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Complexation of alkali cations by calix[4]crown ionophores: conformation and solvent dependent Na^+/Cs^+ binding selectivity and extraction: MD simulations in the gas phase, in water and at the chloroform-water interface

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Calix[4]arenes bridged by crown5 and crown6 moieties represent a promising class of ionophores for big alkali cations. We present a *theoretical demonstration of the possible modulation of the host-guest complementarity and recognition via the conformation of the host, and the solvent.* Molecular dynamics and free energy calculations are reported for the 1,3-dimethoxy-*p-tert*-butyl and the *p*-H-derivatives in the *cone*, *1,3-alternate*, and *partial cone* conformations, simulated in the gas phase and in water. In the gas phase, a decrease in binding affinity is calculated for the three forms of the complexes, from Na^+ to Cs^+. Intrinsically, the largest ions prefer clearly the 1,3-alternate conformers, while Na^+ prefers slightly the cone conformers. In aqueous solution, the change in free energy for mutating the Na^+ calix[4]-crown6 complex to the Cs^+ complex depends markedly on the conformation of the calixarene, and is about 12 kcal/mol weaker for the 1,3-alternate than for the cone form. Taking into account the difference in desolvation energy of the cations (30.4 kcal/mole) leads therefore to *conformation dependent Na^+/Cs^+ binding selectivity*. We predict that Na^+ is bound selectively in the cone form, while Cs^+ is preferred in the 1,3-alternate form, while the partial cone displays no clear Na^+/Cs^+ preference. The selectivity is related to the differences in precise cation location and shielding from the solvent, as a function of the conformation of the host. We conclude that the selective binding of Cs^+ by the 1,3 alternate calix[4]-crown6 is related to solvation effects, rather than to enhanced M^+/π interactions with the aromatic fragments. In non-aqueous solutions such as methanol or acetonitrile, the alternate form of calix[4]-crown6 is predicted to also bind Cs^+ better than Na^+. In dry chloroform, the situation is expected to be close to the gas phase, i.e. Na^+ preferred by all three conformers. For the smaller calix[4]-crown5 host similar conformation dependent binding selectivity are predicted. Finally, we report the first MD simulations on Na^+ and Cs^+ complexes of the *p-tert*-butylcalixC6 ionophore at the water / chloroform interface with an explicit representation of the solvents. The complexes are found to behave as surfactants. After 100 ps they remain close to the interface but sit almost exclusively in the organic phase.

INTRODUCTION

Calixarenes, cyclic oligomers of phenolic units, represent a versatile platform to design receptors for neutral species and cations[1,2]. The derivatization of the phenolic OH groups produces derivatives whose shape, mobility, and binding affinity can be monitored relatively easily[3]. For instance, the ester, amide, keto calix[4]arenes adopt the cone shape, and bind Na^+ selectively in methanol and acetonitrile[4–8] The introduction of polyether bridges in the 1,3 position, and alkylation of the 2,4 position leads to calixcrowns, which combine the binding features of a crown ether moiety, and the lipophilic properties of the aromatic and alkyl groups, suitable for cation extraction from an aqueous to an organic solution[9–11] (Chart 1).

For instance, in $CDCl_3$ saturated with water, the 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown5, which is conformationally mobile, complexes alkali picrates and displays a higher K^+ / Na^+ selectivity and K^+ affinity in its partial cone, than in the cone conformation[11]. Its -crown6 homologue extracts preferentially Cs^+ from an aqueous to an organic solvent, in the sequence $Na^+ < K^+ < Rb^+ < Cs^+$ in $CDCl_3$ saturated with water[3].

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Based on NMR data in CD_3CN, Ungaro *et al.* suggested that the dimethoxy derivative with X = H binds Na^+ in its cone conformation, but binds Cs^+ in the 1,3-alternate conformation[3]. There is thus an interesting conformation dependent Cs^+ / Na^+ binding selectivity which may be of particular interest in the context of Cs^+ separation from radioactive wastes.[12,13].

The purpose of this paper is to present a theoretical investigation on the structural and energetic basis of this Cs^+ / Na^+ selectivity, in terms of intrinsic binding features of the calix[4]crowns and of solvation effects, as a function of the conformation of the receptor and size of the crown. Computational chemistry and molecular dynamics simulations on ionophores have demonstrated the importance of molecular (pre)organization and relaxation, and of solvation effects on binding affinities[14–17]. Following the first free energy perturbation "FEP" calculations on the Cl^- /Br^- binding to the SC24,4H$^+$ cryptand[18], there have been interesting applications concerning the recognition of cations by ionophores "in the gas phase"[19], in water[20–25], methanol[15,27–30] acetonitrile[31,32]. The path of complexation has also been investigated in solution[16,33,34]. In the field of calixarenes, MD and FEP simulations relate to the acid base proportion of phenolic groups of calix[4]arenes[35] and to the binding of alkali cations to calixspherands[24] in aqueous solution. The binding of the uranyle cation by calix[5] and calix[6]arene polyanions has been investigated in water[36]. The importance of solvation effects on ligand wrapping around the cation was demonstrated in the series of cation complexes of calix[4]arene-tetraamides, compared consistently in water[36] and in acetonitrile[31]. It was shown that in solution the structures and cation binding mode were different from the solid state structure of the K^+ complex, and changed from one cation to the other, and from water to a non-aqueous-solvent[36]. In those cases, experimental stability (and sometimes kinetic) constants in pure solvents were available prior to the computational study. In our case, no stability constants have been reported so far to our knowledge on these calixcrowns in a pure solvent[77]. The experimental results concern the extraction of cations from water to an organic phase saturated with water.

More specifically, we consider the alkali cation complexes of 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown-5 and -crown6, with X = *tert*-butyl or H, and R = Me (Chart 1). These hosts will be referred to in short as X-calixC5 or X-calixC6 in the following. The complexes are first investigated in the gas phase in order to determine the structures and relative intrinsic binding affinities of a given conformer for M^+ = Na^+, K^+, Rb^+, Cs^+ as guest. Each receptor is considered in three conformations: cone, 1,3-alternate and partial cone (Chart 1). In a second stage, we immerse the calixC6

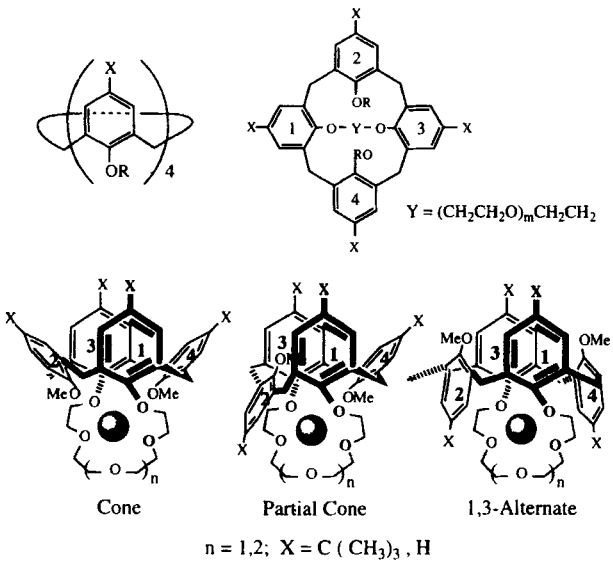


Chart 1 Scheme of calix[4]crown derivatives, and of the cone, 1,3 alternate and partial cone conformers of the 1,3-dimethoxy-calixC5 (n = 1; m = 3) and -calixC6 (n = 2; m = 4).

complexes in water, in order to investigate the structures and relative binding affinities in an aqueous environment. Although these calixcrowns are nearly insoluble in pure water, there are a number of reasons for considering an aqueous phase. First, in extraction experiments, the organic phase contains water "dragged" by the ionophore[38,39], and it is stressed that the local water concentration around this solute may be significant, particularly in the hydrophilic polyether region. A recent MD simulation of ions at a water / dichloroethane interface showed that, even in the organic phase, the ion retains some shells of water[40]. Second, as far as cation / solvent interactions are concerned, water displays important analogies with methanol where these molecules are soluble. Therefore, interactions between the complexed cation and water represent an upper limit, compared to solvents such as acetonitrile, chloroform, methanol. Third, the calculated water coordination to the complexed cation gives also insights into possible counterion effects. In particular, when no water is directly bound to the complexed ion, because of steric shielding, coordination to large counterions such as picrate or perchlorate should be similarly prevented, and the counterion therefore neglected in the simulations. Finally, the behaviour in water will serve as a reference to characterize non-aqueous solutions of these complexes. We have recently simulated the 1,3-alternate calix[4]-*bis*-crown alkali cation complexes in water, in methanol and chloroform, including counterion effects[67]. Mixed water—organic interfaces are being considered in our laboratory. The results obtained in water shed an important light on the question of Na^+ / Cs^+ binding selectivity, and allow to make predictions in methanol and acetonitrile.

An important issue of the present study concerns the question of specific cation-π interactions if any, in relation with the large stability of the Cs^+ complexes of calixC6. Such interactions involving the arene moiety of the host have been involved to rationalize its larger affinity for Cs^+, compared to smaller alkali cations[3, 41, 70]. Our simulations do not support this view, but ascribe the Cs^+ binding to a differential solvation effect.

Finally, we report preliminary investigations on the Na^+ and Cs^+ cone and 1,3-alternate complexes of *p-tert*-butylcalix-C6 at a water / organic interface, explicitly represented, in order to investigate the premises of migration from water to chloroform.

METHODS

We used the AMBER software[42] for molecular mechanics and molecular dynamics simulations, with the following representation of the potential energy:

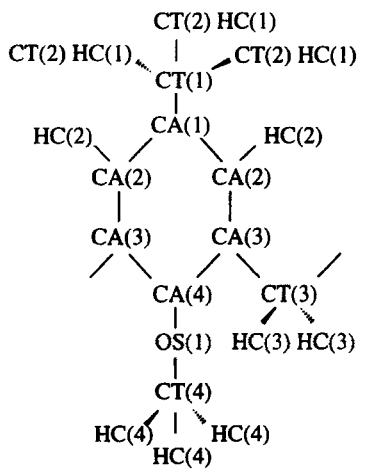
$$E_T = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} V_n (1 + cosn\Phi) + \sum_{i<j} (\varepsilon_{ij} (R^*_{ij}/R_{ij})^{12} - 2\varepsilon_{ij}(R^*_{ij} / R_{ij})^6 + (q_i q_j/\varepsilon R_{ij}))$$

The bonds and bond angles are treated as harmonic springs, and a torsional term is associated to the dihedral angles. The interactions between atoms separated by at least three bonds are described within a pairwise additive scheme by a 1-6-12 potential. The parameters for the calix and for crown moiety, described with explicit CH_2 groups are taken from the AMBER force field[43], using the atom types reported in Chart 2.

The atomic charges of the crown (qO = -0.4) are derived from electrostatic potentials[44], without special scaling factor for 1...4 interactions. For the aromatic part, the charges derived from potentials calculated by *ab initio*[35] or MNDO[36] methods exaggerate the polarity of the carbon atoms. We therefore decided to use Gasteiger charges, which are more "neutral" in order to avoid bias in the cation / aromatic interactions (Chart 2). For comparison we have repeated some free energy mutations with these *ab initio* and MNDO derived charges and with recently reported CHARMM charges[26] for calixarenes. For the cations, we use the Aqvist parameters for all free energy perturbation calculations. This is consistent with the derivation of these parameters on relative and absolute free energies of hydration[45]. Some of the simulations have been repeated with another set for M^+, referred to as the "Amber" set, as used in previous studies of cryptates and crown ether complexes[32]. In particular, all molecular dynamics simulations *in vacuo* were repeated with that set. All simulations have been performed using a dielectric constant $\epsilon = 1$.

The aqueous solution was simulated in a "cubic" box of 28–30 Å length, containing 730 to 1020 H_2O TIP3P[37] molecules, with periodic boundary conditions. The solute was placed at the center of the box and all solvent molecules within 3 Å and beyond 12 Å from the solute were deleted. In solution, the O-H and C-H bonds were constrained to constant values with SHAKE, in conjunction with a time step of 2 fs. In the gas phase, the time step was 1fs, without SHAKE.

After 1000–4000 steps of conjugate gradient energy minimization, the MD simulations were run for 50 ps at 1 atm and 300K (N, P, T ensemble) using the Verlet algorithm, starting with random velocities. A residue based cut-off of 10 Å was used for non-bonded interactions, taking the solute(s) as a single residue. The temperature was maintained to 300 K by velocity scaling



	Gasteiger	ESP *ab initio*[35]	ESP MNDO[36]	CHARMM [26]
calix				
CA(1)	-0.041	0.460	-0.05	-0.115
CA(2)	-0.052	-0.658	-0.37	-0.115
CA(3)	-0.012	0.452	0.23	0.00
CA(4)	0.136	-0.225	-0.05	0.11
CT(3)	0.002	-0.370	-0.24	-0.18
OS(1)	-0.400	-0.264	-0.33	-0.34
HC(2)	0.062	0.243	0.21	0.115
HC(3)	0.036	0.112	0.09	0.09
t-butyl				
CT(1)	-0.013	0.018	0.59	0.115
CT(2)	-0.056	-0.263	-0.36	-0.27
HC(1)	0.024	0.078	0.08	0.09
methyl				
CT(4)	0.170	-0.151	-0.15	-0.04
HC(4)	0.010	0.107	0.09	0.09

Chart 2 Atom types referred to in the AMBER PARM91.DAT force field for the calix[4]-crown fragments. Partial charges used for the calculations obtained by different methods.

in the gas phase, and by coupling to a thermal bath in solution.

