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Complexation of Calix[4]arene With Alkali Metal Cations: Conformational Binding Selectivity and Cation– π Driven Inclusion

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Hartree–Fock, second order Møller–Plesset perturbation theory, and density functional theory calculations were carried out to analyse the complexation of calix[4]arene with cationic species including H⁺ and the alkali metal cations (Li⁺, Na⁺, K⁺, Rb⁺, and Cs⁺). Special emphasis has been placed on conformational binding selectivity, and on the structural characterization of the complexes. Li⁺ and Na⁺ cations are located in the calix[4]arene lower rim. The larger cations (K⁺, Rb⁺, and Cs⁺) complex preferentially with the calix[4]arene cone conformer, and their *endo* (inclusive) complexation is driven by cation– π interactions, leading in the case of K⁺ to a structure that reflects a preferential interaction with two phenol rings. The *endo* complexation of Cs⁺ with calix[4]arene is in agreement with X-ray diffraction data.

Keywords: Complexation of calix[4]arene; Alkali metal cations; Conformational binding; Cation– π driven inclusion

INTRODUCTION

The interactions between charged species and macromolecules are a fundamental aspect related to the complexation mechanism in supramolecular chemistry. In this field, recognition is determined by preferential and specific host–guest intermolecular interactions [1]. In addition, it is also known that the understanding, from a microscopic point of view, of the complexation/recognition mechanism in supramolecular chemistry will provide new routes for the

design of sophisticated sensors at a molecular level [2].

One family of model systems in supramolecular host–guest chemistry is the family of calix[n]arenes [3–7]. Calix[n]arenes are [1_n]-metacyclophanes composed of phenol units bridged by methylene. The calix[n]arene designation is related to the shape of one of the conformers, the cone conformer, that resembles a chalice. Calix[n]arenes can be easily modified and are considered basic platforms supporting different arrays of functional groups able to act as binding sites and leading to a great variety of receptors designed to specific complexing tasks [3,8].

One important aspect of the calix[n]arene structures is their π -rich cavity that favours the inclusion of charged guest compounds that are stabilized by noncovalent binding forces related to cation– π interactions [9–13,15]. The physical model behind cation– π interactions that describe the binding of a cation to the π face of an aromatic structure is based on different contributions, including the electrostatic attraction between the cation and the aromatic quadrupole moment, non-additive polarization effects, and dispersion interactions [9,13]. Cation– π interactions are usually an important contribution to binding energies. One illustrative example is the cation– π binding energy of K⁺... benzene (19 kcal/mol) that is very similar to the binding energy of K⁺...H₂O (18 kcal/mol) [13].

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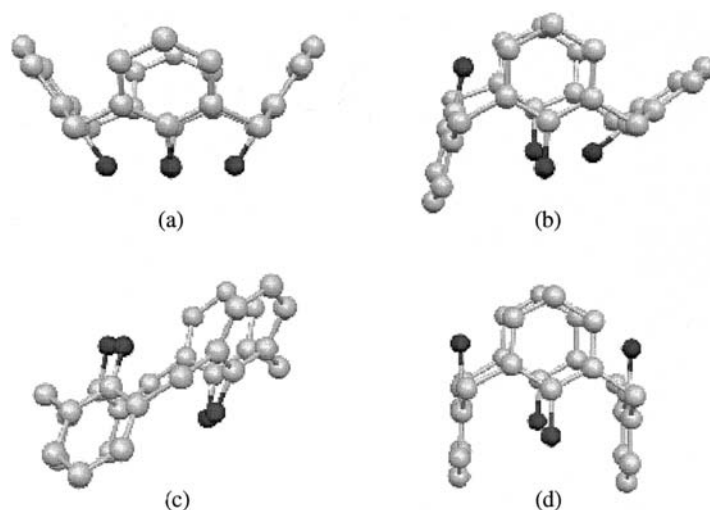


FIGURE 1 Calix[4]arene conformers. (a) cone (C); (b) partial-cone (PC); (c) 1,2-alternate (1,2-A); (d) 1,3-alternate (1,3-A). For clarity, only hydrogens in O–H bonds are shown.

Several experimental [16–26] and theoretical studies [19,27–30] on the complexation of calix[4]arenes with charged species have been reported. Most of the experimental studies were carried out in aqueous or polar media and provide fundamental information about biological recognition. The ability of a designed host to pull an organic cation out of a solvent is a feature typical of many complex biological processes [13]. A recent review article reports data on the solid state complexation of calixarenes with molecular structures [14].

The size and conformational complexity of calix[*n*]arenes or parent systems makes a full *ab initio* approach difficult. Thus, most of the studies on the complexation of calix[4]arenes were based on force field [19,27,28] or semiempirical quantum mechanics calculations [29]. One exception is the Hartree–Fock *ab initio* study of the gas phase complexation of alkali metal cations (Li^+ , Na^+ , and K^+) with the $\text{C}_{36}\text{H}_{36}$ spheriphane [30]. Recently, a density functional study of the calix[4]arene proton affinity and conformational equilibrium has been reported [31].

Very recently, a combined density-functional and second-order perturbation theory study of the complexation of the alkali cations Na^+ and Cs^+ with tetramethoxycalix[4]arene (TMC) has been reported [32]. This study concluded that the host–guest interactions involved in complexation of TMC with alkali cations are much more complex than previously assumed and stressed the importance of this feature for the design of new selective cation receptors. In this system, the methyl groups are attached to the oxygen atoms at the lower rim and intramolecular hydrogen bonding plays no part in

the energetical stabilization of the conformers [3]. Thus, it is expected that the conformational equilibrium of the TMC molecule and the binding modes with alkali cations are significantly different in comparison with calix[4]arene.

