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Combined Crystallographic and Solution Molecular Dynamics Study of Allosteric Effects in Ester and Ketone *p-tert*-Butylcalix[4]arene Derivatives and Their Complexes with Acetonitrile, Cd(II), and Pb(II)

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We describe here a procedure to bridge the gap in the field of calixarene physicochemistry between solid-state atomic-resolution structural information and the liquid-state low-resolution thermodynamics and spectroscopic data. We use MD simulations to study the kinetics and energetics involved in the complexation of lower rim calix[4]arene derivatives (**L**), containing bidentate ester (**1**) and ketone (**2**) pendant groups, with acetonitrile molecule (MeCN) and Cd^{2+} and Pb^{2+} ions (M^{2+}) in acetonitrile solution. On one hand, we found that the prior inclusion of MeCN into the calix to form a **L**(MeCN) adduct has only a weak effect in preorganizing the hydrophilic cavity toward metal ion binding. On the other hand, the strong ion−hydrophilic cavity interaction produces a wide open calix which enhances the binding of one MeCN molecule (allosteric effect) to stabilize the whole (M^{2+})**L**(MeCN) bifunctional complex. We reach two major conclusions: (i) the MD results for the (M^{2+})**1**(MeCN) binding are in close agreement with the "endo", fully encapsulated, metal complex found by X-ray diffraction and in vacuo MD calculations, and (ii) the MD structure for the more flexible **2** ligand, however, differs from the also endo solid-state molecule. In fact, it shows strong solvation effects at the calixarene lower bore by competing MeCN molecules that share the metal coordination sphere with the four C═O oxygens of an "exo" (M^{2+})**2**(MeCN) complex.

Introduction

Macrocyclic calix[*n*]arenes result as products of condensation reaction between *p*-substituted phenols and formaldehydes. By functionalizing the upper and lower bores, it is possible to obtain a wide range of binding abilities.[1−4] Particularly interesting are the bifunctional calix[4]arenes in the cone conformation where the four phenyl rings at the upper bore enclose a hydrophobic cavity able to include small solvent molecules. The lower bore can be derivatized with adequate pendant groups to conform a hydrophilic cavity able to bind metal ions. Allosteric effects are common in large organic systems: conformational modifications in a given molecular region promote changes in other molecular parts. It is not surprising that these effects are also present in such flexible macrocycles as calixarene derivatives. In fact, allosterism in double metal cation complexation (involving groups in the lower and upper rim), in salts and also in sugar complexes with calix[4]arenes have been reported (see ref 2 and references therein).

Recently, we uncovered the ability of tetraethyl ester and tetramethyl ketone *p-tert*-butylcalix[4]arene derivatives (**1** and **2**, see Figure 1) to complex Cd^{2+} and Pb^{2+} ions in acetonitrile (MeCN) solution.[5] In that study, we reported the X-ray crystal structures of the complexes of these ions (as perchlorate) with **1**, (Cd^{2+})**1**(NCMe) and (Pb^{2+})**1**(MeCN), and **2**, (Cd^{2+})**2**(NCMe) and (Pb^{2+})**2**(MeCN), and discussed the molecular features that may be relevant to the complexation processes, including the key role played by the versatile MeCN molecule in complex stabilization.

In a previous work,[6] we presented gas phase molecular dynamics (MD) simulations of the calixarene complexes showing a good agreement between the calculated equilibrium conformations and the observed solid-state structures. However, these macrocyclic compounds bind metal ions in the liquid state and the question arises on whether structural features found in the crystal and in gas phase simulations can be extended to solutions. To understand at the molecular level the chelating process taking place in solution, we performed MD simulations of the complexation kinetics involving the **1** and **2** hosts and the MeCN molecule and the Cd^{2+} and Pb^{2+} ions as guests in the acetonitrile solvent. The results are compared with both in vacuo MD calculations[6] and crystallographic and thermodynamic data.[5]

We explore the solvation kinetics of **1** and **2** and its complexes with Cd^{2+} and Pb^{2+} in MeCN solution. In contrast with compound **1**, the complex of **2** with MeCN survives crystallization by solvent evaporation. Afterward, we describe the unique behavior of the macrocycle complexing the M^{2+} ions in the presence of competing MeCN solvent molecules, a process leading to supramolecular arrangements that depart substantially from the solid-state molecular structure. Finally, we summarize the major conclusions.