The "FEP" (Free Energy Perturbation) calculations were performed with the windowing technique, changing the ϵ, R* parameters of M^+ linearly with λ: $V_\lambda = \lambda . V_{M_1^+} + (1 - \lambda) \cdot V_{M_2^+}$ as suggested in ref.[46]. We mutated successively $Na^+ \rightarrow K^+ \rightarrow Rb^+ \rightarrow Cs^+$. The mutation of one cation M_1^+ (free or complexed) into the next one M_2^+ was achieved in 11 windows. At each window, 1 ps of equilibration was followed by 4 ps of data collection, and the change of free energy ΔG was averaged from the forward and backward cumulated values. The change in ΔG from Na^+ to Cs^+ was obtained from the cumulated free energies involved in the intermediate states.

The starting structures of the cone, partial cone and 1,3-alternate conformers were model built, without using the X-ray structures of calixC5 (free and complexed[10,11]) or of the calixC6 Cs^+ complex[3]. The cation was set at the center of the polyether ring and surrounded by the ether oxygens. After energy minimization by MM the complex was shaken for 50 ps by MD *in vacuo*. The last structure was again energy minimized, and immersed in water.

The analysis of the trajectories was performed with the MDS and DRAW software[47], from the trajectories which were saved every 0.2 ps. Because of the fluctuations of the free or complexed calixcrowns, relative energies cannot be assessed from one structure only. We therefore consider two energies: <E> which is the MD average potential energy and E_{opt} which is the MM minimized structure obtained at the end of the MD simulation. E_{opt} corresponds therefore to a significantly shaken and relaxed structure, as far as the shape of the host, and the location of the M^+ cation are concerned. Despite the large fluctuation in <E> (about 5 kcal / mol *in vacuo*), and the fact that E_{opt} does not correspond to "the absolute minimum" both <ΔE> and ΔE_{opt} energy differences are very similar.

The MD simulation of the complexes at the water / chloroform interface started with two adjacent cubic box of pure solvents (OPLS and TIP3P potentials)[37] of about 30Å × 30Å × 30Å each, with 200–300 chloroform and 800–1000 water molecules. The solute was initially placed at the interface, equally shared by the two solvents. The time evolution was followed for 100 ps at constant volume and T = 300K, using periodic boundary conditions. More details are given in reference 83.

RESULTS

After energy minimization, or after MD simulations *in vacuo* or in solution, the conformation of the host remained of the same type as the starting one. Although these free or complexed hosts may be conformationally mobile, no cone / alternate / partial cone interconversions were observed in the 50 ps simulations at 300K, since they involve time scales beyond the ones considered here, or higher temperatures. Furthermore, the detailed mechanism of conformational changes of the complexes may be complicated and involve solvent assisted decomplexation / recomplexation processes. In the following we present first energy and structural features of the free and complexed hosts in the gas phase. This is followed by the solvation characterisation in water and the important question of binding selectivity in water for the M^+ / calixC6 complexes. Results are displayed in Tables 1–8, and Figure 1–5[54], which account poorly for the beautiful dynamic pictures displayed on the graphic system. Some typical (static) colour pictures are presented in Figure 6.

1—The calixC5 and calixC6 complexes in the gas phase: structures, stability and relative binding affinities

Relative stability, as a function of M^+. In Table 1 are reported the total energies of the complexes, and related ion-host interactions energies. We find in all cases, that the smallest ion complexes are favoured, in the sequence $Na^+ > K^+ > Rb^+ > Cs^+$.

This is shown on a statistical basis by the averages in total energies after the 50 ps MD simulations, as well as by individual structures, obtained by MM minimization of the last set of dynamics. Why is it so? The energy component analysis reveals that this sequence follows the M^+ / host interaction energies (Table 1). At this stage, it is clear that Cs^+ has the poorest interactions with the calixC5 or calixC6 hosts, in all conformers, with X = H or X = *p-tert*-butyl. Further dissection of the host into its crown and calixarene fragments is somewhat arbitrary, in particular for the bridged phenolic oxygens which can be considered either as part of the crown or of the calix. In the first scheme, the M^+ / crown attraction is large and close to the total M^+ / host interaction energy, while the M^+ / calix interaction is repulsive. Using the second scheme reduces the M^+ / crown attraction, but makes the M^+ / calix interaction attractive. Anyway, both schemes make clear that the M^+ / host attraction is dominated by the crown contribution, and that the phenolic oxygens attached to the ring bring an significant contribution to the complexation energy.

Conformational preference of the free hosts and of the cation complexes *in vacuo*. In this section, we compare the relative stability of the cone / 1,3 alternate / partial cone for a given cation complex *in vacuo*, based on the <ΔE> and ΔE_{opt} energies (Table 2).

The free hosts. For the free hosts calixC5 and calixC6,

Table 1 X-calixC5 and X-calixC6 (X = H and X =*tert*-butyl) complexes *in vacuo*. Average total energy (<E>), minimized energy (E_{opt}) and ion-host interaction energy ($E_{M+/Recept.}$) relative to the Na^+ complex (kcal / mole). The total energy for the Na^+ complex is given in parenthesis; AMBER M^+ parameters.

		M^+/H-calixC5				M^+/*p-tert*-butylcalixC5			
		Na^+	K^+	Rb^+	Cs^+	Na^+	K^+	Rb^+	Cs^+
cone	$<\Delta E>$	0.0 (111.7)	22.1	36.2	49.5	0.0 (161.9)	20.9	36.1	51.0
	ΔE_{opt}	0.0 (32.6)	21.8	36.2	49.7	0.0 (37.7)	22.5	36.5	51.8
	$<\Delta E_{M^+}$/Recept.>	0.0 (-87.1)	17.0	28.4	58.4	0.0 (-89.7)	18.6	30.0	62.6
part	$<\Delta E>$	0.0 (109.3)	13.3	23.0	35.6	0.0 (158.8)	10.6	21.2	33.4
	ΔE_{opt}	0.0 (30.6)	13.0	22.6	34.8	0.0 (36.3)	11.3	21.5	33.6
	$<\Delta E_{M^+}$/Recept.>	0.0 (-77.3)	11.5	19.9	28.3	0.0 (-79.1)	10.6	19.6	27.5
1,3-alt	$<\Delta E>$	0.0 (110.9)	4.0	5.4	28.2	0.0 (163.2)	5.0	11.1	25.2
	ΔE_{opt}	0.0 (33.5)	2.7	10.6	22.7	0.0 (42.6)	3.0	8.0	23.5
	$<\Delta E_{M^+}$/Recept.>	0.0 (-70.5)	8.4	15.5	25.3	0.0 (-76.2)	8.4	16.1	27.4
		M^+/H-calixC6				M^+/tert-butylcalixC6			
		Na^+	K^+	Rb^+	Cs^+	Na^+	K^+	Rb^+	Cs^+
cone	$<\Delta E>$	0.0 (135.3)	21.2	28.2	35.6	0.0 (184.8)	20.3	29.0	35.7
	ΔE_{opt}	0.0 (48.6)	21.1	28.9	36.3	0.0 (56.6)	17.8	29.3	37.6
	$<\Delta E_{M^+}$/Recept.>	0.0 (-89.2)	19.1	26.1	32.2	0.0 (-92.2)	17.0	27.0	34.4
part	$<\Delta E>$	0.0 (134.4)	12.2	18.9	24.6	0.0 (185.6)	15.0	18.3	22.8
	ΔE_{opt}	0.0 (47.0)	12.1	20.5	26.3	0.0 (56.6)	15.3	18.5	23.0
	$<\Delta E_{M^+}$/Recept.>	0.0 (-78.2)	7.5	16.2	21.0	0.0 (-75.7)	8.6	10.5	15.2
1,3-alt	$<\Delta E>$	0.0 (137.2)	5.4	11.4	13.7	0.0 (190.8)	5.6	8.4	13.2
	ΔE_{opt}	0.0 (52.3)	5.4	8.7	13.4	0.0 (59.2)	8.7	10.1	16.9
	$<\Delta E_{M^+}$/Recept.>	0.0 (-75.0)	12.0	14.1	20.6	0.0 (-71.9)	9.1	8.9	13.6

with X = *p-tert*-butyl, the alternate form is most stable. For calixC6, the stability decreases in the order alternate > partial cone > cone ($<\Delta E>$ = 0, 4, and 12 ± 7, respectively, and ΔE_{opt} = 0, 4, 11 kcal / mol, respectively). For calixC5, the cone form is again the least stable, but the alternate and partial cone forms have a same energy: $<\Delta E>$ = 0, 0, 8 ± 6 and ΔE_{opt} = 0, 0, 8 respectively.

The calixC6 complexes. The comparison of the three conformers reveals also interesting cation dependent conformational preferences. With X = *tert*-butyl or H, the Cs^+, Rb^+ and K^+ calixC6 complexes are most stable in the 1,3 alternate form (alternate > partial cone > cone). The energy difference between the alternate and cone forms decreases with the size of the cation. With Cs^+, ΔE_{opt} = 18–19 kcal / mol and $< \Delta E >$ = 17–20 kcal / mol. With K^+, ΔE_{opt} = 7–12 and $<\Delta E>$= 9–14 kcal / mol). For the Na^+ complexes, the three conformers are closer in energy, but now the cone is the most stable (cone = partial cone < alternate; ΔE_{opt} = $<\Delta E>$ = 2–6 kcal / mol with both sets of M^+ parameters).

Why does Cs^+ prefer the 1,3-alternate, but Na^+ the cone form? An energy component analysis shows that in the case of Cs^+ the energy of the host within the complex is the leading term (the host is most stable in the alternate form), while the Cs^+ / host interactions are similar in the three conformers with X = H or *tert*-butyl (about -60 kcal / mol; Table 1). This contrasts with Na^+ which prefers the cone calixC6 because Na^+ has clearly better interactions with the cone than with the other conformers.

The calixC5 complexes. In the H- and *p-tert*-butylcalixC5 complexes, the trends are the same as in the calixC6 complexes (Table 2). With K^+, Rb^+ and Cs^+, the alternate form is preferred, in the sequence: alternate > partial cone > cone. The energy scale decreases with the cation size: from 22–26 kcal / mol for Cs^+ to 14–19 kcal / mol for K^+. Na^+ prefers slightly the partial cone over the cone and alternate forms, but the energy range is much smaller than for the other cations: 1–6 kcal / mol for X = *tert*-butyl and 1–3 kcal / mol for X = H.

These conformational preferences result from a balance between two opposed components: the Na^+ and K^+ / host attraction energies are largest in the cone conformation (cone > partial cone > alternate for X = H or *tert*-butyl) but intrinsically the calixC5 is most stable in the alternate form (Figure 1). The Rb^+ cation has nearly identical interactions with the three forms (X = H or *tert*-butyl) because it keeps a similar central position in the ether ring, whereas coordination of the smaller ions may involve the OMe oxygens in the cone form (see next). The Cs^+ cation is too big to fit inside the crown5, and interacts best with the partial cone.

Table 2 X-calixC5 and X-calixC6 (X = H and X = *tert*-butyl) free and complexed, *in vacuo*. Conformation dependent stability, relative to the 1,3-alternate conformation (total energies in parenthesis).