In the present work, we are providing an analysis of the gas phase complexation of calix[4]arene with cationic species including H^+ and alkali metal cations from Li^+ to Cs^+ . This analysis is based on Hartree–Fock and density functional theory calculations. Special emphasis is placed on conformational binding selectivity, which is one fundamental aspect in the complexation of supramolecular species. We are also reporting structural data for the complexes of calix[4]arene with alkali metal cations, and illustrating through the representation of the electrostatic potential over electronic isodensity surfaces some changes on the calix[4]arene electronic structure induced by complexation.

COMPUTATIONAL DETAILS

Geometry optimizations for the four calix[4]arenes conformers (Fig. 1) and their complexes with alkali metal cations (Fig. 4) have been carried out at the Hartree–Fock (HF) level. The structures were determined by complete optimizations without any symmetry constraint. The geometry optimizations have been carried out with the 3-21G (Li^+ – Cs^+) and 3-21G(d,p) (Li^+ – K^+). The 3-21G basis sets for Cs and Rb are from the Extensible Computational Chemistry Environment Basis Set Database.† Additional single-point energy *ab initio* calculations for Li^+ – K^+ were carried out at HF/6-31G,

†The 3-21G basis set for Cs and Rb are from the Extensible Computational Chemistry Environment Basis Set Database, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory which is part of the Pacific Northwest Laboratory, P. O. Box 999, Richland, Washington 99352, USA.

HF/6-31G(d,p), HF/6-311G(d,p), and second order Møller–Plesset perturbation theory MP2/6-31G(d,p) for complexes of Li^+ and Na^+ . Single-point energy B3LYP/6-31G(d,p) density functional calculations using Becke’s three parameter hybrid method [33], and the Lee, Yang and Parr correlation functional (LYP) [34], are also reported.

The binding energies for the complexes of calix[4]arene with Rb^+ and Cs^+ were calculated by using effective core potentials (ECP) derived from energy-adjusted *ab initio* pseudopotential methods [35,36]. The ECP calculations have been carried out with Wood–Boring [37] quasi-relativistic corrections for the metals. The binding energies for complexes involving Rb^+ and Cs^+ are from HF/D95V single-point energy calculations with geometries optimized at HF/3-21G.

We are also reporting Hartree–Fock calculations for complexes of alkali metal cations with phenol. Full geometry optimizations have been carried out at the HF/6-311G(d,p) level. For complexes of Rb^+ and Cs^+ , the calculations have been carried out with ECP [35,36]. We found that the results for these complexes are useful for discussing structural features also present in complexes of calix[4]arenes with alkali metal cations. We have also verified that for the K^+ complex with phenol, all-electron HF/6-311G(d,p) and ECP calculations were in very good agreement.

Vibrational frequencies have been calculated for all the complexes and the structures were characterized as local minima, i.e. all frequencies are real. Zero point vibrational energies were not included in the calculation of the complexation energies. We found that their inclusion for the systems presently studied is not essential, considering the strong binding energies involved. A similar consideration applies to the correction of finite size basis set effects which we have tried to minimize using the largest affordable basis set for each case.

The calculations have been performed with the Gaussian-98 program [38]. Electrostatic potential surfaces have been generated with the Molekel software [39].

RESULTS AND DISCUSSION

Ab Initio Results for Free Calix[4]arene

Figure 1 shows the structure of the four most stable calix[4]arene conformers, cone (C), partial-cone (PC), 1,2-alternate (1,2-A), and 1,3-alternate (1,3-A). The structure of the four calix[4]arene conformers has been recently investigated by density functional theory calculations [31]. Experimental results for the structure [40,41] and free energy difference between

TABLE I Energy difference (ΔE s in kcal/mol) between the calix[4]arene conformers (partial-cone=PC, 1,2-alternate=1,2-A and 1,3-alternate=1,3-A) and the cone conformer (C)

	PC ΔE	1,2-A ΔE	1,3-A ΔE
HF/3-21G*	18.3	21.9	31.9
HF/6-31G†	11.6	20.9	23.1
HF/3-21G(d,p)*	16.0	26.3	28.1
HF/6-31G(d,p)‡	7.0	14.7	13.6
MP2/6-31G(d,p)‡	9.4	18.9	17.1
BLYP/6-31G(d)*	10.7	18.6	18.1
BLYP/6-31G(d,p)¶	10.7	18.3	17.7
B3LYP/6-31G(d,p)¶	10.5	18.4	17.6
CHARMM§	9.6	11.8	17.2
MM3(89)¶¶	9.9	11.7	18.7
MM3(92)#	5.6	6.1	10.6
Experiment**	14.9;13.8		

*Geometry optimized at this level. †Geometry optimized at HF/3-21G. ‡Geometry optimized at HF/3-21G(d,p). ¶Geometry optimized at BLYP/6-31G(d). §From Fischer *et al.* [46]. ¶¶From Harada *et al.* [47] #From Harada *et al.* [48,49] **Free energies of activation ΔG^\ddagger in a solvent (chloroform and benzene respectively) [42].

calix[4]arene conformers in several solvents [42] have been reported. Table I reports data on the conformational equilibrium of free calix[4]arene. *Ab initio* calculations predict, in agreement with density functional and force field results, that the cone calix[4]arene is the most stable conformer. However, some basis set dependence is observed and HF/3-21G calculations seem to overestimate the energy difference between the conformers. Some improvement is observed when polarization functions are included although the results at HF/3-21G(d,p) are still higher than the experimental data. HF/6-31G(d,p) single-point calculations with geometries optimized at HF/3-21G(d,p) are in much better agreement with experiment and other theoretical predictions. In addition, MP2/6-31G(d,p) calculations with HF/3-21G(d,p) geometries predict energy differences between the conformers in excellent agreement with density functional optimizations at BLYP/6-31G(d) level [31]. These results suggest that MP2/6-31G(d,p) energies with geometries optimized at HF/3-21G(d,p) level are an adequate procedure to study the conformational equilibrium of calix[4]arene.

