^{1}H-NMR Experiments

^{1}H-NMR spectra were measured on a Bruker SY200 instrument. In order to obtain spectra of complexes with the sodium and potassium picrates, the solid picrates were stirred with a solution of **Bis-C6** (~10^{-2} mol.L^{-1}) in $CDCl_3$ until equilibrium appeared to be achieved.

Computational Methods

All Molecular Dynamics calculations were carried out with the AMBER 4.0 software[16] on a SG INDIGO 2 R8000 workstation. We used the all-atom parameters and the following representation of the potential energy:[17]

$$E_{pot}=\sum_{bonds}K_r(r-r_{eq})^2+\sum_{angles}K_\theta(\theta-\theta_{eq})^2+\sum_{dihedrals}\frac{Vn}{2}(1+\cos(n\varphi-\eta))+$$

$$\sum_{i<j}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12}-\left(\frac{R^*}{R_{ij}}\right)^{6}\right)\right]+\sum_{i<j}\left[\frac{q_iq_j}{\varepsilon R_{ij}}\right]+$$

$$\sum_{H\text{-}bonds}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12}-\left(\frac{R^*}{R_{ij}}\right)^{10}\right)\right]$$

The atomic charges on **Bis-C6** were calculated with the MNDO semi-empirical method and scaled up with a 1.26 scaling factor to allow a good fit with 6-31G*/ESP values commonly used for crown-ether moieties.[18] The ion parameters came from Aqvist[19] and were adapted to the AMBER force field (TIP3P water and periodic boundary conditions). The 1–4 non bonded contributions were scaled down by a factor of 0.5. Parameters for the nitrate ion were taken from reference[20].

Structures (**3**) and (**4**) are derived from the X-ray structure of the binuclear complex (**2**), Na_2**Bis-C6**$(NO_3)_2(H_2O)_2$, from which we have eliminated both water molecules (**3**), or generated a mononuclear complex by eliminating one $NaNO_3H_2O$ moiety (**4**). Structure (**5**) is a mononuclear complex built with SYBYL[21] and minimized *in vacuo* without nitrate and water. Structure (**6**) is the equilibrated aqua structure obtained from (**5**) by MD in water.[12] For both structures (**5**) and (**6**), sodium is located in the calixarene cavity. We have further added to both those structures one nitrate counter-ion as closely as possible to the cation, giving structures (**5′**) and (**6′**).

All these sodium complexes with nitrate counter-ions were minimized, then submitted to 100 ps of Molecular Dynamics (MD) at 300 K *in vacuo* with a time step of 1.0 fs, a dielectric constant of 1.0 and a residue-based cut-off set at 10 Å. The trajectories were visualized by the MD/DRAW software and analyzed by the MDS software[22]. Unless otherwise specified in Table III, the first five picoseconds, corresponding to the equilibration of the systems, were not taken into account in the analysis and averages were calculated over 95 ps of MD run.

In water, the Molecular Dynamics simulations used a time step of 2.0 fs, and a 12 Å cut-off. The SHAKE procedure[23] 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 a temperature and pressure bath. All the starting structures were immersed in a TIP3P cubic box, removing water molecules within 2 Å of the solute. These systems were energy minimized and submitted to at least 100 ps of Molecular Dynamics (100 ps of MD in water took approximately 24 CPU hours). Averages were calculated on equilibrated systems (no more structural or solvation changes). In the energy analysis, we separated the contribution due to complexed water (hydration water, labelled *hyd* in Table IV) from the contribution due to bulk water around the complex.

DISCUSSION

Crystal Structures

ORTEPII[24] drawings of the molecular units of (**1**) and (**2**) are represented in Figures 1 and 2, selected bond lengths and angles given in Table I and selected torsion angles in Table II.

Compound (**1**) crystallizes in the same space group ($C2/c$) as the previously reported compounds **Bis-C6**$\cdot 4CH_3CN$ (**7**), Cs**Bis-C6**$(NO_3)\cdot 2CH_3CN$ (**8**) and Cs_2**Bis-C6**$(NO_3)_2\cdot 2CH_3CN$ (**9**)[4], and with cell parameters only slightly, but significantly, different from those of these compounds. Not surprisingly, the crown-ether conformation is identical in (**1**) and in (**7**), (**8**) and (**9**), *i.e.* $g^+g^-g^+g^-g^+$ in the notation of Fyles and Gandour[25] for the O-C-C-O torsion angles. The potassium ion, disordered on the two coordination sites, is unequally bonded to the six crown-

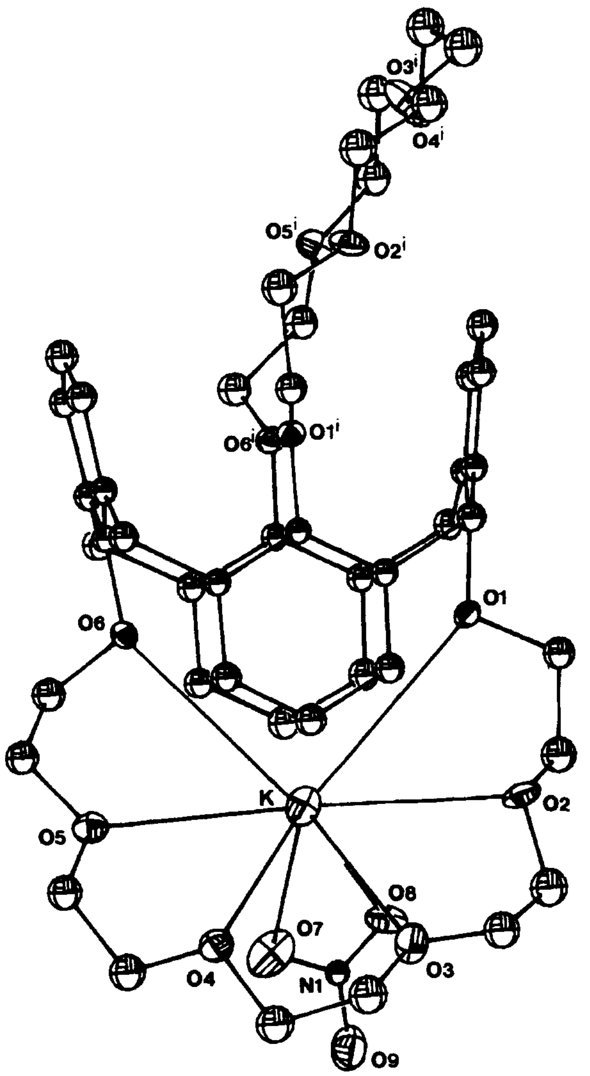


FIGURE 1 Molecular unit of KBis-C6(NO_3)2CH_3CN(**1**), $i = -x, y, ½-2$. Solvent molecules omitted.