		H-calixC5				*p-tert*-**butylcalixC5**			
		cone	part	1,3-alt		cone	part	1,3-alt	
free	<ΔE>	10.7	5.9	0.0	(170.6)	7.9	-0.6	0.0	(227.1)
	ΔE_{opt}	8.5	4.3	0.0	(93.9)	7.6	0.1	0.0	(104.2)
Na^+	<Δ E>	0.8	-1.6	0.0	(110.9)	-1.3	-4.4	0.0	(163.2)
	ΔE_{opt}	-0.9	-2.9	0.0	(33.5)	-4.9	-6.3	0.0	(42.6)
K^+	<Δ E>	18.9	7.7	0.0	(114.9)	14.6	1.2	0.0	(168.2)
	ΔE_{opt}	18.2	7.4	0.0	(36.2)	14.6	2.3	0.0	(45.6)
Rb^+	<Δ E>	31.6	16.0	0.0	(116.3)	23.7	5.7	0.0	(174.3)
	ΔE_{opt}	24.7	9.1	0.0	(44.1)	23.6	7.2	0.0	(50.6)
Cs^+	<Δ E>	22.1	5.8	0.0	(139.1)	24.2	3.5	0.0	(188.7)
	ΔE_{opt}	26.1	9.2	0.0	(56.2)	23.4	3.8	0.0	(66.1)
		H-calixC6				*p-tert*-**butylcalixC6**			
		cone	part	1,3-alt		cone	part	1,3-alt	
free	<Δ E>	8.4	1.9	0.0	(195.3)	12.0	4.4	0.0	(246.5)
	ΔE_{opt}	9.2	5.3	0.0	(108.2)	10.6	4.0	0.0	(119.3)
Na^+	<Δ E>	-1.9	-2.8	0.0	(137.2)	-6.0	-5.2	0.0	(190.8)
	ΔE_{opt}	-3.7	-5.3	0.0	(52.3)	-2.6	-2.6	0.0	(59.2)
K^+	<Δ E>	13.9	4.0	0.0	(142.6)	8.7	4.2	0.0	(196.4)
	ΔE_{opt}	12.0	1.4	0.0	(57.7)	6.5	4.0	0.0	(67.9)
Rb^+	<Δ E>	14.9	4.7	0.0	(148.6)	14.6	4.7	0.0	(199.2)
	ΔE_{opt}	16.5	6.5	0.0	(61.0)	16.6	5.8	0.0	(69.3)
Cs^+	<Δ E>	20.0	8.1	0.0	(150.9)	16.5	4.4	0.0	(204.0)
	ΔE_{opt}	19.2	7.6	0.0	(65.7)	18.1	3.5	0.0	(76.1)

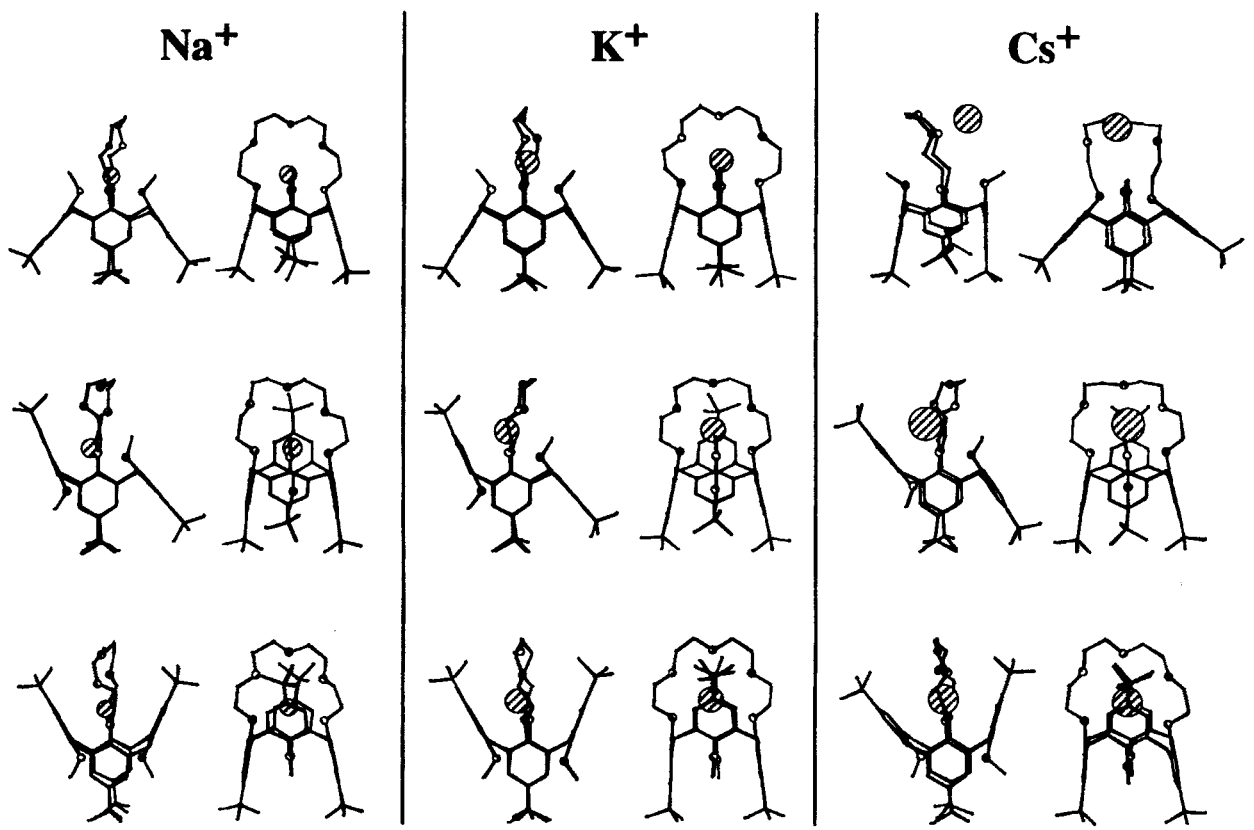


Figure 1 Snapshots of Na^+, K^+ and Cs^+ *p-tert*-butylcalixC5 complexes in the cone, partial cone, and 1,3-alternate forms (energy minimized last sets of MD *in vacuo*; orthogonal views).

Relative cation binding affinities *in vacuo*, for a given conformer of calixC6 and calixC5. Insight into the relative binding affinities is obtained by calculating the change in free energy when one complex is mutated into the other ("computational alchemy"[48-51]). One advantage of these calculations is the low statistical fluctuations (less than 1 kcal / mol), compared to the differences in total energies (about 10 kcal / mol *in vacuo*). In addition, via the sampling procedure, it involves enthalpic and entropic components of the free energy.

The results reported in Table 3 make clear that in all calixC5 and calixC6 complexes, *for one given conformer*, the smallest ion Na^+ is intrinsically preferred, in the same order ($Na^+ > K^+ > Rb^+ > Cs^+$) as the total energies of the complexes, or the cation—host interaction energies. Quantitatively, the Na^+–Cs^+ ΔG_4 difference is more sensitive to the conformation of the host than to the nature of X. For X = H / *tert*-butyl, ΔG_4 is larger in the cone (35.1 / 39.2) than in the partial cone (26.9 / 26.8) and alternate form (17.9 / 20.5) kcal / mol, respectively). This is because Cs^+ prefers clearly the alternate form, while Na^+ does not display such a marked conformational preference.

For the calixC5 complexes, the Na^+–Cs^+ free energy difference is also conformation dependent and larger in the cone than in the partial cone and alternate forms (44.1 / 45.1, 32.0 / 29.5 and 21.3 / 23.1 kcal / mol, respectively for X = H / *tert*-butyl).

Structural features of the calixcrowns and their complexes *in vacuo*. All structures are in essence dynamic, and differ somewhat from one cation to the other. We refrain to describe them in detail, and focus on the cation binding features, and overall shape of the aromatic part and of the polyether ring as a function of the cation size, for a given conformation of the host. We present snapshots of the Na^+, K^+ and Cs^+ complexes of *p-tert*-butylcalixC5 *in vacuo* (Figure 1). The calixarene fragment is described by the average angles ω_{13} between the crown substituted phenyls and ω_{24} between two anisole rings. By mechanical coupling, these angles are related to the O...O distances between opposed phenolic oxygens, and to the C...C distances between opposed *ipso* aromatic carbons.

We define the position of the M^+ cation with respect to the calixarene moiety (M^+ distances to the center of the four aromatic rings) and to the polyether ring (M^+ distance to center of mass of the polyether oxygens). The results obtained with the Amber M^+ parameters are reported in Table 4. The Aqvist's M^+ parameters give very similar structures, and are not reported.

The free calixcrowns. Comparison of *p-tert*-butylcalixC5 / *p-tert*-butylcalixC6 uncomplexed hosts shows that the crown5 or crown6 bridges do not strain the calixarene moiety: for a given conformer, the ω_{13} angle is nearly independent on the length of the ether bridge. Comparing calixC5 and calixC6, the $O_{Me}...O_{Me}$ and $O_{crown}...O_{crown}$ distances are nearly identical in the cone forms (about 3.4 / 4.9 and 3.4 / 5.0 Å, respectively), and about 0.2 Å larger in the 1,3-alternate form of calixC6 (about 4.1 / 4.5 and 4.3 / 4.7 Å, respectively).

The ω_{13} angle is however somewhat conformation dependent (18° / 16° in the cone; 14° / 18° in the partial cone and 30° / 23° in the 1,3-alternate form). In calixC5 and calixC6 the ω_{24} angle between the anisole rings is larger than ω_{13} and is more open in the cone (99° / 100°) than in the partial cone (43° / 46°) or alternate (53° / 43°). The cones can be pictured therefore as "flattened". The symmetry of the four aromatic rings is roughly C_{2v} for the cone and the 1,3-alternate forms, instead of C_{4v} and D_{2d}, respectively. In the partial cone, it is C_s. Taking into account the crown fragment lowers the symmetry, since it is very mobile, and exchanges

Table 3 X-calixC5 and X-calixC6 *in vacuo* (X=H and X=*tert*-butyl): Differences in free energies ΔG_4 (kcal / mole) with Aqvist M^+ parameters (and with Amber parameters, in parenthesis)[a].

		Na^+ -> K^+	K^+ -> Rb^+	Rb^+ -> Cs^+	Na^+ -> Cs^+
H-calixC5	cone	19.3	8.4	16.4	44.1
	part	14.0	6.3	11.7	32.0
	alt 1,3	7.3	4.3	9.7	21.3
p-tert-**butylcalixC5**	cone	19.9	8.8	16.4	45.1
	part	12.4	5.6	11.5	29.5
	alt 1,3	9.8	4.3	9.0	23.1
H-calixC6	cone	18.3	7.0	9.8	35.1
	part	16.2	4.4	6.3	26.9
	alt 1,3	10.0	3.2	4.7	17.9
p-tert-**butylcalixC6**	cone	22.1 (21.8)	7.1 (9.9)	10.0 (7.8)	39.2 (39.5)
	part	15.5 (14.5)	4.8 (6.0)	6.5 (5.9)	26.8 (26.4)
	alt 1,3	12.2 (11.7)	3.0 (3.8)	5.3 (4.3)	20.5 (19.8)
	ab initio[b]	9.6	2.7	4.9	17.2
	MNDO[c]	14.7	3.1	5.7	23.5
	CHARMM[d]	14.5	4.0	6.5	25.0

a) unless otherwise specified the Gasteiger charges are used on the calixarene host; *b)*with *ab initio* charges (from reference 35); *c)* with MNDO charges (from reference 36); *d)* with CHARMM charges (from reference 26) on the calixarene host

Table 4 X-calixC5 and X-calixC6 (X = H and X = *tert*-butyl) M^+-complexes *in vacuo*. Average distances between M^+ and the center of mass of the (five or six) crown ether oxygens (<dM⁺..cmOcr>) and between M^+ and the center of mass of the aromatic units (<dM⁺..cmAr>) (Å). Statistical fluctuations are about 0.2 Å in most complexes.

				M^+ / X-calixC5			M^+ / X-calixC6		
				Na^+	K^+	Cs^+	Na^+	K^+	Cs^+
cone	X = H	<dM⁺..cmAr>	a)	4.9	5.2	7.6	4.9	5.4	6.0
	tert-butyl		a)	4.9	5.3	7.8	4.9	5.4	6.0
	H	<dM⁺..cmOcr>		1.0	0.6	3.2	1.5	1.3	1.2
	tert-butyl			1.0	0.7	3.3	1.5	0.8	1.2
part	H	<dM⁺..cmAr>	b)	2.8	3.0	3.3	2.8	3.1	3.4
			c)	4.7	5.1	5.6	4.6	5.2	5.8
	tert-butyl		b)	2.9	3.1	3.3	2.9	3.1	3.5
			c)	4.7	5.1	5.6	4.6	5.3	5.8
	H	<dM⁺..cmOcr>		1.2	0.8	1.4	2.0	1.0	0.7
	tert-butyl			1.3	0.9	1.3	2.2	1.4	0.7
1,3-alt	H	<dM⁺..cmAr>	d)	3.1	3.2	3.5	3.2	3.4	3.7
			e)	4.6	4.8	5.0	4.6	5.1	5.5
	tert-butyl		d)	3.4	3.5	3.5	3.3	3.4	3.7
			e)	4.7	4.9	5.0	4.1	4.9	5.4
	H	<dM⁺..cmOcr>		1.0	0.8	0.9	1.6	1.0	0.7
	tert-butyl			1.0	0.8	0.8	2.6	1.5	0.8

a) average M^+ distance to aromatic rings 1,2,3,4, b) to aromatic ring 2, c) to aromatic rings 1,3,4, d) to aromatic rings 2,4 and e) to aromatic rings 1,3 (see Chart 1).

between asymmetrical forms, with one or two *trans* OC-CO dihedral angles. This means that the crown part of calixC5 and calixC6, like the simple 18-crown-6 analogue[52] is not preorganized for complexation. In the solid state, the cone *p-tert*-butylcalixC6[53], the cone *p-tert*-butylcalixC5, or the partial cone and 1,3 alternate 1,3-diethoxy-*p-tert*-butylcalixC5 are not preorganized either[11]. In the cation complexes, all OC-CO angles become gauche, and the oxygens point to the M^+ cation, with $\omega_{13} < \omega_{24}$ as in the free hosts.