Hydrogen bonding in the calix[4]arene cone conformer is illustrated in Fig. 2 and *ab initio* results for the structure are reported in Table II. We can observe very good agreement between HF/3-21G(d,p) calculations and experimental data, indicating that HF/3-21G(d,p) optimizations are adequate to model the structure of calix[4]arenes. This is supported by a recent study of the structure and conformational equilibrium of thiacalix[4]arene showing that HF/3-21G(d,p) and B3LYP/6-31G(d,p) methods predict very similar structures [43]. The present *ab initio* results are also in very good agreement with recent density functional theory calculations [31].

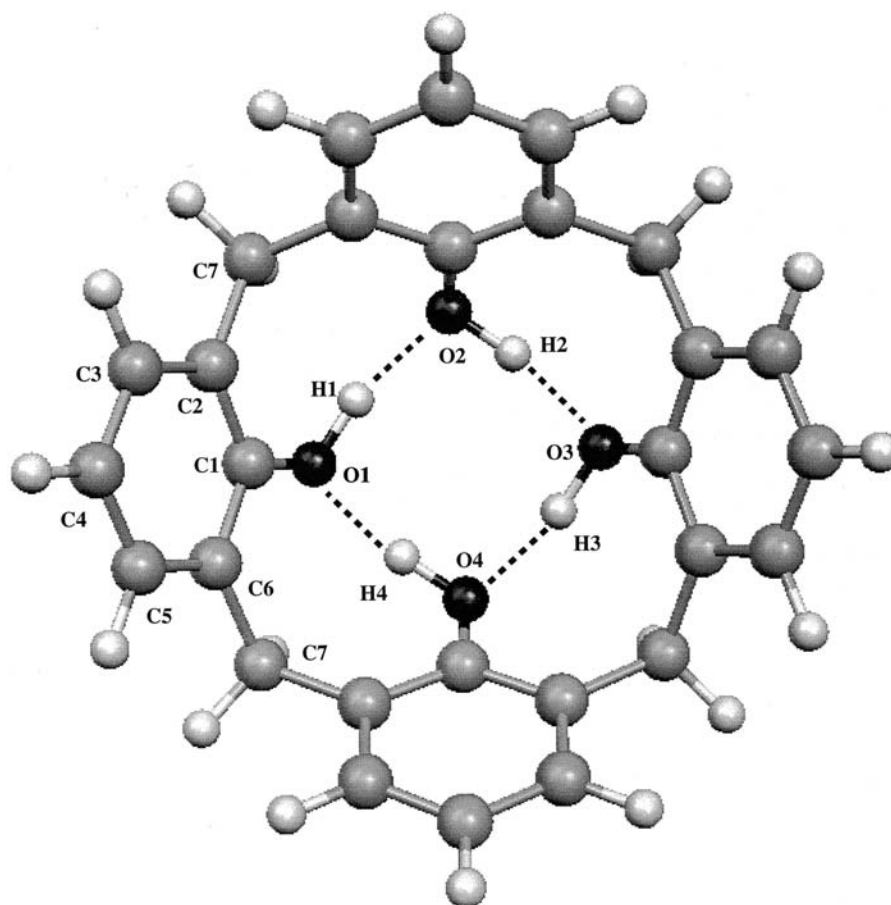


FIGURE 2 Hydrogen bonding in the calix[4]arene cone conformer.

Conformational Binding Selectivity

Cation- π interactions play an important role in the complexation of alkali metal cations with benzene and with an extensive series of aromatic structures [10,11], and several studies suggest a strong correlation between the total binding energy and the electrostatic contribution to the interaction

energy [10,12]. Thus, in the complexation of alkali metal cations with benzene [9,13], binding energies are according to the trend $\text{Li}^+ > \text{Na}^+ > \text{K}^+ > \text{Rb}^+$, which is a normal electrostatic sequence. The electrostatic sequence suggests that dispersion interactions or polarization effects may be not of much relevance and that the cation could be represented by a charged "hard-sphere" of larger

TABLE II Data for the structure of cone calix[4]arene. We present results from HF theory, density functional theory, force field (MM3), and data from experiment

	HF/3-21G(d,p)	BLYP/6-31G(d)*	MM3†	Exp.‡
Bond distances (Å)				
C ₁ -C ₂	1.39	1.42		1.41;1.38
C ₁ -C ₆	1.39	1.41		1.40;1.39
C ₂ -C ₃	1.39	1.41		1.39;1.38
C ₂ -C ₇	1.53	1.54		1.53
C ₁ -O	1.39	1.39		1.41;1.37
O-O	2.63	2.67	3.05	2.64
Angles (°)				
C ₁ -C ₂ -C ₃	118.4	117.6		117.3
C ₁ -C ₂ -C ₇	121.7	122.3		121.9
C ₁ -C ₆ -C ₇	120.6	121.4		120.8
C ₂ -C ₇ -C ₆	111.5	113.9	113.0	
C ₂ -C ₁ -C ₆	121.5	122.1		121.6
O ₁ -C ₁ -C ₂	121.5	120.9		119.1
O ₁ -C ₁ -C ₆	117.0	116.9		119.3;117.8

* From Bernardino *et al.* [31]. † From Harada *et al.* [47]. ‡ From Ungaro *et al.* [40].