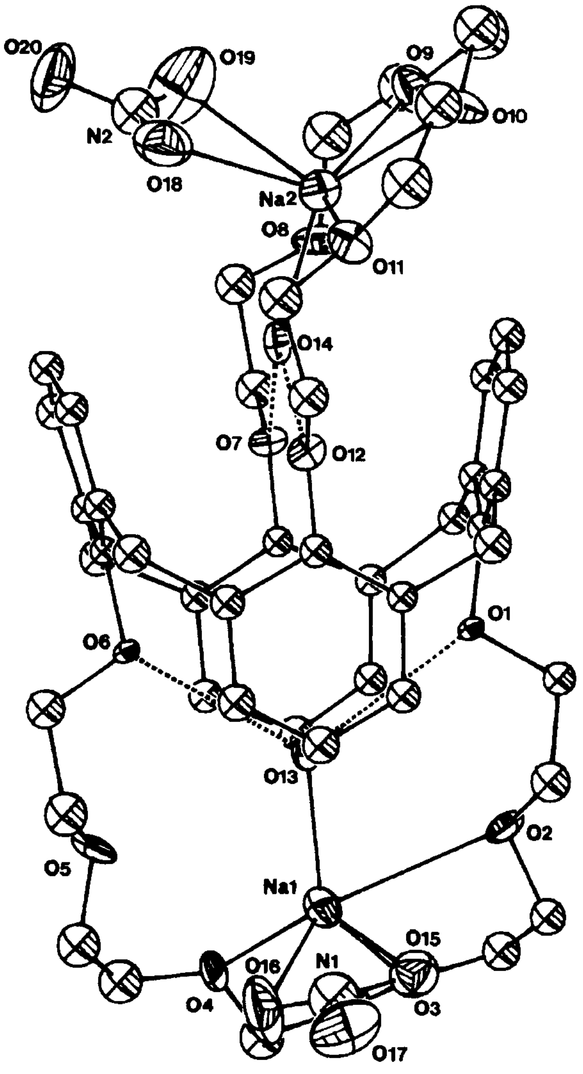


FIGURE 2 Molecular unit of Na_2Bis-C6$(NO_3)_2(H_2O)_2 \cdot CH_3CN$ (**2**). Possible hydrogen bonds in dashed lines. Solvent molecule omitted.

ether oxygen atoms, with distances ranging from 3.068(9) to 3.672(8) Å (mean value 3.20(9) for the four shorter ones (with O(2), O(3), O(4) and O(5)) and 3.63(6) for the two longer (with O(1) and O(5)): the potassium ion is thus displaced towards the crown-ether extremity with respect to the position of the cesium ions in (**8**) and (**9**). The nitrate ion is bidentate, as in (**8**) and (**9**), with K-O distances of 2.57(2) and 2.77(2) Å, slightly lower than that observed for the monodentate nitrate ion in the potassium/dibenzo-18-crown-6 inclusion complex.[26] The six ether oxygen atoms are in a plane within ±0.31(1) Å, the potassium ion being at 0.831(5) Å from this mean plane.

The potassium-ether oxygen distances are significantly higher than the sum of the ionic and van der Waals radii (2.73 Å) and higher than the largest coordination distances estimated by

TABLE I Selected bond lengths (Å) and angles (°) in compounds (**1**) and (**2**) (bond lengths and angles of the macrocycles do not deviate from the usual ones)

Compound (**1**)			
K-O(1)	3.672(8)	K-O(2)	3.230(9)
K-O(3)	3.068(9)	K-O(4)	3.280(9)
K-O(5)	3.209(9)	K-O(6)	3.582(8)
K-O(7)	2.57(2)	K-O(8)	2.77(2)
K...C(13)	3.50(1)	K...C(14)	3.05(1)
K...C(15)	3.45(1)	K...C(21)	3.98(1)
K...C(22)	3.56(1)	K...C(23)	3.85(1)
Compound (**2**)			
Na(1)...O(1)	4.40(1)	Na(2)...O(7)	4.43(1)
Na(1)-O(2)	2.86(2)	Na(2)...O(8)	3.23(2)
Na(1)-O(3)	2.44(2)	Na(2)-O(9)	2.46(2)
Na(1)-O(4)	2.49(2)	Na(2)-O(10)	2.55(2)
Na(1)...O(5)	3.30(2)	Na(2)-O(11)	2.54(2)
Na(1)...O(6)	4.54(2)	Na(2)...O(12)	4.21(2)
Na(1)-O(13)	2.24(2)	Na(2)-O(14)	2.18(2)
Na(1)-O(15)	2.55(2)	Na(2)-O(18)	2.48(3)
Na(1)-O(16)	2.38(3)	Na(2)-O(19)	2.54(3)
O(13)...O(1)	2.88(2)	O(14)...O(7)	2.82(2)
O(13)...O(6)	2.89(2)	O(14)...O(12)	2.84(2)
O(1)...O(13)...O(6)	114.5(5)	O(7)...O(14)-Na(2)	123.9(7)
O(6)...O(13)-Na(1)	124.1(5)	O(7)...O(14)...O(12)	118.6(6)
O(1)...O(13)-Na(1)	118.0(5)	O(12)...O(14)-Na(2)	112.9(6)