The calixC5 complexes. Na^+ and K^+ fit best inside the crown of the three conformers. The cone and alternate forms have approximate C_{2v} symmetry on the average, and the alternate form is C_s. The Cs^+ and Rb^+ cations are too big for calixC5, and in the cone complexes, they move outside the ether ring (X = H or *tert*-butyl). In the alternate forms (X = *tert*-butyl or H) they are more or less "squeezed" between the aromatic walls and prevented from moving out when X = *tert*-butyl. In the partial cone Rb^+ and Cs^+ complexes, the cations remain encapsulated by the crown, between one aromatic unit and one MeO group for both substituents.

Within all calixC5 and calixC6 complexes, the M^+...O distances follow the size of M^+. A given cation M^+ is not strictly equidistant from all ether binding sites and subtle changes are found from one conformer to the other. Similar features have been observed in the X-ray structure of the 1,3-diethoxy-*p-tert*-butylcalixC5 K^+ cone and partial cone complexes, where the K^+...O distances range from 2.67 to 3.0 Å[3]. Ungaro *et al.* noticed that, although the partial cone is more stable than the cone complex in chloroform, the $K^+...O_{crown}$ and $K^+...O_{Et}$ distances are somewhat longer in the partial cone[3]. Our calculations reproduce nicely this structural feature: the $K^+...O_{Me}$ distance is 2.73 Å in the cone, and 2.83 Å in the partial cone form; the average of the five $K^+...O_{crown}$ distances is 2.86 Å in the cone and 2.95 Å in the partial cone form. In the Rb^+ complex, the Rb^+...O distances display the same trend from the cone to the partial cone.

The calixC6 complexes. In view of the conformation dependent Cs^+ / Na^+ binding selectivity found for the calixC6 host, we focus particularly on the position of the cation within these complexes. The crown cavity of calixC6 is clearly too large for Na^+, which oscillates between the four phenolic oxygens and the crown ether oxygens in the cone, partial cone and alternate conformers. As a result, the ether ring is distorted and non-planar on the average.

The alternate Na^+ complex is "flattened", since one Na^+...OMe attraction distorts the calixarene moiety from C_{2v} to C_s symmetry. As a result, the ω_{24} angle is larger for Na^+ (62°) than for K^+, Rb^+ or Cs^+ (45° to 48°). The stability of the Na^+ calixC6 cone, compared to 1,3 alternate complex may be related to the four short $Na^+...O_{phenyl}$ distances (2.4–2.5 Å), whereas in the alternate form there are two short (2.4 Å), and two long (3.2 Å) contacts. Cs^+ fits clearly better in the 1,3-alternate or partial cone than in the cone form of calixC6. In the cone

complex, Cs^+ is roughly at the center of the ether ring, but close to (and somewhat repulsed by) the two Me groups. The crown is bent away from the symmetry plane of the calixarene fragment, as in the solid state structure of the Rb^+ 1,3-dimethoxy-*p-tert*-butylcalixC6 complex[11] which adopts interestingly a flattened C_s rather than a "regular" C_{2v} cone, presumably related to the picrate....Rb^+ coordination in the solid state. This Cs^+ coordination by the cone contrasts with the alternate form, where Cs^+ sits at the center of the ring, and the symmetry of the complex, including the ether ring, is close to C_{2v} (with X = H or *tert*-butyl). In the X-ray structure of the 1,3-dimethoxy-H-calixC6 Cs^+ 1,3-alternate complex, the ether ring is not planar, but slightly bent away from the symmetry plane between the two anisole rings[3]. Our calculation suggest that this is not an intrinsic feature of the complex, but likely induced by the Cs^+...picrate coordination in the solid state or by packing interactions. One may question whether the *tert*-butyl groups on the crown side can destabilize the Cs^+ complex, via a steric repulsion with Cs^+. The mimized structures show that this is not the case, since the ω_{24} angle is nearly the same with X = H or *tert*-butyl, and the same with Cs^+ as with Rb^+ or K^+ (about 40–48°). From a kinetic point of view, it is likely however that the *tert*-butyl "gate" provides a barrier for cation inclusion.

In the alternate complexes, as M^+ gets smaller, it translates gradually from the center of the ether ring (from 0.8 Å for Cs^+ to 2.6 Å for Na^+; Table 4), to a deeper position between anisoles 2 and 4. As far as the aromatic fragments are concerned, the crown substituted phenyls 1 and 3 are more parallel to each other than the anisole rings, due to the constraints imposed by the ether bridge and the cation. This is a general trend for the 1,3-alternate calixC6 and calixC5 free hosts and their for complexes (Figure 2).

Concerning the partial cone forms of calixC6, Cs^+ and Rb^+ fit the best in the crown, whereas Na^+ and K^+, too small are respectively 1.4 and 2.2 Å from the center of the crown (Table 4).

Motions of the calixC5 and calixC6 hosts. The average structural features reported above mask somewhat the dynamic properties of the complexes. In fact, as shown for calix[4]arene-tetraamides[36], there are significant motions of the aromatic fragments and substituents. The position of the cation, the precise conformation and "cavity size" of the polyether ring and the shape of the aromatic moiety are time dependent, and coupled to each other. Figure 2 shows the ω_{13} and ω_{24} angles as a function of time, for the Na^+ and Cs^+ complexes of *p-tert*-butylcalixC6 in the cone and 1,3-alternate conformations, *in vacuo* and in water. As noted above, the ω_{13} angle is on the average smaller than ω_{24}, but some cone

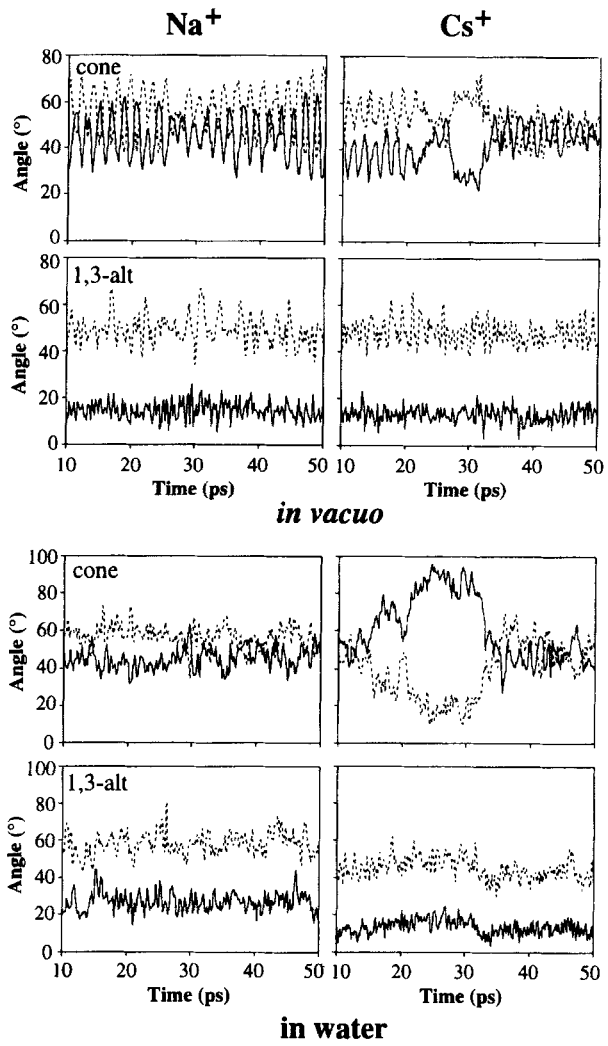


Figure 2 Angles ω_{13} (full line) and ω_{24} (dotted line) between opposite aromatic rings (see Chart 1) of Na^+ and Cs^+ *p-tert*-butylcalixC6 complexes as a function of time: cone and 1,3-alternate complexes *in vacuo* and in water.

forms are close to C_{4v}. Notice also, in the Cs^+ cone complex, the irregular behaviour between 25–35 ps, related to the bending of the crown6, and repositioning of Cs^+. The high frequency oscillations (about 1 ps^{-1}) are clearly anti correlated in the cone form (correlation coefficient close to -0.8), and the amplitudes are larger with Na^+ (about 25°) than with Cs^+ (about 15°). In the other forms, no such correlation is found. Comparison of these plots shows that the oscillation frequencies may be modulated by the environment, by M^+ and by the conformation of the host.

2- The calixC6 complexes in water: cation shielding and relative binding affinities

In water, we simulated the calixC6 host in the cone, partial cone and 1,3-alternate conformations, in their free and complexed states (typical structures are displayed in

Figures 3 and 6). It was clear indeed from the gas phase results that calixC5 is too small for Cs^+. All simulations in water started from "inclusive complexes", i.e. with M^+ more or less close to the center of the polyether ring, as obtained *in vacuo*. Interestingly, most of the complexes remained so with X = *tert*-butyl, but some decomplexed when X = H, as a result of their poor stability. This is the case for the Na^+ alternate, and for the Rb^+ and Cs^+ cone complexes. With X = *tert*-butyl, no such decomplexation took place from the cone conformation, simulated in the same conditions, even after 50 additional ps of simulation. This contrasted behaviour is quite surprising, since the H or *tert*-butyl groups are remote from the cation, and are not directly involved in the cation coordination. In fact, when X = H, a detailed analysis revealed that upon decomplexation of Cs^+ or Rb^+ some water molecules diffuse into the cone. With X = *tert*-butyl, no such water migration took place, because of the "hydrophobic gate" provided by the four *tert*-butyles. There are thus long range "top-bottom interactions" via solvent molecules (Figure 3 and 6).

Cation shielding from the solvent. The $M^+...O_w$ rdf's (radial distribution functions) for X = H and *tert*-butyl show distinct hydration features for the alternate, compared to the cone (Figure 4) and partial cone forms. First of all, in the alternate forms with X = *tert*-butyl, all cations are shielded from the solvent (no peak in the rdf's). This contrasts with the cone forms, where respectively 1.9, 2.2 and 4.7 water molecules are directly coordinated to K^+, Rb^+ or Cs^+. Na^+ is not hydrated, since it sits deeply near the phenolic ethers and remote from the other ether oxygens. The *p-tert*-butylcalixC6 partial cone provides also efficient shielding to the solvent for most cations, whose coordination numbers are small (1.0, 0.8, 0.9, 1.0 respectively for Na^+, K^+, Rb^+ and Cs^+).

In the H-calixC6 complexes, all cations are more or less in contact with water. In the Na^+, K^+, Rb^+, Cs^+ series, the coordination numbers are respectively 0.6, 1.0, 3.4, 7.5 in the cone conformer, and 3.9, 1.0, 2.0, 2.2 in the alternate conformers. For the Na^+ alternate and Cs^+ cone complexes, the numbers are only indicative, since the cations decomplex during the MD simulation. In the partial cone, the cation is less shielded than with the *p-tert*-butylcalixC6, and the K^+, Rb^+ and Cs^+ cations also decomplexed during the MD.

The pictures obtained by the rdf's are fully consistent with the energy component analysis reported in Table 5

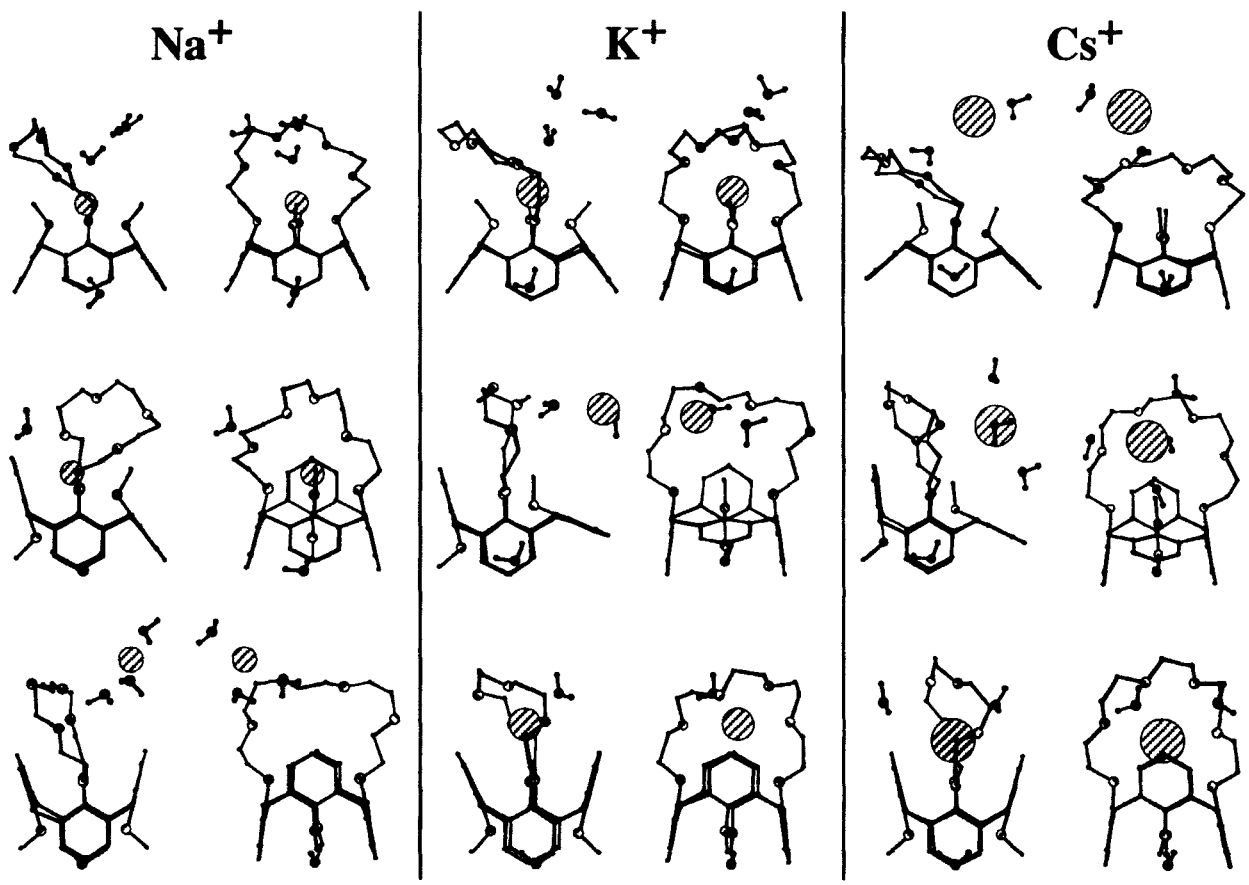


Figure 3 Snapshots of the Na^+, K^+ and Cs^+ H-calixC6 complexes in water in the cone (top), partial cone (middle), and 1,3-alternate (bottom) forms including selected water molecules; last set of MD; orthogonal views.