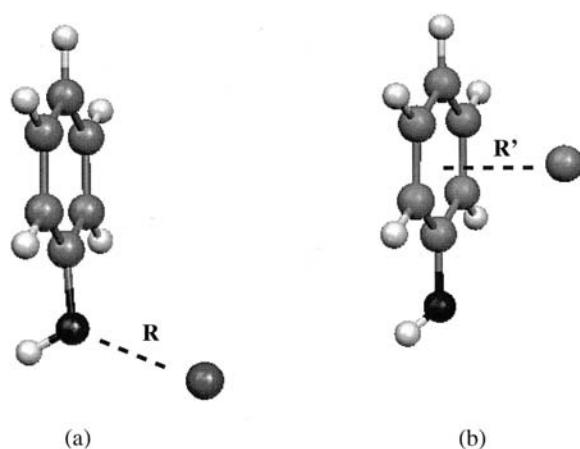


FIGURE 3 Binding modes of alkali metal cations with phenol. (a) Cation binding to the O–H group; R (in Å) is the distance between the cation and the oxygen atom. R is: 1.81 (Li^+); 2.20 (Na^+); 2.62 (K^+); 2.84 (Rb^+); 3.07 (Cs^+). Binding energies (in kcal/mol): 38.7 (Li^+); 26.2 (Na^+); 18.1 (K^+); 14.3 (Rb^+); 11.8 (Cs^+). (b) Cation– π complex; R' is the distance (in Å) between the cation and the phenol ring centroid. R': 1.95 (Li^+); 2.46 (Na^+); 2.99 (K^+); 3.19 (Rb^+); 3.54 (Cs^+). Binding energies (in kcal/mol): 39.4 (Li^+); 24.3 (Na^+); 16.4 (K^+); 12.7 (Rb^+); 10.6 (Cs^+).

diameter for the bigger ones leading to a smaller electrostatic interaction with the molecular structure.

The structures of the binding modes of cationic species with benzene [12] reflect the strong binding of the cations to the π face of the aromatics. Recently, density functional theory calculations on the complexation of the methyl cation with benzene [15] suggested that the stabilization of carbocation intermediates in biochemical reactions via cation– π interactions can be correctly afforded to carbocations over different parts of a benzene ring and at distances greater than typical covalent bonding distances. In the complexation of alkali metal cations with phenol, the cation interacts both with the O–H group and the π face of phenol. This is illustrated in Fig. 3 where we present two possible binding modes for the complexes of alkali metal cations with phenol. In Fig. 3, R and R' correspond, respectively, to the distances between the cation and oxygen and between the cation and the centroid of the phenol ring. In the caption of this figure we also report the values of R, R' and binding energies from HF/6-311G(d,p) optimizations. For Rb^+ and Cs^+ the calculations have been carried out with effective core potentials [35,36]. We find that for both structures (a and b in Fig. 3), binding energies follow the normal electrostatic sequence. However, our results also indicate that, excepting Li^+ , the energy difference between the two binding modes decreases with cation size.

In the complexation of cations with calix[4]arenes, two aspects are worth referring to: the interactions between a charged species and the calix[4]arene depends on the specific conformation of the host; and cation– π interactions can be certainly enhanced

by a cooperative effect due to the simultaneous presence of several aromatic structures. The first aspect characterizes conformational binding selectivity and the second one suggests that the role of cation– π interactions is more important for the present system than in the case of simple aromatic structures. Moreover, it is known that the calix[4]arene cone conformer is energetically stabilized due to the formation of a hydrogen bond cyclic array in the lower rim. We find that this feature is also present in the complexes of calix[4]arene with cationic species. Thus, we can anticipate that the complexation of calix[4]arene with alkali metal cations involves a competition between different factors, including the interactions of the cation with the O–H groups and with the π faces of phenol, hydrogen bonding interactions in the calix[4]arene lower rim, and size effects.

H^+ , Li^+ , and Na^+

Table III reports energy data related the complexation of calix[4]arene with charged species. Total energies for the free calix[4]arene conformers, represented by X, are also reported. HF results for the complexation energies exhibit some basis set dependence. However, some general trends concerning conformational binding selectivity are not very sensitive to the theoretical level of the calculations. For example, the proton affinity data for calix[4]arene clearly indicate that H^+ prefers the 1,2-A conformer. This is the case for all the calculations, except the single-point HF/6-311G(d,p) calculation with geometry optimized at HF/3-21G(d,p), which indicates no clear preference between the cone (C) and the 1,2-alternate (1,2-A) conformers. The present prediction for the calix[4]arene proton affinity based on MP2/6-31G(d,p) calculations (-221.4 kcal/mol) is in very good agreement with a recent BLYP/6-31G(d) density functional calculation (-219.3 kcal/mol) [31].

Data for the complexation of Li^+ with calix[4]arene indicate preferential complexation with the 1,3-A calix[4]arene conformer. However, in this case all calculations also suggest some competition between the 1,2-A and 1,3-A conformers. Similar behaviour can be observed in the complexation of Na^+ with calix[4]arene, where no clear preference between the 1,2-A and 1,3-A conformer is observed. Our better prediction for the complexation energy of 1,3-A calix[4]arene with Li^+ is -91.6 kcal/mol at MP2/6-31G(d,p) with geometry optimized at HF/3-21G(d,p). This result is very similar to the B3LYP/6-31G(d,p) single-point calculation (-92.1 kcal/mol). The complexation energies of 1,3-A calix[4]arene with Na^+ are ≈ 30 kcal/mol lower than those predicted for Li^+ .