TABLE II Successive torsion angles (°) of the crown-ether chains in compounds (**1**) and (**2**). C_{calix} indicates the carbon atoms of the calixarene unit. For compound (**2**), crown 1 corresponds to Na(1), crown 2 to Na(2)

	Compound(**1**)	Compound (**2**)	
		crown 1	crown 2
$C2_{calix}$-$C1_{calix}$-O-C	–90(1)	–89(2)	–91(2)
$C3_{calix}$-$C1_{calix}$-O-C	90(1)	93(2)	92(2)
$C1_{calix}$-O-C-C	–178(1)	170(1)	175(1)
O-C-C-O	–62(1)	72(2)	71(2)
C-C-O-C	–158(1)	138(2)	154(2)
C-O-C-C	–176(1)	–173(1)	171(2)
O-C-C-O	68(1)	–70(2)	–57(3)
C-C-O-C	171(1)	176(1)	–174(2)
C-O-C-C	–168(1)	178(1)	168(2)
O-C-C-O	–68(1)	51(2)	43(3)
C-C-O-C	177(1)	167(2)	–168(2)
C-O-C-C	178(1)	155(2)	172(2)
O-C-C-O	67(1)	53(3)	–38(3)
C-C-O-C	172(1)	–169(2)	–152(2)
C-O-C-C	–177(1)	–156(2)	–101(2)
O-C-C-O	–71(1)	–68(2)	–69(2)
C-C-O-$C4_{calix}$	–120(1)	–177(1)	–169(1)
C-O-$C4_{calix}$-$C5_{calix}$	–68(1)	–95(2)	–88(2)
C-O-$C4_{calix}$-$C6_{calix}$	112(1)	83(2)	87(2)

Kasuga *et al.*[27] for eight-coordination (3.05 Å). The present values are also higher than those determined for potassium ions complexed by calix[4]crown-5 derivatives (2.76(1) to 2.87(1) (mean value 2.81(4)) Å or 2.748(8) to 3.01(1) (mean value 2.87(12)) Å, depending on the macrocycle conformation)[28] or crown ethers: 2.73 to 2.98 (mean value 2.85(8)) Å for five-coordination (mononuclear complex with benzo-15-crown-5[5e], binuclear complex with dibenzo-24-crown-8[5g]), 2.71 to 2.83 (mean value 2.76(4)) Å for six[6c,26], 2.77 to 3.07 (mean value not available) Å for seven.[29] The size of the crown cavities in **Bis-C6** is larger than in 18-crown-6 due to the presence of the calixarene moiety: it corresponds roughly to the cavity size in 21-crown-7 (the O(1)...O(6) distance is about 4.9 Å in the complexes investigated, comparable with the distance between O(j) and O(j + 2) in the crowns), but the rigidity induced by the calixarene prevents an optimal binding to the cation. The potassium ion is located at a mean distance of 3.6(3) Å from the six terminal carbon atoms of the two nearer aromatic rings, comparable with potassium-aromatic ring distances already published (3.27 to 4.30 Å)[5g,26].

The molecular unit of compound (**2**) does not possess any symmetry element. The space group and cell parameters are different from those of compounds (**1**), (**7**), (**8**) and (**9**). Both crown-ether conformations are different from the free **Bis-C6** one: the O-C-C-O torsion angles correspond to the sequence $g^+g^-g^+g^-$ for crown 1 and $g^+g^-g^+g^-g^-$ for crown 2, some C-O-C-C angles being rather far from the ideal *anti* value of 180°. A particular feature of this structure is that both a sodium ion and a water molecule (O(13) and O(14)) are included in each crown-ether moiety. The sodium ions are bonded to three oxygen atoms from the crown-ether chains, with distances ranging from

2.44(2) to 2.86(2) (mean value 2.6(1)) Å, two from the nitrate ions, with distances ranging from 2.38(3) to 2.55(2) (mean value 2.49(8)) Å, and one from the water molecules, with distances of 2.18(2) and 2.24(2) Å. These sodium-water distances are slightly lower than those reported in the literature, which range from 2.27 to 2.35 (mean value 2.31(3)) Å[5b,d,f,6b]. The sodium ion is thus far more displaced towards the outer part of the crown-ether chain than the potassium ion in (**1**) with respect to the central position of cesium in (**8**,**9**), which enables the penetration of a water molecule in the same cavity. Each water molecule forms possible hydrogen bonds with two of the ether oxygen atoms bonded to the calixarene unit, with contacts between 2.82(2) and 2.89(2) (mean value 2.86(3)) Å. The six oxygen atoms of each crown are in a plane within ±0.26(1) and 0.44(1) Å respectively, the sodium ions being at 1.05(1) and 0.82(1) Å and the water molecules at 0.63(1) and 0.54(1) Å, on the same side of these mean planes.

In the sodium/crown-ether complexes already reported, the Na-O distances depend upon the cavity size and flexibility. The smaller distances are obtained for the benzo-15-crown-5 complex, in which they range from 2.35 to 2.43 (mean value 2.39(3)) Å[5b,d]. In the complexes formed with dibenzo-18-crown-6[5a,b,c] and dicyclohexano-18-crown-6[5f], the Na-O distances are larger, since they range from 2.63 to 2.89 (mean value 2.74(9)) Å and from 2.68 to 2.97 (mean value 2.8(2)) Å respectively. In the case of 18-crown-6, they range from 2.45 to 2.62 (mean value 2.55(7)) Å: in this case, the flexibility of the ligand enables a partial folding around the cation[6b]. The sodium-oxygen distances in (**2**) are also slightly lower than those determined in the case of tetranactin and nonactin ether oxygen atoms (between about 2.77 and 2.83 Å).[30] In spite of a quite different structure, those distances are comparable to the ones found in the case of *p-tert*-butylcalix[4]arene bridged in 1,3 positions by a *m*-teranisyl chain (2.38 to 2.60 (mean value 2.5(1)) Å.[31]