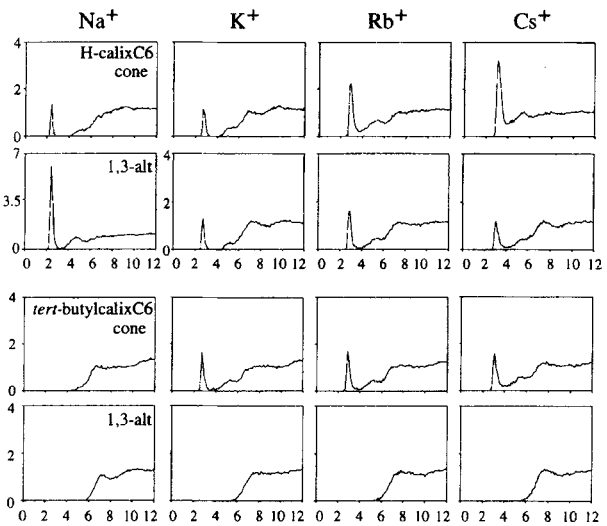


Figure 4 $M^+...O_{water}$ rdf's for the X-calixC6 (X = H and X = *tert*-butyl) Na^+, K^+, Rb^+ and Cs^+ complexes in the cone and 1,3-alternate forms. The two top lines correspond to the H-calixC6 complexes, the two bottom lines to the *p-tert*-butylcalixC6 complexes.

for the *p-tert*-butylcalixC6 complexes. First, for the 1,3-alternate form, the M^+ / water interaction energy is remarkably constant and attractive (-21 ± 5 kcal / mol) for all cations. This means that these complexes are isosteric, *i.e.* behave as a big cation of approximately constant size, with no direct cation—water coordination. This contrasts with the cone conformers. Although the free Na^+ cation has intrinsically larger interactions with water than Cs^+, it has within the complex smaller interactions with water than Cs^+ (respectively -28 ± 5 and -60 ± 12 kcal / mole), because of the lack of direct water coordination to Na^+, whereas Cs^+ is coordinated to 4.7 water molecules. This is an interesting feature, compared to the alkali cation *222* cryptates, where the cation shielding from water was similar for Na^+, K^+ and Cs^+ *222* cryptates[14].

Solvation has little effect on the precise form of the solute, which will not be discussed in detail. For instance, for the 1,3-alternate or cone *p-tert*-butylcalixC6 complexes, the ω_{13} or ω_{24} angles between aromatic rings are within a few degrees the same in water as in *in vacuo*. The differences are less than the statistical fluctuations (about 7°). It can therefore be inferred that the gross structural features obtained in the gas phase or in water will also hold in non-aqueous solvents such as chloroform or methanol, as confirmed by subsequent calculations[67].

The water coordination to some complexed cations pulls M^+ somewhat outside. As an interesting example, the Cs^+ cone *p-tert*-butylcalixC6 "complex" is of inclusive type, but not the H-calixC6 analogue, where Cs^+ dragged by water moves outward the ring on the pathway for decomplexation, like in the 18-crown-6 Cs^+ complex[55]. However when the cation is not bound to water, the structures are nearly the same in water as *in vacuo*. This is the case in particular for the Na^+ cone, Cs^+ alternate and Cs^+ partial cone complexes of *p-tert*-butylcalixC6.

Free energy mutations on the calixC6 complexes in water: relative binding affinities as a function of the conformation of the host and of solvent. In solution, the binding selectivity of cation M_1^+ compared to M_2^+ is measured experimentally by $\Delta G_c = \Delta G_1 - \Delta G_2$ (scheme below). These data are not available to us presently. The computer approach follows the alchemical route, by mutating M_1^+ into M_2^+ in their free (ΔG_3) and complexed states (ΔG_4). As a result of the thermodynamic cycle, $\Delta G_c = \Delta G_3 - \Delta G_4$. The results are reported in Table 6. The ΔG_3 values are the same as those obtained by Aqvist in somewhat different conditions (SPC water within a sphere, instead of TIP3P water in a cubic box with periodic boundary conditions)[45].

Table 5 M^+ complexes of *p-tert*-butylcalixC6 in water. Average ion-host (E_{M^+} / Host), ion-water (E_{M^+} / Water) and host-water interaction energies ($E_{Host\ /\ Water}$) relative to the Na^+ complex (kcal / mole). The total energies for the Na^+ complex are given in parenthesis; Aqvist M^+ parameters.

		M^+ / *p-tert*-butylcalixC6					
		Na^+		K^+	Rb^+	Cs^+	free
cone	nb_{H_2O} [a]	961		1011	1019	1024	1022
	$\Delta E_{M+\ /\ Host}$	0.0	(-91.2)	23.9	29.7	44.8	
	$\Delta E_{M+\ /\ Water}$	0.0	(-27.9)	-24.0	-24.5	-32.4	
	$\Delta E_{Host\ /\ Water}$	0.0	(-56.7)	7.4	6.6	10.3	-68.6
part	nb_{H_2O} [a]	841		895	853	892	874
	$\Delta E_{M+\ /\ Host}$	0.0	(-74.7)	13.9	12.9	17.6	
	$\Delta E_{M+\ /\ Water}$	0.0	(-47.8)	9.6	10.2	9.6	
	$\Delta E_{Host\ /\ Water}$	0.0	(-51.2)	-3.4	4.4	4.8	-67.3
1,3-alt	nb_{H_2O} [a]	932		893	932	837	918
	$\Delta E_{M+\ /\ Host}$	0.0	(-68.0)	11.9	9.4	14.5	
	$\Delta E_{M+\ /\ Water}$	0.0	(-20.9)	-0.9	-0.9	-0.8	
	$\Delta E_{Host\ /\ Water}$	0.0	(-54.6)	3.0	1.4	4.3	-61.2

a) number of H_2O molecules in the simulation box

$$\begin{array}{ccc} & \Delta G_1 & \\ M_1^+ + \mathbf{R} & \rightarrow & \mathbf{R}\,M_1^+ \\ \Delta G_3 \downarrow & & \downarrow \Delta G_4 \\ M_2^+ + \mathbf{R} & \rightarrow & \mathbf{R}\,M_2^+ \\ & \Delta G_2 & \end{array}$$

We first consider the *p-tert*-butylcalixC6 complexes, which remain of inclusive type during the mutations, as during the MD simulations. In the aqueous solution, the ΔG_4 free energies are close to those calculated *in vacuo*, and follow the same order for the three conformers: $Na^+ > K^+ > Rb^+ > Cs^+$. As *in vacuo*, the ΔG_4 free energy for mutating Na^+ to Cs^+ is smaller for the 1,3-alternate than for the cone form (21.5 and 36.6 kcal / mol, respectively). Taking into account the difference in free energies of hydration (30.4 kcal / mol), gives $\Delta G_c = \Delta G_3 - \Delta G_4$ = -6.2 kcal / mol for the cone form, and 8.9 kcal / mol for the 1,3-alternate form. In other words, we predict that in *an aqueous environment, the cone calixC6 binds Na^+ better than Cs^+, whereas the 1,3-alternate form binds Cs^+ better than Na^+*. For the partial cone conformer, no marked Na^+ / Cs^+ selectivity is found.

The same conclusion can be reached by using the "water corrected gas phase model" with $\Delta G_c = \Delta G_3 - \Delta G_{4gas}$, since ΔG_{4gas} and ΔG_{4water} values are very close for a given conformer (Figure 5).

Let us now consider the H-calixC6 complexes. In water, some of the ΔG_4 values are only indicative, since the cations may decomplex during the mutation or during the 50 ps MD equilibration. This is the case for Rb^+ and Cs^+ cone complexes, and for the Na^+ 1,3-alternate complex of H-calixC6. In those cases, there is therefore no thermodynamic equilibrium. Anyway, for the 1,3-alternate complexes, it is clear that Cs^+ is preferred over Na^+ which spontaneously dissociates. For the other pairs of cations, energy differences ΔG_c are less than 1 kcal / mol and the K^+, Rb^+ and Cs^+ complexes have similar stability. In the cone complexes, we predict Na^+ to be preferred over K^+ (ΔG_c = 4.2 kcal / mol), as for the *p-tert* butylcalixC6. This similarity is not surprising, since H or *tert*-butyl groups are remote from the cation binding site. The K^+ cone complex is more stable than the Rb^+ and Cs^+ complexes which dissociate during the mutation. For the partial cone H-calixC6 complexes, only Na^+ remained complexed. The K^+, Rb^+ and Cs^+ cations decomplexed spontaneously during the equilibration step.

For the calixC5 complexes, no FEP study in explicit water solution was performed, but some insight can be gained by using the "water corrected gas phase approach". Results displayed in Figure 5 demonstrate, like for the calixC6, a clear *conformation dependent cation binding selectivity*. Na^+ is preferred over Cs^+ by the cone conformer while for the partial cone and 1,3-alternate form the binding selectivity is less pronounced, and the sequence is $K^+ \approx Rb^+ \approx Cs^+ > Na^+$. More quantitative computational insights would require explicit MD and FEP studies with explicit water.

Relative free energies of Na^+ / Cs^+ extraction from water to an organic phase

Our calculation allow to gain insight into the *extraction* of alkali-cations from an aqueous to an organic phase, based on the following scheme:

$$\begin{array}{ccc} & \Delta G_1 & \\ M_{1_{wat}}^+ + \mathbf{R}_{org} & \rightarrow & \mathbf{R}\,M_{1_{org}}^+ \\ \Delta G3_{wat} \downarrow & & \downarrow \Delta G4_{org} \\ M_{2_{wat}}^+ + \mathbf{R}_{org} & \rightarrow & \mathbf{R}\,M_{2_{org}}^+ \\ & \Delta G_2 & \end{array}$$

The following assumption are made: (i) the concentration of free ions in the organic phase is negligible, they are only in water, (ii) the free and complexed ionophore *R* are present only in the organic phase; (iii) in the organic phase, the difference in solvation free energies ΔG_{4org} are close to the values in water ΔG_{4vacuo}. This scheme is therefore equivalent to the "water corrected gas phase model" referred to above.

The difference in extraction selectivity between the cations M^+_1 and M^+_2 is $\Delta G_{ext} = \Delta G_{3wat} - \Delta G_{4org} \approx \Delta G_{3wat} - \Delta G_{4gas}$. It is clear from Table 3 and Figure 5 that again we would conclude that *the 1,3-alternate form of p-tert-butylcalixC6 extracts Cs^+ better than Na^+* (ΔG_{ext} =

Table 6 *p-tert*-butylcalixC6 in water: Differences in free energies ΔG_4 and relative free energies of complexation $\Delta G_c = \Delta G_3 - \Delta G_4$ (kcal / mol) Aqvist M^+ parameters.

		Na^+ -> K^+	K^+ -> Rb^+	Rb^+ -> Cs^+	Na^+ -> Cs^+
	ΔG_3	17.6	5.1	7.7	30.4
cone	ΔG_4	21.1	6.6	8.9	36.6
	$\Delta G_3 - \Delta G_4$	-3.5	-1.5	-1.2	-6.2 [a]
part	ΔG_4	18.5	6.7	7.0	32.2
	$\Delta G_3 - \Delta G_4$	-0.9	-1.6	0.7	-1.8
1,3-alt	ΔG_4	12.4 [c]	3.2	5.9	21.5
	$\Delta G_3 - \Delta G_4$	5.2	1.9	1.8	8.9 [b]

a) Na^+ preferred over Cs^+; *b)* Cs^+ preferred over Na^+; *c)* mutation achieved in 101 windows for a total simulation time of 505 ps. Using the standard procedure (11 windows; 55 ps) give an important hysteresis, with ΔG_4 = 18.3 kcal / mol for Na^+ -> K^+ and ΔG_4 = -11.8 kcal / mol for K^+ -> Na^+.