TABLE III Total energies E (in a.u) for the four calix[4]arene conformers represented by $X = C$ (cone), $X = PC$ (partial-cone), $X = 1,2 - A$ (1,2-alternate), and $X = 1,3 - A$ (1,3-alternate). ΔE (in kcal/mol) is the complexation energy corresponding to the process $[X-A^+] \rightarrow X+A^+$, where $A = H^+, Li^+ - Cs^+$. Values in parentheses are energy differences (in kcal/mol) relative to the cone conformer

	E	ΔE^*			
	X	X-H ⁺	X-Li ⁺	X-Na ⁺	X-K ⁺
HF/3-21G+					
C	-1366.17550	-231.7 (0)	-94.5 (0)	-64.5 (0)	-44.9 (0)
PC	-1366.14623	-225.9 (5.8)	-102.7 (-8.2)	-77.5 (-13)	-39.3 (5.6)
1,2-A	-1366.12777	-244.4 (-12.7)	-113.7 (-19.2)	-88.6 (-24)	-40.2 (4.7)
1,3-A	-1366.12452	-216.6 (15.1)	-122.6 (-28.1)	-90.3 (-25.8)	-41.4 (3.5)
		HF/6-31G‡			
C	-1373.26269	-226.7 (0)	-83.3 (0)	-51.9 (0)	-35.2 (0)
PC	-1373.24417	-217.6 (11.6)	-86.0 (9.1)	-58.6 (-6.7)	-34.3 (0.9)
1,2-A	-1373.22925	-233.3 (-6.6)	-92.2 (-8.9)	-62.7 (-10.8)	-27.1 (8.1)
1,3-A	-1373.22585	-213.9 (12.8)	-97.5 (-14.2)	-62.9 (-11)	-27.7 (7.5)
		HF/3-21G(d,p) †			
C	-1366.33534	-235.7 (0)	-98.7 (0)	-72.4 (0)	-60.5 (0)
PC	-1366.30982	-229.4 (6.3)	-101.9 (-3.2)	-86.1 (-13.7)	-54.1 (6.4)
1,2-A	-1366.29348	-244.7 (-9)	-111.6 (-12.9)	-96.7 (-24.3)	-57.0 (3.5)
1,3-A	-1366.29052	-221.2 (14.5)	-119.6 (-20.9)	-100.1 (-27.7)	-60.7 (-0.2)
		HF/6-31G(d,p) ¶			
C	-1373.81606	-222.5 (0)	-75.1 (0)	-45.6 (0)	-38.8 (0)
PC	-1373.80507	-210.3 (12.2)	-74.2 (0.9)	-53.3 (-7.7)	-31.8 (6.5)
1,2-A	-1373.79263	-223.2 (-0.7)	-80.8 (-5.3)	-56.2 (-10.6)	-22.4 (16.4)
1,3-A	-1373.79437	-213.7 (8.8)	-82.6 (-7.5)	-54.3 (-8.7)	-24.4 (14.4)
		HF/6-311G(d,p) ¶			
C	-1374.07443	-220.7 (0)	-73.5 (0)	-44.5 (0)	-33.8 (0)
PC	-1374.06510	-208.4 (12.3)	-72.1 (1.4)	-50.5 (-6)	-28.1 (5.7)
1,2-A	-1374.05331	-220.4 (0)	-77.1 (-3.6)	-51.9 (-7.4)	-18.3 (15.5)
1,3-A	-1374.05414	-212.2 (8.5)	-79.6 (-6.1)	-50.0 (-5.5)	-20.8 (13)
		MP2/6-31G(d,p) ¶			
C	-1378.26626	-221.4 (0)	-73.8 (0)	-33.4 (0)	-
PC	-1378.25121	-209.4 (12)	-76.5 (-2.7)	-51.9 (-18.5)	-
1,2-A	-1378.23608	-225.5 (-4.1)	-89.1 (-15.3)	-58.5 (-25.1)	-
1,3-A	-1378.23897	-214.7 (6.7)	-91.6 (-17.8)	-58.9 (-25.5)	-
		B3LYP/6-31G(d,p) ¶			
C	-1382.40441	-222.0 (0)	-70.8 (0)	-37.9 (0)	-36.6 (0)
PC	-1382.38654	-209.1 (12.9)	-77.4 (-6.6)	-51.4 (-13.5)	-27.5 (9.1)
1,2-A	-1382.37305	-226.5 (-4.5)	-86.0 (-15.2)	-59.3 (-21.4)	-21.0 (15.6)
1,3-A	-1382.36888	-219.3 (2.7)	-92.1 (-21.3)	-63.6 (-25.7)	-29.9 (6.7)

* ΔE_s (in kcal/mol) based on single-point HF/D95V calculations with effective core potentials for complexes with cone calix[4]arene are: -31.7 (K⁺); -28.7 (Rb⁺); -25.5 (Cs⁺). † Optimized geometry at this level of the theory. ‡ Single-point calculation with the HF/3-21G geometry. ¶ Single-point calculation with the HF/3-21G(d,p) geometry.

Figure 4(a) shows the structure of 1,3-A calix[4]arene with Li⁺. The cation is located at the calix[4]arene lower rim. The distance between Li⁺ and the four equidistant oxygen atoms (O₁) is 1.90 Å. The Li⁺-O distance is in good agreement with X-ray data for a tetralithium derivative of *p*-tert-butylcalix[4]arene [44], for which the experimental values are in the 1.92–2.089 Å range.