^{1}H-NMR Experiments

The room temperature ^{1}H-NMR spectrum of **Bis-6** in $CDCl_3$, shown in Figure 3a indicates that the crown-ether chains are conformationally labile on the NMR time-scale and that **Bis-C6** may be regarded as having effective D_{2h} symmetry due to the presence of only one triplet at 6.86 ppm ($J_{H\text{-}H}$ = 7.6 Hz) and one doublet at 7.09 ppm ($J_{H\text{-}H}$ = 7.6 Hz) for the respective *para* and *meta* protons of the phenolic residues. The metal:ligand ratio in solution, as estimated by integration of the picrate proton resonances *versus* those of the aromatic protons, is 1:1 for both potassium and sodium complexes, after 96 hours of reaction between the solid picrates and a chloroform solution of **Bis-C6**. The running of NMR spectra for longer times leads to the same stoichiometry. For both metal ions, the marked changes in polyether methylene resonances (Figure 3b, c) indicate the formation of an endocyclic bonding to crown-ether chains in agreement with the crystalline structures. The negligible changes observed for the aromatic triplet and doubler indicate that the metal cations prefer to be coordinated with the oxygen donor atoms of the crown-ether loop with probably no π–interactions with the aromatic rings: they can be better explained by a slight conformation change of the molecular structure. The slight coalescence observed at the level of the aromatic triplet in the 1:1 sodium/**Bis-C6** complex may indicate that this complex is less stable than the potassium one, due to a possible metal-ligand exchange.

Molecular Dynamics Simulations

We have previously reported calculations on some sodium and cesium bis-crown complexes in water without a counter-ion.[12] These simulations clearly indicated the possibility for one water molecule to be located in the mean plane of the complexing crown in sodium complexes. But the initial structure of the simulation being a mono-

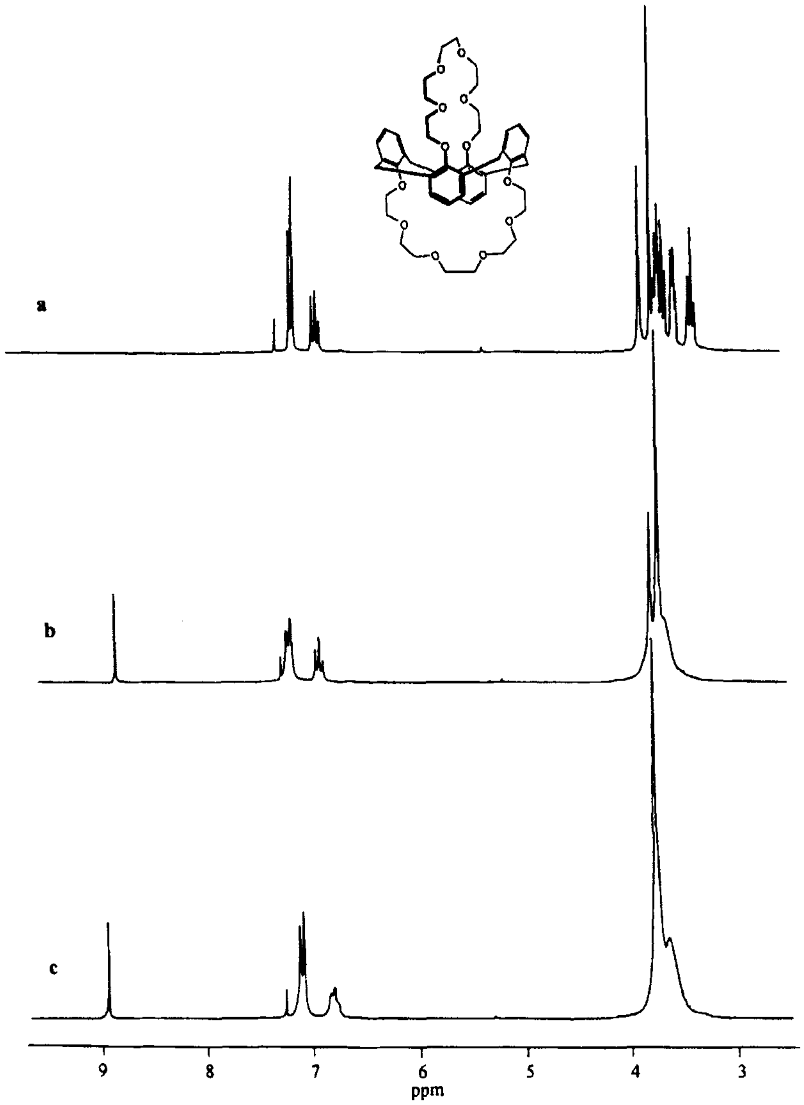


FIGURE 3 200 MHz ^{1}H-NMR spectra, in $CDCl_3$ and at room temperature, of: (a) the free ligand **Bis-C6**; (b) the 1:1 complex K^+Pic^-: **Bis-C6**; (c) the 1:1 complex Na^+Pic^-: **Bis-C6** (Pic^- = picrate anion).

nuclear complex minimized *in vacuo*, the water molecule entered the crown above the cation, which was located in the calixarene cavity (Figure 4, structures (**5**) and (**6**)). These results depend on the force field used in the MD simulations: Wipff *et al.*, working on the *1,3-alternate* dimethoxy-calix[4]arene-crown-6 with Aqvist cations but a less polarized set of charges for the calixarene cavity[8] have shown that the sodium complex is not stable in water and the sodium ion decomplexes after a 50 ps MD run in water.