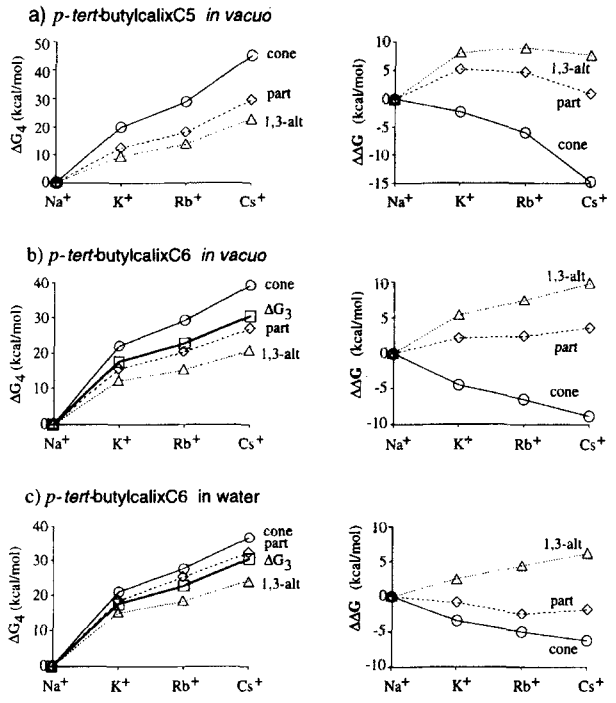


Figure 5 Graphical representation of FEP results for *p-tert*-butylcalixC5 *in vacuo* (a) *p-tert*-butylcalixC6 *in vacuo* (b) and in water (c). Left: relative free energy for mutating the free cation (ΔG_3) or the complexed cation (ΔG_4). Right: relative binding affinities $\Delta G_c = \Delta G_3 - \Delta G_4$ (see text). For (a) and (b) *in vacuo*, we use $\Delta G_{3(wat)} - \Delta G_{4(vacuo)}$ ("water corrected gas phase model"). The Na^+ complex is taken as a reference for all mutations, *i.e.* corresponds to M_1^+ in the thermodynamic cycle (see above). A negative $\Delta\Delta G_c$ value for M_2^+ implies that Na^+ is preferred over M_2^+.

+9.8 kcal / mol), while *the cone form would extract Na^+ better than Cs^+* (ΔG_{ext} = -8.8 kcal / mol).

This prediction has been fully confirmed from the computational side by MD simulation in pure chloroform[82], and from the experimental side by extraction studies[3].

Dynamics of the Na^+ and Cs^+ *p-tert*-butylcalix-C6 complexes at a chloroform / water interface. We simulated the Na^+ and Cs^+ complexes of *p-tert*-butylcalixC6 at a chloroform / water interface in order to test computationally their time evolution, and in particular whether they spontaneously migrate to chloroform. Because such calculations are quite computer time demanding, they were restricted to short time scales (100 ps). This should not be sufficient to observe a complete diffusion of the solute, but may be enough to escape from a metastable situation, and to observe important trends. This is indeed what is found.

At the beginning, all solutes were placed at the interface, symmetrically shared by the chloroform and water phases (Figure 7, top). In all cases, the solute moves rapidly (less than 20 ps) to chloroform, but seems to be "anchored" at the interface. All solutes rotate in such a way that the hydrophobic *tert*-butyl groups are completely immersed in chloroform, while the polyether chain remains in loose contact with water (Figure 7). Again important conformation dependent behaviour is observed. The Cs^+ 1,3-alternate complex remains inclusive, whereas the Cs^+ cone complex spontaneously dissociates: Cs^+ diffuses by about 14 Å towards the bulk aqueous phase, while the host remains at the interface, with water molecules hydrogen bonded to crown ether oxygens. The Na^+ cone and 1,3 alternate complexes remain inclusive, with Na^+ deeply anchored by the four phenoxy oxygens, as in pure water, and the crown partially hydrated. Thus, all M^+ complexes seem to remain near the interface, almost completely immersed in chloroform.

One possible explanation of these "stationary state" is the lack of a accompanying counterion in these simulations. We therefore simulated the Cs^+ 1,3-alternate complex, in the presence of a picrate counterion, initially loosely bound to Cs^+ (Figure 7, bottom), under the same conditions as above. After 100 ps, this complex also remains close to the interface, as without counterion, however with a different orientation: the S_4 symmetry axis of the calixarene is now more parallel to the interface, the picrate anion remains in loose contact with the Cs^+ crown moiety of the solute and adopts an orientation tangential to the interface. Then, the soft picrate anion, widely used in extraction experiments, seems to display a comparable preference for the two phases and remains exactly parallel to the interface. This contrasts with the Cl^- anion which, simulated under the same conditions, diffuses rapidly from the interface to the water phase[83].

DISCUSSION

We report computations on the binding of alkali cations to 1,3-dimethoxy-calix[4]arene-crown5 and -crown6, and compare the binding selectivity for the different ions as a function of the conformation of the host, *in vacuo* and in an aqueous environment

Not surprisingly, for all conformers of these hosts, the intrinsic binding selectivity is largest for Na^+, and follows the sequence $Na^+ > K^+ > Rb^+ > Cs^+$ in the gas phase, as for 18-crown-6 or the *222* cryptand complexes, or alkali cation water interactions in the gas phase[56]. Intrinsically, none of the conformers prefers Cs^+ over Na^+.

The best receptor for Cs^+ in water known to date to our knowledge is the SC24 tricyclic cryptand, which also displays a high Cs^+ / Na^+ selectivity ($\log_{Ks}$ = 3.4 and 1.6, respectively)[57], based on its large, rigid and preorganized cavity. Large bicyclic cryptands such as *322* are less

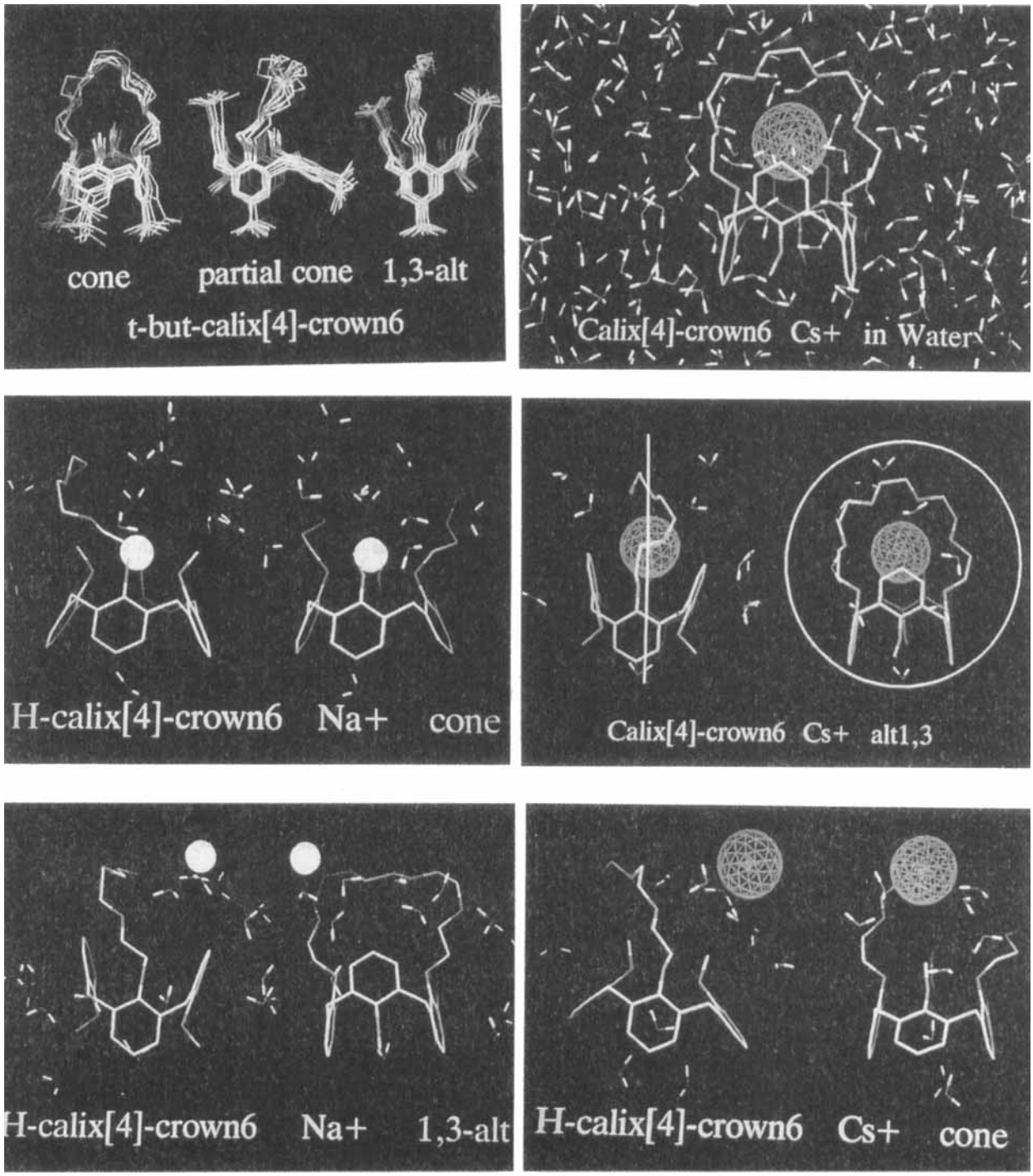


Figure 6 (Color): Top: the *p-tert*-butylcalixC6 host free *in vacuo* (cumulated views, after 50 ps of MD) and the calixC6 Cs^+ complex in the box of water molecules. Middle: the H-calixC6 complexes in water, after 50 ps: the stable Na^+ cone and Cs^+ 1,3-alternate complexes. Bottom: the unstable H-calixC6 Cs^+ cone, and Na^+ 1,3-alternate complexes in water, after 50 ps. Orthogonal views. (See Color Plate XXV.)

specific ($\log_{Ks}$ = 2.0 for Cs^+ and 1.65 for Na^+), because they are flexible and able to wrap around cationic guests of various sizes. These cryptate complexes, however, adopt similar conformations in most of their cation complexes, due to topological constraints [55]. The case of calixcrowns studied here is different since they may adopt different conformations, such as cone, partial cone, 1,3-alternate which, depending on the bulkiness of R substituents, are conformationally locked or labile [3]. One advantage of the calculations is to select a given form and compute its structure, binding properties and selectivity. We find that a given complex displays marked conformational preferences *in vacuo*. In particular, Cs^+ prefers the 1,3-alternate over the partial cone and the