Figure 4(b) shows the structure of 1,2-A calix[4]arene with Na⁺. Our calculations indicate two very similar distances (2.24 and 2.25 Å) between Na⁺ and the oxygen atoms (O₂ and O₁). X-ray data for a related system, the [*p*-tert-butylmethoxycalix[4]arene-sodium-toluene]⁺ cation, has been reported [45]. Although the comparison between this system and our cone calix[4]arene-Na⁺ complex is not direct some common features can be observed. Na⁺ interacts with the four oxygen atoms in the calix[4]arene lower rim. The experimental [45] average Na⁺-O distance is 2.3 Å, in very good agreement with our values.

Our results show that for the smaller cations (Li⁺ and Na⁺) the complexation with calix[4]arene is energetically stabilized by electrostatic interactions with oxygen atoms in the calix[4]arene lower rim. These cations bind preferentially to the calix[4]arene 1,2-A and 1,3-A conformers. However, the experimental structures for the complex of a tetralithium derivative of *tert*-butylcalix[4]arene with Li⁺ [44], and for the [*p*-tert-butylmethoxycalix[4]arene-sodium-toluene]⁺ cation [45] indicate that the calix[4]arene macrocycle adopts a cone conformation. Thus, we stress that there is as yet no experimental evidence that Li⁺ and Na⁺ form complexes with other calix[4]arene conformers.

K⁺, Rb⁺, and Cs⁺

K⁺ complexes preferentially with the cone conformer and it is the first alkali metal cation that is

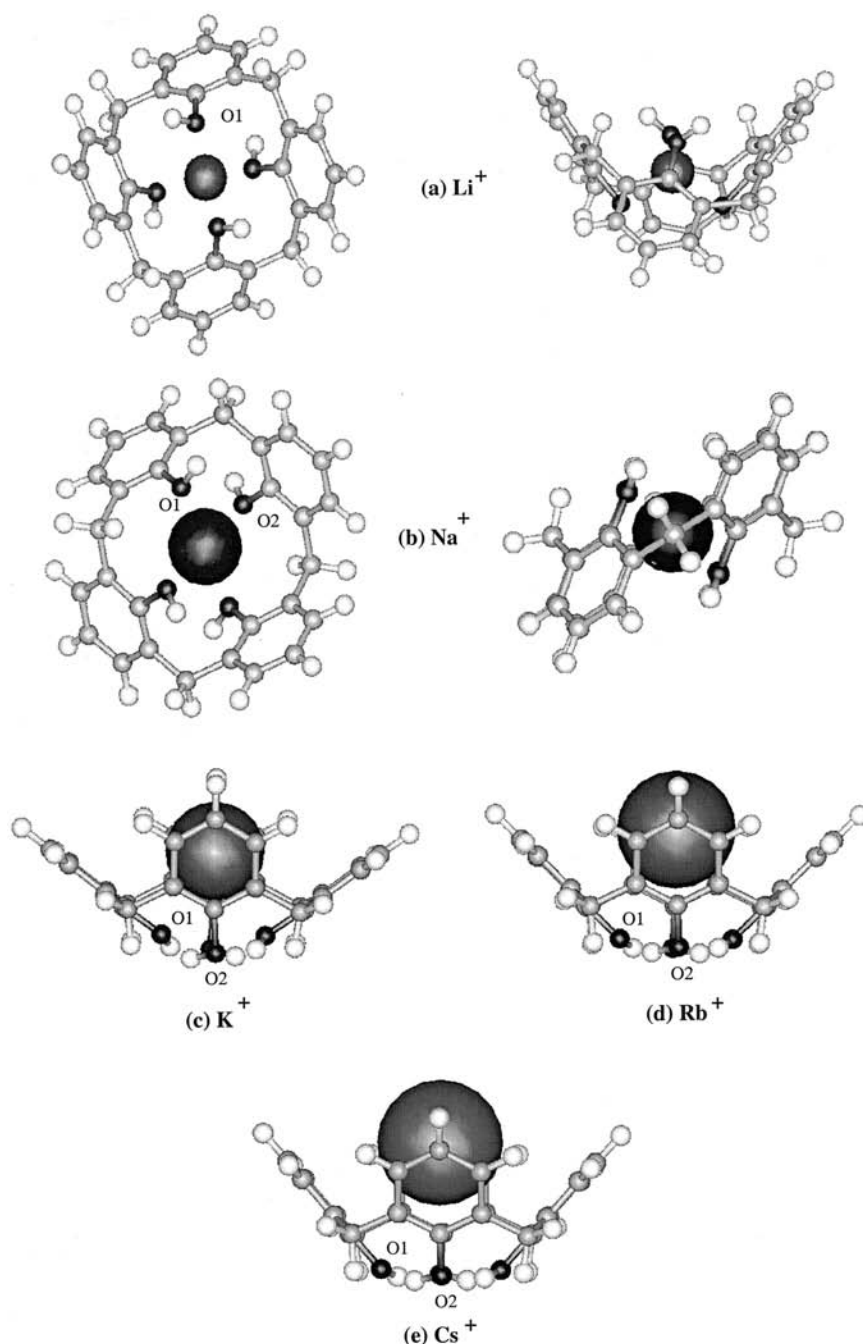


FIGURE 4 Complexes of calix[4]arene with alkali metal cations. The size of the cations correspond to their diameters (in Å): 1.52 (Li^+); 2.04 (Na^+); 2.76 (K^+); 3.04 (Rb^+); 3.40 (Cs^+). For Li^+ (a) and Na^+ (b) top (left) and side (right) views are shown. Li^+ (a) and Na^+ (b) are close to the plane defined by oxygen atoms. Distances (in Å) between the cations and oxygen atoms: 1.90 (Li^+); 2.25 (Na^+). Distances (in Å) between the larger cations and the nearest phenol centroid: 2.93 (K^+); 3.10 (Rb^+); 3.50 (Cs^+). Distances (in Å) between the larger cations and the nearest oxygen atom (O_2) in the lower rim: 2.97 (K^+); 3.25 (Rb^+); 3.69 (Cs^+).