Counter-ion effects on the structure and stability of cationic macrocyclic complexes are difficult to study by simulation in a water phase due to the frequent separation of the ion pair.[8,10,20] We have suggested that, whatever the force field used, the structures of the sodium complexes ought to be different in the presence of a counter-ion, due to

TABLE III Structural and energetic data for 100 ps MD simulations on sodium complexes at 300 K *in vacuo*

	mononuclear complexes			binuclear complexes		
	4	**5′**	**6′**	2	**3**	X-ray*
dNa_1-O_w	2.34(8)	–	2.35(9)	2.36(10)	–	2.24
$<dNa_1$-$O_C>$	3.45(77)	3.45(48)	3.44(76)	3.46(85)	3.42(47)	3.34(85)
$dNa_1...MC_1$	1.32(21)	1.23(27)	1.47(22)	1.47(23)	1.22(33)	1.37
dNa_2-Ow	–	–	–	2.36(12)	–	2.18
$<dNa_2$-$O_C>$	–	–	–	3.45(81)	3.39(62)	3.23(81)
$dNa_2...MC_2$	–	–	–	1.46(23)	1.22(30)	1.11
E_{inter}^{Na/NO_3}	–489(8)	–489(8)	–485(28)	–974(32)	–1141(138)	
E_{inter}^{Na/H_2O}	–96(4)		–96(8)	–167(8)	–	
$E_{inter}^{Na/ligand}$	–213(12)	–230(52)	–226(32)	–472(24)	–472(72)	
$E_{inter}^{Na/Na}$	–	–	–	42(60)	142(58)	

* distances (Å) measured on the X-ray structure of compound (**2**). In other columns, averages calculated over the entire MD run after equilibration of the complex (5ps, except simulation from structure (**5′**): 15ps).
MC: mass centre of the crown oxygen atoms.
<dNa-Oc>: mean value of the 6 single cation-crown oxygen atoms distances.
(): fluctuation.
E_{inter}: interaction energy (kJ).

the lack of complementarity between the cation and the crown-6 ligand and to the dominant electrostatic interactions between the cation and the nitrate counter-ion.[12,32] Such a counter-ion influence has been reported in simulations of M^+pic^- complexes with **Bis-C6** in pure chloroform where the 'pulling' effect due to the picrate anion has been observed in the sodium complex.[9]

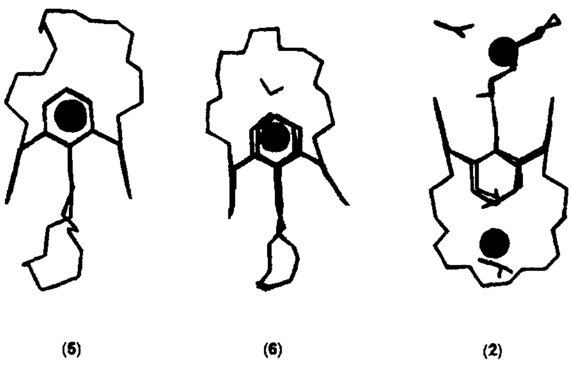

(**5**) (**6**) (**2**)

FIGURE 4 Structures of sodium complexes (**5**) and (**6**) used as starting points for the simulations *in vacuo* (nitrate ions further added to give (**5′**) and (**6′**); (**2**): structure derived from X-ray diffraction data. Hydrogen atoms of the ligand are not represented.

The NMR and X-ray structural data described above show that, in a non-dissociating solvent, the sodium ion is in interaction with its counter-ion in the part of the crown opposite to the calixarene unit. The crystalline structure of the binuclear complex (**2**), crystallized in a non water-free chloroform/acetonitrile mixture, is evidence for the presence of water molecules in the mean plane of the crown in interaction with the sodium ions. But, compared to the simulations performed without counter-ion, the water molecules are located 'under' the cation, due to the dominant sodium/nitrate interactions. The initial position of the sodium in the crown, which depends on whether the counter-ion is taken into account in the model, has an influence on the final structure of aqua complexes. So we started our simulations *in vacuo* from structures (**5′**) and (**6′**), first minimized without nitrate, with further addition of nitrate counter-ions, or from structures (**3**) and (**4**) derived from the crystalline structure of (**2**).

TABLE IV Structural and energetic data for MD simulations on sodium complexes at 300 K in a water box. Averages calculated after equilibration of the complex (see text)

	binuclear (**3**) non minimized	mononuclear (**6′**) after minimization
$<dNa_1\text{-}O_c>$	3.32(81)	3.16(62)
$dNa_1...MC_1$	1.19(24)	0.86(30)
E_{inter}^{Na/NO_3}	–443(20)	–443(20)
$E_{inter}^{Na/ligand}$	–242(16)	–272(36)
$E_{inter}^{Na/H_2O\ hyd}$	–92(12)	17(4)
$E_{inter}^{Na/H_2O\ bulk}$	46(28)	46(28)
$E_{inter}^{ligand/H_2O\ hyd}$	–33(12)	–71(16)

MC: mass centre of the crown oxygen atoms.
<dNa-Oc>: mean value of the 6 single cation-crown oxygen atoms distances.
(): fluctuation.
E_{inter}: interaction energy (kJ).