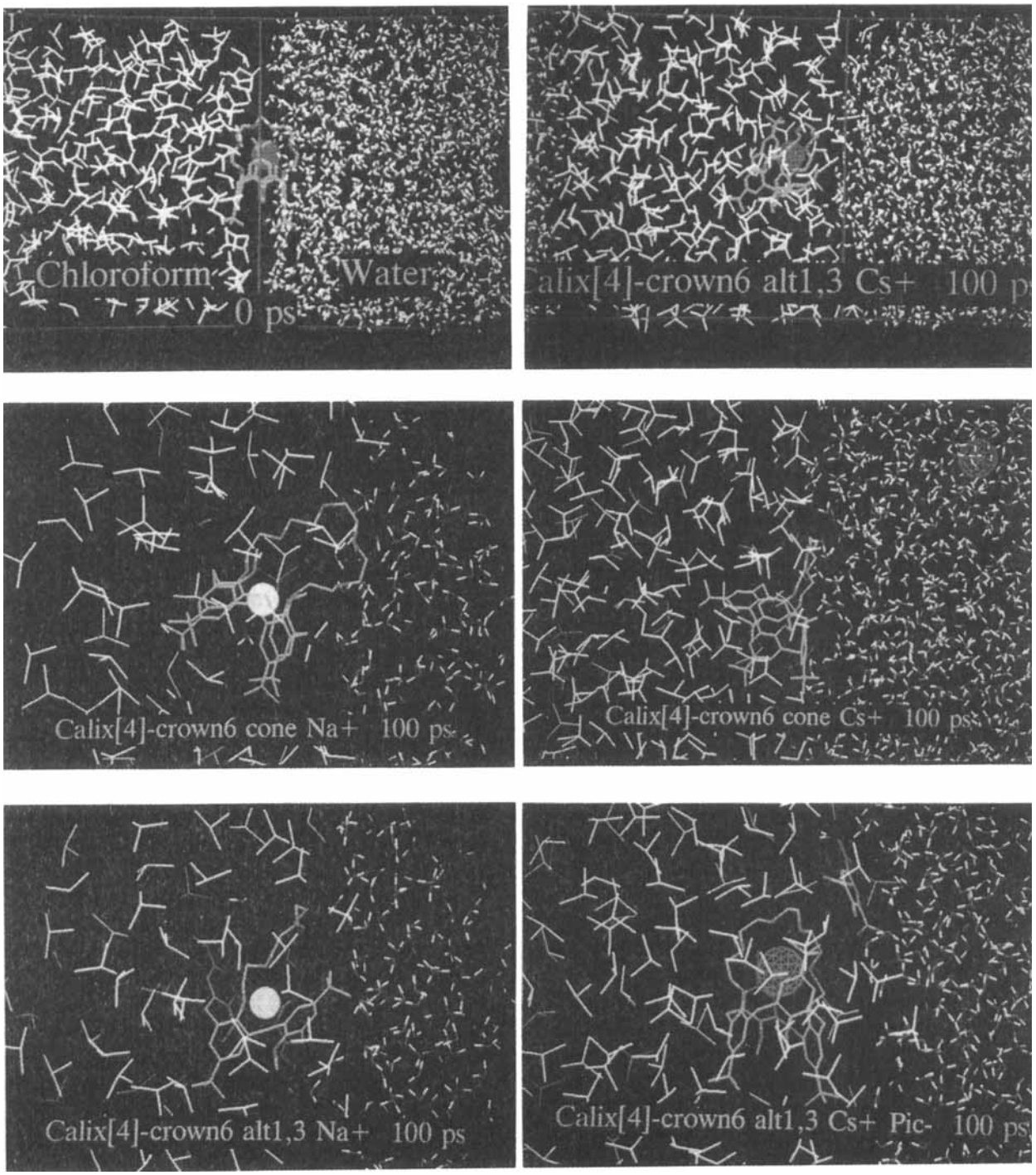


Figure 7 (Color): Na^+ and Cs^+ complexes of *p-tert*-butylcalixC6 at the chloroform / water interface. Top: the 1,3-alternate Cs^+ complex at 0 ps (left) and after 100 ps (right). Middle: the cone Na^+ (left) and Cs^+ (right) complexes after 100 ps. Bottom: the 1,3-alternate Na^+ (left) and Cs^+Pic^- (right) complexes after 100 ps. (See Color Plate XXVI.)

cone conformations while the Na^+ complex is most stable in the cone form of calixC6.

Conformation dependent Na^+ / Cs^+ binding affinity in an aqueous environment

In solution, the binding selectivity results from a compromise between the host / guest attractions, and solvation effects. An important contribution is the desolvation energy of M^+ upon complexation[58], which is largest for Na^+ and smallest for Cs^+. A second contribution is the solvation of the complexed cation, which is nearly constant for the 1,3-alternate calixC6 complexes, but conformation and ion dependent for the other complexes. We show that the interplay of solvation, and the confor-

mation dependent M^+ / host attractions lead to a *marked conformation dependent Na^+ / Cs^+ binding affinity* of calix[4]crowns. The cone form of calixC6 binds Na^+ better than Cs^+, while the 1,3-alternate form prefers Cs^+. Our conclusion is based first on free energy simulations in water, which take into account the dynamic properties of the solute and the solvent and, in principle, entropy effects. This is supported also by MD experiments on the H-calixC6 complexes in water, starting with cations encapsulated within the crown ether ring: Na^+ decomplexes from the 1,3-alternate form, and Cs^+ from the cone form, whereas the Cs^+ alternate and Na^+ cone complexes are stable and remain inclusive in the same conditions. This is also fully consistent with two experimental results. First, NMR shows that in acetonitrile the Na^+ complex of 1,3-dimethoxy-calixC6 is cone, while its Cs^+ complex is 1,3-alternate[3]. Second, in terms of stability and preorganization, it is also remarkable that the Cs^+ complex of the conformationally locked 1,3-alternate 1,3-diisopropoxy-calixC6 is more stable than the Cs^+ complex of the conformationally mobile dimethoxy analogue, likely as a result of the preorganization of the host[3].

For the calixC5 host, the calculations were restricted to the gas phase to limit the computer time, and because it was clear that this host is too small for Cs^+. Based on the calculations, no conclusion can be therefore drawn concerning the binding selectivity in solution. To a first approximation, one may correct the gas phase ΔG_4 free energies by the differences in dehydration free energies ΔG_3. The results (Figure 5) give a *conformation dependent binding selectivity for H-calixC5*, in the order $Na^+ > K^+ > Rb^+ > Cs^+$ for the cone, $Na^+ < K^+ > Rb^+ > Cs^+$ for the partial cone, and $Na^+ < K^+ < Rb^+ > Cs^+$ for the 1,3-alternate form. This crude procedure is however somewhat questionable, especially when the cation is not shielded from water. Experiments in $CDCl_3$ saturated with water give a peak for K^+ for the three conformers of conformationally locked 1,3-diethoxy-calixC5, with a stability increasing in the order: cone < 1,3-alternate < partial cone [3]. For the conformationally mobile 1,3-dimethoxy-calixC5, the Rb^+ and K^+ cations are extracted selectively from water to chloroform, presumably in the flattened cone conformation[10]. How these extraction results relate to structure and complex stability in pure solvents remains to be clarified by further studies.

Conformation of the free calixcrowns and of their complexes in solution: on the *importance of conformation dependent solvation energies*

In view of possible kinetic exchange between several conformers, it would be desirable to predict which conformer of the free or complexed host is most stable in solution. A detailed energy component in solution cannot answer this question, because (i) the boxes of solvent have different numbers of particles, (ii) the energy cost for creating a cavity in the solvent depends on the shape and size of the solute, and (iii) there are large statistical fluctuations in solution.

For the free hosts, NMR studies in chloroform solution indicate that calixC5 and calixC6 uncomplexed are present mostly in the cone form[10]. The calculations *in vacuo* predict however a larger stability for the 1,3-alternate form. We believe that this is not inconsistent, but may be instead taken as an indication of significant *conformation dependent solvation energies*. This is not uncommon, as shown previously for 18-crown-6 [32], and the 222 cryptand[30] in water and in acetonitrile [32]. Based on MD and Monte Carlo simulations on crown ethers and the 222 cryptand we demonstrated the *importance of solvent granularity*, with a particular emphasis on bridging water molecules which bring a major contribution to the solvation energy[59]. As a result, some conformers with zero dipole moment were calculated to be much better hydrated than others with large dipole moments, but whose topology does not allow for bridging solvation pattern[60]. In the case of calixcrowns, filling of the cone by solvent molecules such as MeCN, H_2O or MeOH may bring a significant stabilization of that form, compared to the 1,3-alternate of partial cone[36]. Stabilization of the cone by dipolar interactions is generally accepted [61], but "complexation" of weakly polar molecules such as $CHCl_3$ is also stabilizing (about 5 kcal / mol, mostly of van der Waals origin)[62]. Conformation dependent solvation by a weakly polar solvents can also be considered, as an interplay of solvent accessible hydrophilic and hydrophobic surfaces. In fact we performed recently MD simulations on H-calix[4]-*bis*-crown5 and -crown6 complexed by M^+ cations in chloroform (explicit representation), and found significant solute-solvent interaction energies, mostly of van der Waals origin (about -52 and -60 kcal / mol, respectively)[67]. For the *p-tert*-butylcalix[4]arene$^-$ anion[62] in pure chloroform, we found about -60 kcal / mol. For the cone, partial cone and 1,3-alternate forms of H-calixC6, an empirical estimation of the "solvation free energies" by the GB / SA method implemented in MACROMODEL gives -25.0, -22.6 and -21.3 kcal / mol respectively in chloroform (Table 7). These numbers follow the order of the conformation dependent solvent accessible surface (respectively 1118, 1064 and 998 $Å^2$) and demonstrate that, even in weakly polar solvents such as chloroform or dichloromethane, *conformation dependent solvation of the solute* has to be taken into account. This is confirmed by MD simulations in chloroform solution, using an explicit representation of the solvent, with different protocoles[82]. They show that the cone conformer of calixC6 has larger inateraction with chloroform thatn the 1,3-alternate one (Table 7).

The solvation effect by water on conformational preferences is supported qualitatively by the energy analysis of X-calixC5 and X-calixC6 in water. For these hosts, as *in vacuo*, the 1,3-alternate forms are more stable than the cone form (<ΔE> = 11 and 8 kcal / mol, respectively for X = *tert*-butyl and <ΔE> = 9 and 4 kcal / mol, respectively for X = H). However, the cone forms have clearly larger interactions with water (<ΔE> = 8 and 7 kcal / mol, respectively for X = *tert*-butyl and <ΔE> = 6 and 7 kcal / mol, respectively for X = H), because crown ethers are better solvated. The empirical estimation of the solvation energies of H-calixC6 using MACROMODEL also indicates that the cone is better "hydrated" than the partial cone or 1,3-alternate forms (E_{solv} = -19.4, -13.2 and -12.7 kcal / mol, respectively) (Table 7).

From a computational side, it was noticed in a previous molecular mechanics study on tetramethoxy-calix[4]-arenes with the CHARMM force field[63] that the calculated stability of the 1,3-alternate may be exaggerated. We dissected therefore our minimized energies E_{opt} into electrostatic, van der Waals, and other components, and found that the electrostatic terms favours clearly this form over the cone. However, repeating the calculations with a dielectric constant ϵ of 2 or 10 still predicted the 1,3-alternate to be more stable (ΔE_{opt} = 7 and 3.5 kcal / mol, respectively) (Table 7). The "size" of aromatic carbons was also varied, repeating the MD simulations and minimizations with a smaller R* parameter (1.65 instead of 1.85 Å). The same trends was found, as above, in favour of the 1,3-alternate form. These results, taken together with the above analysis of conformation dependent solvation energies, suggest therefore that the differences between gas phase and solution stability are markedly modulated by the solvent. Environment effects in the solid state may also perturb the structure, compared to the "gas phase" simulated structure[64].

For the cation complexes, we calculate that *in vacuo* Na^+ prefers the cone, while Cs^+ prefers the 1,3-alternate form. In solution, the complex interplay between ion-solvent, host-solvent and host-guest interactions may also lead to conformational preferences, which cannot be predicted from the computations only.

Conformation dependent binding selectivity in non-aqueous solvents. Although our calculations have been performed in water, it can be speculated that in solvents such as acetonitrile or methanol, where the calixcrowns are soluble, the 1,3-alternate form of calixC6 will also bind selectively Cs^+ over Na^+. The argument is based on the fact that the difference in free energies of solvation ΔG_3 of these ions is similar in water, methanol and acetonitrile (30.4, 32.1 and 29.7 kcal / mol, respectively[65]), and on the cation shielding from the solvent in the complex. As a result, the ΔG_3-ΔG_4 should be positive, i.e. Cs^+ complexed better than Na^+. This speculation has been confirmed recently by the experimental determination of stability constants in methanol[66] and by an extensive MD-FEP study of the conformationally locked calix[4]-*bis*-crown6 in methanol[67]. For the other forms, where the cation is not shielded from solvents, no simple conclusion can be drawn.

In dry chloroform, we anticipate that the binding sequence should be the same as in the gas phase, i.e. Na^+ preferred ($Na^+ > K^+ > Rb^+ > Cs^+$) by the three forms, with a larger affinity in the cone than in the 1,3-alternate form. This is fully confirmed by our recent MD FEP simulations on the M^+ calix[4]-*bis*-crown5, -*bis*-crown6 and 1,3-dimethoxy-*p*-*tert*-butylcalixC6 complexes[67,82].

On the effect of OR substituents. In the 1,3-alternate form, the OMe groups are not involved in the binding sphere of the cation, and one anticipates that a OMe ->

Table 7 *p*-*tert*-butylcalixC6 host uncomplexed. Relative minimized energies *in vacuo* (ΔEopt) and solvation energies (kcal / mole) of the three conformers[a]. Total energies are given in parethesis.

	R^*_{CA} [b]	ϵ[c]	cone	part	1,3-alt	
ΔE_{opt} [d]	1.85	1	10.6	4.0	0.0	(119.3)
		1	0.5	0.4	0.0	(10.4)
		2	7.0	2.4	0.0	(85.2)
		10	3.5	0.5	0.0	(57.9)
	1.65	1	8.0	2.4	0.0	(88.0)
		2	4.6	2.1	0.0	(52.9)
		10	0.9	1.7	0.0	(24.4)
$\Delta E_{hydr.}$ (TIP3P water)[e]			-7.4	-6.1	0.0	(-61.2)
$\Delta E_{hydr.}$ (GB / SA)[f]			-6.7	-0.5	0.0	(-12.7)
$\Delta E_{solv.}CHCl_3$ (GB / SA)[f]			-3.7	-1.3	0.0	(-21.3)
$\Delta E_{solv.}CHCl_3$[g]			-2.3	3.7	0.0	(-62.7)
$\Delta E_{solv.}CHCl_3$[h]			-4.4	-0.6	0.0	(-69.2)
$\Delta E_{solv.}CHCl_3$[i]			-2.6	1.8	0.0	(-77.6)

a) Unless otherwise specified the Gasteiger charges are used on the host *b)* van der Waals R* parameter of aromatic carbons; *c)* dielectric constant for calculating the coulomb interaction; *d)* CHARMM charges (from reference 26) on the calixarene host, *e)* average hydration energies from MD simulations in a box of explicit water molecules; *f)* solvation energies from the empirical model of Still *et al.* (MACROMODEL software), *g)* rigid chloroform (10 Å cut-off); *h)* rigid chloroform (15 Å cut-off); *i)* flexible chloroform (15 Å cut-off).