well inside the calix[4]arene cone structure (see Fig. 4(c)). The K^+ *endo* complexation induces some interesting structural modifications in the calix[4]arene cone conformer which are related to rotations of the phenol rings. These modifications are illustrated in Figs. 4(c) and 5, which show a preferential interaction of K^+ with two phenol rings that are much closer to the cation than the other two. Distances between K^+ and the centroid of

the phenol rings are 2.93 and 3.86 Å. The first one of these distances is very similar to the distance between K^+ and the centroid of phenol (2.9 Å) in the cation- π complex of K^+ with phenol (see Fig. 3). The distances between K^+ and the oxygen atoms O_1 and O_2 (see Fig. 4(c)) are 3.11 and 2.67 Å, respectively. A possible explanation for this structure can be related to size effects. K^+ is too large to interact with the O-H groups in the lower rim but it is not big

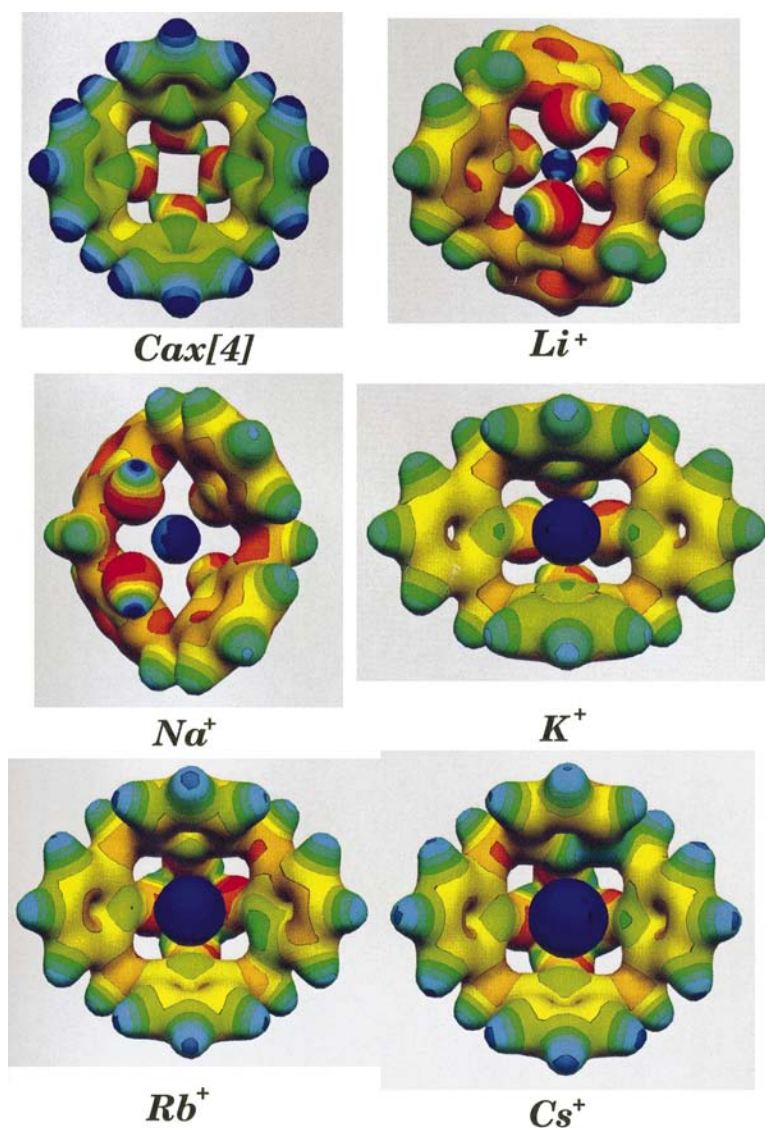


FIGURE 5 Electrostatic potential for complexes of alkali metal cations with calix[4]arene. The electrostatic potential Φ (in a.u.) is represented over electronic isodensity ρ (in $\text{e}\text{\AA}^{-3}$) surfaces of volume V_s (in \AA^3). The color-coding is the following: red corresponds to the minimum (negative) potential Φ_- and blue to the maximum (positive) potential Φ_+ . All figures correspond to $\rho=0.04 \text{ e}\text{\AA}^{-3}$. Free calix[4]arene: $V_s = 148.3$, $\phi_- = -0.191$, $\phi_+ = 0.107$; Li^+ : $V_s = 148.9$, $\phi_- = -0.047$, $\phi_+ = 0.330$; Na^+ : $V_s = 150.4$, $\phi_- = -0.025$, $\phi_+ = 0.310$; K^+ : $V_s = 153.3$, $\phi_- = -0.073$, $\phi_+ = 0.360$; Rb^+ : $V_s = 156.3$, $\phi_- = -0.115$, $\phi_+ = 0.363$; Cs^+ : $V_s = 158.2$, $\phi_- = -0.117$, $\phi_+ = 0.346$;

enough to interact with the four π faces of calix[4]arene.

The cone calix[4]arene complexes with Rb^+ and Cs^+ are also shown in Figs. 4 and 5. The structures of these conformers are based on HF/3-21G optimizations. We have verified that this theoretical level is adequate to predict the structure of the free cone calix[4]arene and that the results are very similar to those predicted at HF/3-21G(d,p), which are in good agreement with experiment. The complexation energies for complexes of cone calix[4]arene with Rb^+ and Cs^+ are from single-point HF/D95V calculations with ECP [35,36]. Our predictions for the complexation energies are -28.7 kcal/mol for Rb^+ and -25.5 kcal/mol for Cs^+ . We have also verified that the complexation

energy of K^+ with cone calix[4]arene based on ECP calculations (-31.7 kcal/mol) is in very good agreement with the all-electron results reported in Table III.