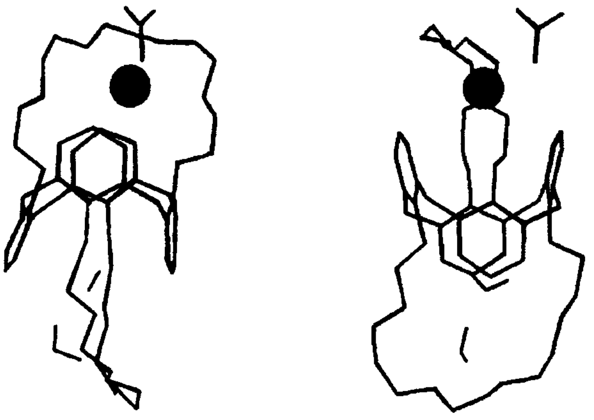


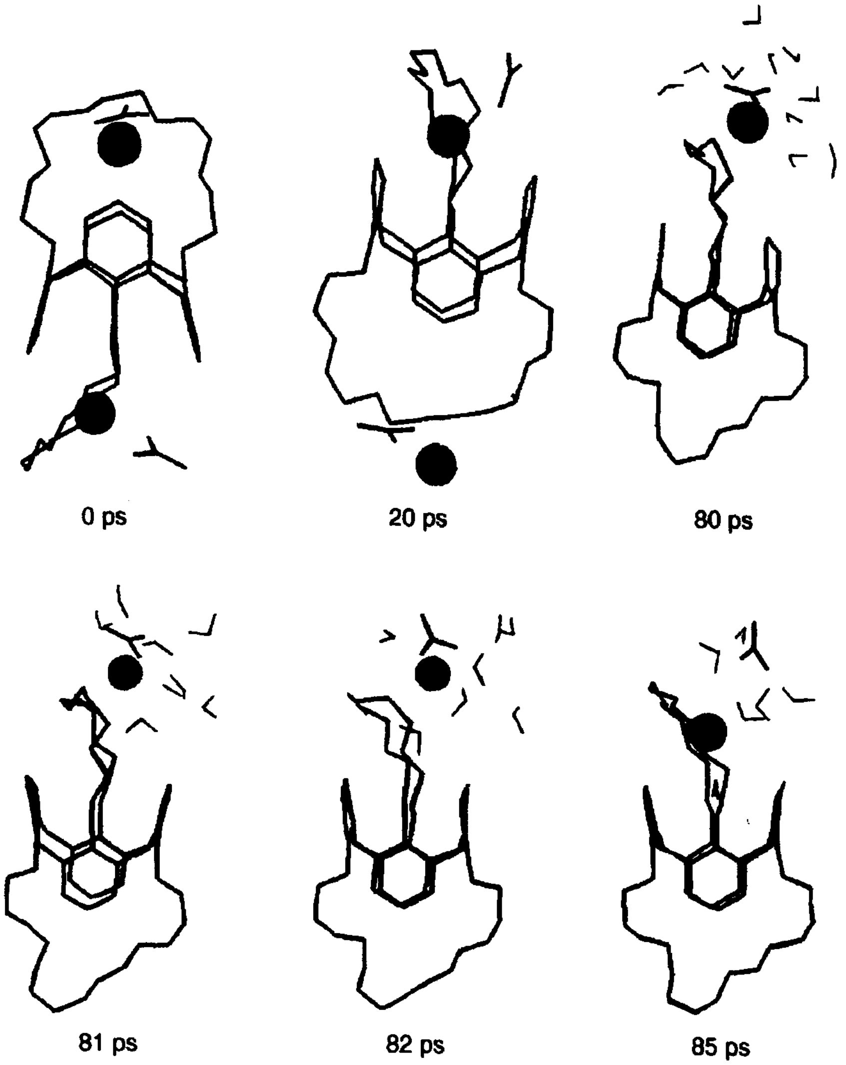
FIGURE 5 Mononuclear structure equilibrated in water, starting from (5′). Snapshot at 200 ps of MD. Orthogonal views. Visualization of water molecules within 5 Å of the complex mass centre. Hydrogen atoms of the ligand are not represented.

Simulations in vacuo

The averages calculated after equilibration of the five systems are reported in Table III. During all the simulations, the nitrate counter-ions remained bidentate. We have made the hypothesis that simulations starting from structures (**2**), (**4**) and (**6′**) with the counter-ion *in vacuo* can roughly model the behaviour of the sodium complex in a non-dissociating solvent that contains small amounts of water. Since the first minimization of structures (**2**) and (**4**), the water molecules reoriented towards the cation, to optimize the $Na...O_w$ interactions. It is worth noticing that, after 15 ps of MD, structure (**6′**) rearranged into structure (**4**): Na^+ moved towards the top of the crown and subsequently, the water molecule moved to go under the cation. At the beginning of the MD run starting from structure (**5′**), we could also see a rapid movement of the cation towards the top of the crown. In summary, whatever the initial position of the cation or the water molecules, the structural averages collected from the 100 ps MD run at 300 K did not show significant differences between the mononuclear and the binuclear complexes. The energy analysis showed that structure (**3**) (binuclear complex without water), is not favoured due to the cation-cation repulsion energy of 142 kJ. In a water free solvent, the mononuclear complex must be the most probable structure. The simulation *in vacuo* starting from structure (**2**) showed that water acts as a buffer between both cations, diminishing the cation-cation repulsion to 42 kJ. In a non-dissociating solvent with trace amounts of water, one could expect to find both mono- and binuclear complexes, with the sodium cation coordinated to a water molecule, the nature of the main species depending on the salt concentration. These results concerning the stoichiometry are consistent with those of Varnek and Wipff[9] from simulations *in vacuo* and in chloroform, which cannot preclude the formation of binuclear complexes in presence of an excess of metal salt and suggest a change in the complex nature upon the presence of trace amounts of water.

Simulations in water

We obtained different solvation schemes when starting from mononuclear or binuclear complexes. When starting from a mononuclear species minimized *in vacuo* (MD simulation from (**5′**), 1363 water molecules in the box), we observed a rapid



0 ps 20 ps 80 ps

81 ps 82 ps 85 ps

FIGURE 6 Snapshots of the structures obtained during the MD run in water starting from the non-optimized binuclear structure (3). Visualization of water molecules within 5 Å around the cation. Hydrogen atoms of the ligand are not represented.

solvation of the calixcrown, one water molecule penetrating into the calixarene cavity and another one into the free crown during the first ten picoseconds of MD. The ion pair remained intimate and we did not see any more changes for 200 ps of MD, after which we stopped the calculation. Structural and energetic averages (Table IV) were calculated between 10 and 100 ps of MD in water. What is surprising in the equilibrated structure (Figure 5) is that water does not participate in the cation stabilization: there is no first solvation peak in the radial distribution function (rdf) around Na^+, and the interaction energy between Na^+ and hydration water is slightly positive. The cation is closer from the centre of the crown and the interaction energy $E^{Na/ligand}_{inter}$ is enhanced with respect to the values *in vacuo*. This simulation afforded a very stable structure, that appears to be poorly representative of what can be found after cation complexation in a water-rich medium.