OR substitution (R bulkier alkyl groups) will make the host more lipophilic, but not perturb its binding ability and selectivity. In the partial cone calixC6, where one OMe group shields M^+ from the solvent, the OMe -> OR substitution should have also little effect. In the cone form, the OR groups may shield the cation from solvent, and perturb significantly the binding ability.

The question of cation-π interactions. In the 1,3-alternate form of calixC5 and calixC6 complexes, the cation is in close contact with aromatic rings. For instance, the average of the four distances between M^+ and the center of the two pairs of opposite aromatic rings are (3.3 / 4.1), (3.4 / 4.9) and (3.7 / 5.4)Å respectively for the Na^+, K^+, Cs^+ *p-tert*-butylcalixC6 complexes, and (3.1 / 4.6), (3.4 / 5.1) and (3.7 / 5.5) respectively for the H-calixC6 complexes (Amber M^+ parameters, Table 4). In the solid state structures of calixarene complexes such short contacts are also found (*e.g.* in the Cs^+ dimethoxy-H-calixC6 alternate, K^+ 1,3-diethoxy-*p-tert*-butylcalixC5 cone and partial cone[3], or Rb^+ 1,3-dimethoxy-*p-tert*-butylcalixC5 flattened cone[10] complexes). In the solid state of the Cs^+ calix[4]arene-salt, Cs^+ sits inside the cone[68,69]. It has been speculated that the unusual ionophoric behaviour of calix[4]arene derivatives in the 1,3-alternate conformation involves cation - π interactions[3,41,70]. We do not support the view of "special" interactions in favour of Cs^+ or large alkali cations. In the gas phase, the benzene molecule displays instead the largest attractions with the smallest alkali cation Li^+, and the binding sequence is $Li^+ > Na^+ > K^+ > Rb^+$. This is supported by high quality quantum mechanical calculations[71] and gas phase experiments[72,73]. The aromatic residues behave as large delocalized pseudo-anions, and follow the same binding sequence as $M^+ Cl^-$, i.e. have the weakest interaction energy with Cs^+[71]. In the gas phase the phenolate residues of calixarenes should display the same sequence, as found in our calculations on all complexes using a standard 1-6-12 potential for non-covalent interactions, without special additional term[85]. Taking into account the aqueous solvent reverses the trend in binding affinities, and demonstrates that *the stability of the Cs^+ 1,3-alternate complex results mostly from differential solvation effects*. Although Cs^+ interacts less with the calixC6 than Na^+, it is more easily desolvated. Within the complex however, Cs^+ remains attracted by the phenolate dipoles, and by the soft delocalized aromatic electronic cloud, but this is not the leading energy contribution. In the case of soft cations such as Ag^+, which is also complexed by the 1,3-alternate calix[4]arenes[41] it is clear that the interactions with the aromatics are of different nature as for Cs^+, and involve significant orbital overlap and charge transfer between the partners.

Possible counterion effects in solution. In aqueous solution, the complexed cation is separated from its counterion, which may be to a first approximation neglected in the calculations. In non-aqueous solvents, the status of ion pairs is less clear, and depends on the ligand. For instance, it was shown by MD simulations that in acetonitrile solution, the cryptate 222 K^+ dissociates from Cl^-, while 18-crown-6 K^+ Cl^- remains as an intimate ion pair[32]. In cation extraction experiment from water to chloroform, the precise role of counterions is not clear. For instance, the picrate anion is not only more soluble in the organic phase, but may be also involved in direct coordination to the complexed M^+, as suggested by several solid state analogy[3,10]. According to MD and PMF simulations on the 18-crown-6 K^+ X^- complex (X = Cl or Picrate) the X^- counterion forms an intimate pair with K^+ in acetonitrile, but dissociates rapidly in water[74]. In acetonitrile, the lifetime of intimates M^+ X^- ion pairs is shorter with picrate than with Cl^- anions[74]. The conformation and substituent dependent water coordination to M^+ found in our simulations suggests that counterion effects should also be conformation dependent. Counterions cannot form an intimate ion pair with the *p-tert*-butylcalixC6 alternate M^+ complex, in contrast with the H-calixC6 alternate, or *p-tert*-butylcalixC6 cone complexes. This question requires further experimental and theoretical investigations. On the related conformationally locked 1,3-alternate M^+ calix[4]-*bis*-crown6 complexes simulated in methanol starting with the picrate counterion in intimate contact with M^+, ion pair dissociation took place rapidly with the Na^+ and K^+ complexes, but not with the most stable Cs^+ complex[67].

In non-aqueous solvents such as pure chloroform, counterions form intimate ion pairs with the free cations, and possibly with some of the complexed cations. We have indeed shown that in chloroform, the M^+ complexes of calix[4]-*bis*-crown6 remain in contact with the Pic^- counterion, which therefore modifies the relative binding affinities determined by FEP simulations. Similarly, the calix[4]arene$^-$ anion forms an intimate ion pair with alkali cations in chloroform, but dissociates in water[62].

The H / *tert*-butyl upper rim substituents on the calixarene: thermodynamic / kinetic effects. We have shown that most of the calculated structural and binding features of the X-calixC5 or X-calixC6 complexes are nearly identical when X = H or *tert*-butyl. The major difference *in vacuo* concerned the large cation 1,3-alternate calixC5 complexes, where the *tert*-butyl groups prevent the Rb^+ and Cs^+ cations, too big for this host, to move out. In aqueous solution, we found that the *tert*-butyl groups provide a kinetic barrier for decomplexation of the 1,3-alternate Na^+ calixC6 and partial cone K^+, Rb^+ and Cs^+ calixC6 complexes, compared to

the H-calixC6 analogues. This means that the barrier for complexation should also be higher with X = *tert*-butyl than with H, because partial solvation of the cation is hindered in the transition state. It is therefore possible that some of the complexes cannot form, for kinetic reasons. This may be particularly the case for the *p-tert*-butylcalixC6 1,3-alternate complexes, or their conformationally locked analogues (e.g. *p-tert*-butylcalix[4]-*bis*-crown6).

The question of force field effects. In order to address the possible effects of the potential energy representation on calculated structures and affinities, we investigate two critical components, related respectively to the cation and to the aromatics moieties, which may be in close contact. For M^+ we used two representations, referred to as the Amber and Aqvist parameters. They were compared previously for cryptate complexes in acetonitrile solution, and found to give very close structural and energy results for $Na^+ - Cs^+$ [32]. We confirm (Table 3) that the ΔG_4 free energy difference for Na^+ / Cs^+ obtained *in vacuo* are very close with the two sets.

Another issue was the electrostatic representation of the phenolate fragments. The charges derived by Grootenhuis *et al.* using 6-31G* electrostatic potentials give very polar aromatic carbons (0.46; -0.66; 0.45; -0.23)[35]. The set of charges derived from MNDO electrostatic potentials, used previously for calix[4]arene-tetraamide complexes, is also somewhat polar (-0.05; -0.37; 0.23; -0.05[36]), which might bias the interaction with cations. The charges depend on the basis set and quantum mechanical method[75], fitting procedure[75], and inclusion of polarization term[76]. We therefore decided to use very weakly polar set for the aromatic fragment throughout this whole study. The free energy simulations ΔG_4 *in vacuo* were repeated on the *p-tert*-butylcalixC6 complexes, using the Grootenhuis 6-31G* derived charges[35], and our MNDO[36] derived charges. The 1,3-alternate form was chosen because it displays the shortest contacts between M^+ and the aromatic groups. In fact, the ΔG_4 calculated with these charges for Na^+ / Cs^+ are respectively smaller (17.2 kcal / mol) and larger (23.5 kcal / mol) than the ΔG_4 calculated here with the Gasteiger charges (20.5 kcal / mol). Using the CHARMM charges[26] gives ΔG_4 = 25.0 kcal / mol (Table 3). The largest differences come from the Na^+ / K^+ mutation, i.e. involve the cation which is the most weakly bound. This strengthens our qualitative conclusions on the Na^+ / Cs^+ conformation dependent binding selectivity, which is therefore not critically dependent on our force field representation.

Complexed ionophores at the chloroform / water interface. Preliminary molecular dynamics investigation are reported for the Na^+ and Cs^+ complexes of *p-tert*-butylcalixC6, starting exactly at a chloroform / water interface. These complexes are found to first migrate somewhat to the organic phase, and then to remain more or less in contact with the interface, without achieving further migration to the chloroform phase. The complexed inonophore remains adsorbed at the interface like surfactants. Such behaviour may seem surprising given the ionophoric properties of these calix[4]arenes[3]. We checked that making the calix[4]crown more lipophilic by substituting O-methyl by O-octyl groups did not lead to spontaneous diffusion to chloroform either. Indeed, the Cs^+ Picrate$^-$ complex of 1,3-di(n-octyloxy)calix[4]-crown6 remained similarly anchored at the interface for 350 ps of simulation, with the alkyl chains pointing to chloroform, and the complexed crown in contact with the water interface[82]. The computational side clearly deserves further studies concerning the time scale simulated, the size of the solvent boxes, the force field representation of the solvents (in particular polarization effects in chloroform), etc. However, the present results strongly suggest that migration from the interface to chloroform is not a simple downhill process. Whether it involves some kinetic barrier or a "flat energy profile" is not clear at the present stage.

The gradient of ion concentration, known experimentally to force the extraction or transfer, but not represented in the calculation, may also be of critical importance. More detailed mechanistic studies, involving the status of ion pairs in the two phases and the water dragging effect, are required. Computations on related systems involving energy component analysis, investigation of protocols and PMF calculations of ion migration are presently prepared in our laboratory.

CONCLUSION

We have reported the first theoretical investigations on calix[4]crowns and their alkali cation complexes with a systematic comparison of three typical conformers. Based on MD and FEP simulations *in vacuo* we find that intrinsically, the three conformers of the host bind Na^+ better than Cs^+. However, taking into account explicitly the solvent effects leads to a marked *conformation dependent binding selectivity in water*. The *p-tert*-butylcalixC6 in its cone conformation is a poor binder for Cs^+, and is predicted to form a more stable complex with Na^+. In the 1,3-alternate form, a complete reversal is calculated, and Cs^+ is calculated to be bound preferentially over Na^+. It is predicted that the same selectivity for Cs^+ should be displayed by conformationally rigid 1,3-alternate hosts such as calix[4]-*bis*-crown6, or

dialkoxy-derivatives OR (R larger than Me) in water, methanol and acetonitrile. This has been confirmed recently in a MD FEP study of calix-*bis*-crown6 in these solvents[67]. For the partial cone conformer, no marked Na^+ / Cs^+ selectivity is found. Similar trends are found for the H-calixC6 host in water environment, which remains as a kinetically stable Cs^+ complex in its 1,3-alternate form, and a stable Na^+ complex in the cone form, whereas the Cs^+ cone and Na^+ 1,3-alternate complex dissociate rapidly in solution.

Beyond the complexation in a pure homogeneous solvent, the extraction or transfer of ions from an aqueous to an organic phase mediated by ionophores represents a process of fundamental importance in chemistry and biology. Up to now, there are no clear microscopic pictures of the related mechanistic events. We present the first simulations on complexed ionophores, with or without counterion, at the chloroform / water interface. They raise questions about the nature of driving forces for ion extraction: enthalpic / entropic origin, solute-solvent and solvent-solvent interactions, status of ion pair in the two phases, etc. It is hoped that computer simulations[83,84] and experimental studies will shed light on the "lock and key" recognition process.

Although the present computations are close to the present state of the art, we would not be surprised if experimental results on complexation or extraction, when available, are quantitatively different. It was found for instance that the peak of selectivity of K^+ by the *222* cryptand in water, methanol and acetonitrile was qualitatively accounted for, but somewhat exaggerated[32]. Most of the previous theoretical studies on binding selectivity was obtained after the experimental stability constants were known. The present study will hopefully stimulate such experiments[77], and further refinement of theoretical approaches. In particular, the role of water in the organic phase on the efficiency and selectivity of extraction has to be investigated at the microscopic level. The conformation of the lock, of the lock-and-key complex, and the recognition process, in essence dynamics, are clearly environment and solvent dependent.

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77 This manuscript was submitted in July 1994. A preliminary report was presented before[78]. Since then, three important publications appeared concerning the Na^+ / Cs^+ extraction of conformationally flexible / rigid calix[4]arene derivatives[79-81]; the stability constants in methanol have also been determined[80]. Alkali cations transport experiments through supported liquid membranes and extraction data has been reported for various calix-crown and calix-*bis*-crown derivatives as ionoophores[81]. These results fully support our conclusion on the conformation dependent Na^+ / Cs^+ selectivity and on the high Cs^+ ionophoricity of the 1,3-alternate form of calix-C6.
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