The complexes of Rb^+ and Cs^+ also involve cation- π interactions with two phenol rings, although the cone distortion induced by complexation is much less pronounced. The distances between Rb^+ and the phenol ring centroid are 3.1 and 3.8 \AA . The first value is similar to the distance between Rb^+ and the centroid of the phenol molecule (3.19 \AA) in the cation- π complex of Rb^+ with phenol (see Fig. 3). This feature illustrates the role played by cation- π interactions, and it is also observed in the complexation of Cs^+ with the calix[4]arene cone conformer, for

which some structural information is also reported in Fig. 4.

Experimental data on the structure of alkali metal cations with calix[4]arene are scarce, and apparently no information is available even for the complexes of simple aromatic molecules with charged species [13]. X-ray diffraction measurements of the crystal phase of the *p*-*tert*-butylcalix[4]arene-Cs⁺ complex [16] indicates that the Cs atom is held within the calix[4]arene cup and that the complex may involve a binding mode which corresponds to interactions with the charge distribution over the four phenol rings. The experimental distance from Cs to phenol ring centroid is 3.57 Å [16], which is in very good agreement with one of the distances (3.5 Å) predicted by our calculations. A recent solid-state NMR study of alkali metal ion complexes of *p*-*tert*-butyl-calixarenes [26] suggests that *p*-*tert*-butyl-calix[4]arene forms complexes with the small cations (Li⁺ and Na⁺) due to “steric recognition” and that the larger cations (Rb⁺ and Cs⁺) are included in the *p*-*tert*-butyl-calix[4]arene structure.

The present results for the complexation of calix[4]arene with the larger alkali metal cations (K⁺, Rb⁺, and Cs⁺) indicate that these complexes are stabilized by cation- π interactions with the π faces of the phenol rings. The binding modes corresponding to the *endo* complexation of these cations with the calix[4]arene cone conformer preserve the cyclic array of hydrogen bonding in the calix[4]arene lower rim, which also contributes to the energetical stabilization of the complexes.

Electrostatic Potential

In Fig. 5 the electrostatic potential is represented over an electronic isodensity surface of $\rho = 0.04 \text{ e} \text{ \AA}^{-3}$. On these surfaces, red regions are those of relatively lower or more negative electrostatic potential and blue regions correspond to higher or more positive electrostatic potential. The lower and upper limits of the electrostatic potential are reported in the figure caption.

For the smaller cations, complexation means binding to the oxygen atoms in the lower rim and in these cases (Li⁺ and Na⁺), Fig. 5 suggests a strong charge reorganisation in the complexed calix[4]arene relative to the free macrocycle. Inclusion of the larger cations preserves the array of cyclic hydrogen bonding in the lower rim and does not modify in a very significant way the electrostatic potential in this region. However, the interaction of the larger cations with the phenol π faces induces some modification of the electrostatic potential over these surfaces. This is well illustrated in Fig. 5 for K⁺, Rb⁺, and Cs⁺.

We believe that the analysis based on the representation of the electrostatic potential over

isodensity surfaces is essentially qualitative [13]. However, in the present case it allows us to visualize and to discuss how the binding of a cation to an aromatic structure modifies the charge distribution and the electrostatic potential relative to the free structure. Moreover, this analysis also complements the previous discussion related to the binding energies and illustrates how the complexation of alkali metal cations with calix[4]arene involves the competition of several factors including coulombic interactions, polarization effects, and size effects.

CONCLUSION

This work reports *ab initio* calculations for the structure and conformational equilibrium of free calix[4]arene, and for the complexation of calix[4]arene with cationic species (H⁺ and Li⁺-Cs⁺).

A very good agreement between *ab initio* results and experimental data for the structure of free calix[4]arene has been observed. In addition, the present *ab initio* predictions for the conformational equilibrium of free calix[4]arene and for the cone calix[4]arene proton affinity are in very good agreement with recent density functional theory calculations [31].

Conformational binding selectivity of calix[4]arene with cationic species exhibits a clear dependence on the cation size. The smaller cations interact preferentially with oxygen atoms in the calix[4]arene lower rim. The predicted structures indicate that these cations are approximately located at a plane defined by the oxygen atoms in the calix[4]arene lower rim. For Li⁺ and Na⁺, the complexed conformers are stabilized by electrostatic interactions between the cations and the oxygen atoms, showing that, for these species, the most stable binding modes are not determined by cation- π interactions.

For the larger cations, the picture that emerges from our study is quite different. The most stable free calix[4]arene conformer, the cone conformer, is preferred by the K⁺ cation. K⁺ is the first alkali metal cation that is included deeply inside the cone calix[4]arene structure. This complex is mainly stabilized by cation- π interactions between K⁺ and the π faces of two phenol rings.

We are also predicting that the complexations of calix[4]arene with Rb⁺ and Cs⁺ are driven by cation- π interactions. In agreement with crystal phase X-ray diffraction experiments for the caesium complex of *p*-*tert*-butylcalix[4]arene [16], we also find that Cs⁺ penetrates deeply into the cavity of the calix[4]arene cone conformer.

Our results clearly indicate that the complexation of calix[4]arene with alkali metal cations is determined by several factors, and that the conformational binding selectivity for the present system involves

hydrogen bonding, cation- π interactions and size effects.

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