The behaviour of the molecular system was completely different starting from binuclear structures: in these cases, the presence of the second ion pair prevented a rapid solvation of the ligand. Starting from the non-optimized structure (**3**) (1234 water molecules in the box), one ion pair decomplexed after 20 ps of MD in water and did not interact any more with the other ion pair which remained complexed. We did not see any hydration of the ligand and, at 80 ps of MD, the second ion pair was decomplexed in a strong interaction with the surrounding water (three H_2O in the first solvation shell around Na^+), but still remained near the crown. Then, one of the water molecules belonging to the cation hydration shell penetrated into the crown and attracted back the cation into the ligand. At 90 ps, the ion pair, separated during the complexation, returned intimate and we obtained a stable mononuclear structure with one water molecule in the crown, 'under' the cation. The rdf curve around Na^+ showed that, in this equilibrated structure, there is only one water molecule in the cation first hydration shell. No subsequent hydration of the free crown was observed and the calculation was stopped at 150 ps of the MD run (averages were calculated between 100 and 150 ps). Snapshots from this simulation are collected in Figure 6.

Another simulation was performed in water, starting from the binuclear structure (**3**), minimized *in vacuo* (100 ps of MD). One cation went down into the calixarene cavity, pushing the second ion pair towards the higher part of the crown. At 5 ps of MD run, we could see the same phenomenon as previously described: decomplexation of the cation and further complexation due to the introduction of a water molecule in the crown. Unfortunately, we could not carry on further the study of this MD run because the separation of this ion pair occurred and we could not be sure of the real stability of the binuclear complex due to the stabilizing interactions between the free nitrate and the Na^+ which remained in the crown.

The observations during these simulations seem to be representative of the process of cation complexation: the hydrated ion pair which is near enough to the free, non hydrated ligand, is attracted into the crown after the introduction in the crown of one water molecule of the cation hydration shell. During this process, the cation loses its other coordinated water molecules. The corresponding dehydration energy (about 188 kJ for two H_2O) is compensated by the interaction energy between the cation and the ligand $E_{inter}^{Na/ligand} = -242$ kJ. A similar result has already been observed in chloride capture by the tetraprotonated cryptand SC24.[33] The originality of our result is due to the lack of structural complementarity between the ligand and Na^+, responsible for the cation complexation to be assisted by water.

CONCLUSION

Both structures reported here involve cations too small for the crown-ether cavity. In such cases, Dunitz *et al.* considered four possible structural arrangements[6a], *i.e.* *i)* the cation sits at the centre of the crown with non-optimal coordination distances, *ii)* the cation deviates from the centre, *iii)* the cation 'rattles' in the cavity and *iv)* the crown-ether changes its conformation. The structure of complex (**1**) clearly corresponds to the first solution, the one of complex (**2**) to the three others (in which the off-centre position of the sodium ions plays a prominent role), to which a new feature must be added: the completion of the coordination sphere by a co-included molecule. The sodium case can also be viewed as the complexation of the $Na(H_2O)$ moiety, whose centre occupies approximately the same location as the cesium ion in complexes (**8**) and (**9**).

The similarity between the potassium and cesium complexes suggests a lack of specificity of **Bis-C6** towards one or the other of these two ions. However, the potassium-ether oxygen atoms distances are not optimal, which suggests that the ligand/cation complementarity is less satisfying than in the cesium case, the cavity being too large. Furthermore, the interactions between cesium and the π electrons of the aromatic rings are absent with potassium, as indicated by NMR measurements (it must be noted however that potential energy calculations have recently shown that a stabilizing contribution of almost 25 kJ/mol could arise from π-interactions between K^+ and one benzene ring in the partial cone complex of 1,3-diisopropoxy-*p-tert*-butylcalix[4]arene-crown-5, with K^+...aromatic carbon distances ranging from 3.45(1) to 3.55(1) Å).[28]

The selectivity of **Bis-C6** for cesium with respect to sodium ions may be explained on the basis of the complementarity and preorganization principles, as defined by Lein and Cram.[34] The cation-oxygen atom interactions are more important with cesium than with sodium, as indicated by the variation in the ion location and the number of coordinated oxygen atoms: the cation/ligand complementarity thus appears much more important for cesium than for sodium ions. The greater difficulty to obtain the **Bis-C6**/sodium complex (see experimental part) than the cesium or potassium ones is evidence for the lower stability of the former. In the present case, the crown reorganization accompanying the complexation of two different species (sodium and water) may also contribute to the high selectivity observed in solution for cesium, even in a medium highly concentrated in sodium ions[1,2]: the formation of the cesium complex may be enhanced by the preorganization of the ligand[4] which reduces the complexation energy. It must be noted that the preorganization of this ligand not only involves the *1,3-alternate* calixarene form[35], but also a particularly well suited crown conformation.

Molecular Dynamics simulations on the **Bis-C6**/$NaNO_3$ complex have underlined the lack of affinity of **Bis-C6** towards the Na^+ cation. In MD simulations in water, water molecules are needed to form a stable complex: the water molecule coordinated to the cation and located in the crown plays an active role in the complexation mechanism.

References

[1] Asfari, Z., Bressot, C., Vicens, J., Hill, C., Dozol, J.F., Rouquette, H., Eymard, S., Lamare, V. and Tournois, B. (1995). *Anal. Chem.*, **67**, 3133.

[2] Asfari, Z., Wenger, S. and Vicens, J. (1994). *J. Incl. Phenom.* **19**, 137, Hill, C., Dozol, J.F., Lamare, V., Rouquette, H., Eymard, S., Tournois, B., Vicens, J., Asfari, Z., Bressot, C., Ungaro, R. and Casnati, A. (1994). *J. Incl. Phenom.* **19**, 399.

[3] Thuéry, P., Nierlich, M., Bressot, C., Lamare, V., Dozol, J.F., Asfari, Z. and Vicens, J. (1996). *J. Incl. Phenom.*, **23**, 305.

[4] Asfari, Z., Naumann, C., Nierlich, M., Thuéry, P., Bressot, C., Lamare, V., Dozol, J.F. and Vicens, J. (1996). *New J. Chem.*, **20**, 1183.

[5] (a) Bright, D. and Truter, M.R. (1970). *J. Chem. Soc. B*, 1544, (b) Bush, M.A. and Truter, M.R. (1970). *J. Chem. Soc. Chem. Commun.*, 1439, (c) Bush, M.A. and Truter, M.R. (1971). *J. Chem. Soc. B*, 1440, (d) Bush, M.A. and Truter, M.R. (1972). *J. Chem. Soc. Perkin Trans.* 2, 341, (e) Mallinson, P.R. and Truter, M.R. (1972). *J. Chem. Soc. Perkin Trans.* 2, 1818, (f) Mercer, M. and Truter, M.R. (1973). *J. Chem. Soc. Dalton Trans.*, 2215, (g) Mercer, M. and Truter, M.R. (1973). *J. Chem. Soc. Dalton Trans.*, 2469.

[6] (a) Dunitz, J.D., Dobler, M., Seiler, P. and Phizackerley, R.P. (1974). *Acta Crystallogr.*, **B30**, 2733, (b) Dobler, M., Dunitz, J.D. and Seiler, P. (1974). *Acta Crystallogr.* **B30**, 2741, (c) Seiler, P., Dobler, M. and Dunitz, J.D. (1974). *Acta Crystallogr.*, **B30**, 2744.

[7] (a) Guilbaud, P., Varnek, A. and Wipff, G. (1993). *J. Am. Chem. Soc.*, **115**, 8298, (b) Varnek, A. and Wipff, G. (1993) *J. Phys. Chem.*, **97**, 10840, (c) Varnek, A., Wipff, G., Glebov, A.S. and Feil, D. (1995). *J. Comput. Chem.*, **16**, 1.

[8] Wipff, G. and Lauterbach, M. (1995). *Supramol. Chem.*, **6**, 187.

[9] Varnek, A. and Wipff, G. (1996). *Theochem, J. Mol. Struct.*, **363**, 67.

[10] Lauterbach, M. and Wipff, G. (1996). *Phys. Supramol. Chem.*, NATO ASI Series, L. Echegoyen and A. Kaifer, Eds., Kluwer, Dordrecht, 1.

[11] Wipff, G., Engler, E., Guilbaud, P., Lauterbach, M., Troxler, L. and Varnek, A. (1996). *New. J. Chem.*, **20**, 403.

[12] Lamare, V., Bressot, C., Dozol, J.F., Vicens, J., Asfari, Z., Ungaro, R. and Casnati, A. (1997). *Sep. Sci. Technol.*, **32**, 175.

[13] Sheldrick, G.M. (1985). SHELXS-86: *Program for the Solution of Crystal Structures*, University of Göttingen, Germany.

[14] *International Tables for X-ray Crystallography* (1974). **Vol. IV**, Kynoch Press, Birmingham, England. Present distributor: Academic Publishers, Dordrecht, The Netherlands.

[15] MolEN: (1990). *An Interactive Structure Solution Procedure*, Enraf-Nonius, Delft, The Netherlands.

[16] Pearlman, D.A., Case, D.A., Caldwell, J.A., Seibel, G.L., Singh, U.C., Weiner, P. and Kollman, P.A. (1991). AMBER 4.0. University of California, San Francisco.

[17] Weiner, S.J., Kollman, P.A., Nguyen, D.T. and Case, D.A. (1986). *J. Comput. Chem.*, **7**, 230.

[18] Marrone, T.J., Hartsough, D.S. and Merz, K.M. (1994). *J. Phys. Chem.*, **98**, 1341.

[19] Aqvist, J. (1990). *J. Phys. Chem.*, **94**, 8021.

[20] Guilbaud, P. and Wipff, G. (1993). *J. Phys. Chem.*, **97**, 5685.

[21] SYBYL 6.1, (1994). Molecular Modeling Software, TRIPOS Inc.

[22] Engler, E. and Wipff, G. MDS and MD DRAW 1.0.

[23] Ryckaert, J.P., Ciccotti, G. and Berendsen, H.J.C. (1977). *J. Comput. Phys.*, **23**, 327.

[24] Johnson, C.K. (1976). ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA.

[25] Fyles, T.M. and Gandour, R.D. (1992). *J. Incl. Phenom.*, **12**, 313.

[26] Rogers, R.D. and Atwood, J.L. (1984). *J. Crystallogr. Spectrosc. Res.*, **14**, 1.

[27] Kasuga, N., Nakahama, S., Yamaguchi, K., Ohashi, Y. and Hori, K. (1991). *Bull. Chem. Soc. Jpn.*, **64**, 3548.

[28] Ugozzoli, F., Ori, O., Casnati, A., Pochini, A., Ungaro, R. and Reinhoudt, D.N. (1995). *Supramol. Chem.*, **5**, 179.

[29] Czugler, M. and Kalman, A. (1982). *Acta Crystallogr.*, **B38**, 799.

[30] Sakamaki, T., Iitaka, Y. and Nawata, Y. (1977). *Acta Crystallogr.*, **B33**, 52.

[31] Dijkstra, P.J., Brunink, J.A.S., Bugge, K.E., Reinhoudt, D.N., Harkema, S., Ungaro, R., Ugozzoli, F. and Ghidini, E. (1989). *J. Am. Chem. Soc.*, **111**, 7567.

[32] New Macrocyclic Extractants for Radioactive Waste Treatment. Ionizable Crown Ethers and Functionalized Calixarenes. CCE Contract n° F12W-CT-0062, final report (in press).

[33] Owenson, B., MacElroy, R.D. and Pohorille, A. (1988). *J. Am. Chem. Soc.*, **110**, 6992.

[34] Lein, G.M. and Cram, D.J. (1985). *J. Am. Chem. Soc.*, **107**, 448.

[35] (a) Ungaro, R., Casnati, A., Ugozzoli, F., Pochini, A., Dozol, J.F., Hill, C. and Rouquette, H. (1994). *Angew. Chem. Int. Ed. Engl.*, **33**, 1506, (b) Casnati, A., Pochini, A., Ungaro, R., Ugozzoli, F., Arnaud, F., Fanni, S., Schwing, M.J., Egberink, R.J.M., de Jong, F. and Reinhoudt, D.N. (1995). *J. Am. Chem. Soc.*, **117**, 2767.