The main goal of the simulations is to determine the kinetics of complex formation in solution and to compare it with the

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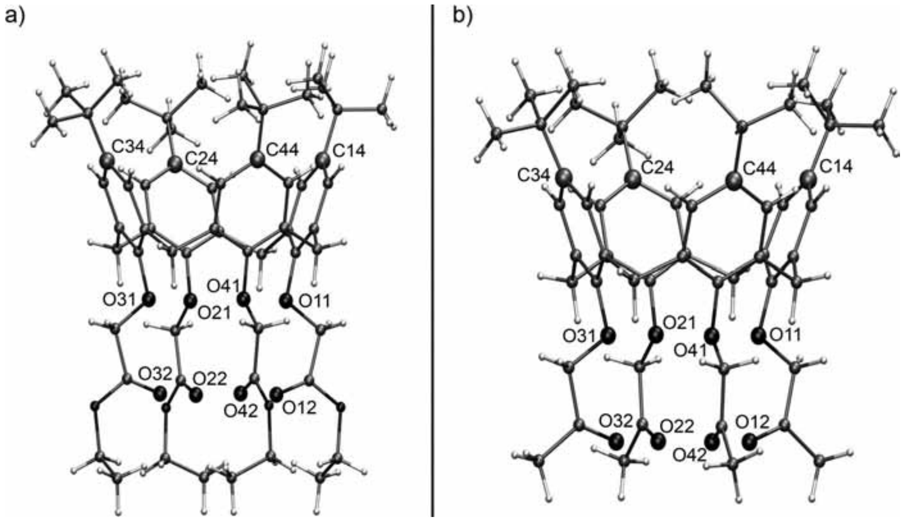

Figure 1. Side view of the two calixarene ligands studied in this work. Atoms of hydrogen, carbon, and oxygen are shown in white, gray, and black, respectively. The atoms used in our structural analysis are labeled and displayed as large balls. For clarity, the labels of the other atoms are not shown. (a) Tetraethyl ester *p-tert*-butylcalix[4]arene (**1**). (b) Tetramethyl ketone *p-tert*-butylcalix[4]arene (**2**).

static counterpart observed in the solid state. The influence of the solvent on the formation of calixarene−ion complexes is a key factor, both in the competition with the macrocycle for the ion binding and in the stability of this association. Usually, the crystals are grown by slow solvent evaporation where stable complexes preexisting in the solution are found in the solid state, but now surrounded by much less crystallization solvent molecules which merely stabilize the crystal packing.

Methodology and Computational Details

The simulations were carried out employing the GROMACS[7] package with the calixarene and solvent atoms interactions described by the OPLS-AA (Optimized Parameters for Liquid Simulations-All Atoms) force field.[8] The Lennard-Jones parameters to model the van der Waals interactions of the Cd^{2+} and Pb^{2+} ions were taken from a recent paper.[9] Partial charges assigned to ring carbons bound to CH_2 groups that link the monomers were assumed to be zero as described in ref 10. Minor modifications in the standard OPLS-AA charges assigned to atoms of the hydrophilic cavity were necessary to ensure the null total charge of the molecule. The complete list of parameters used to model the calixarene ligands is available as GROMACS topology files in Supporting Information. As initial molecular configurations we adopted the equilibrium ones obtained by in vacuo MD calculations.[6] Normally, the experimental solute concentrations are of a few 10^{-3} mol dm^{-3},[5] too low to mimic in our calculations due to the computationally unreachable large box sizes necessary to reproduce such high dilutions. Despite this, we tried to approach the experimental conditions as closely as possible by employing in all simulations periodic boundary conditions on boxes of about 45 Å in size containing a calixarene ligand and filled with 865 acetonitrile molecules, which correspond to the solvent experimental density and theoretical solute concentrations of the order of a few tens of 10^{-3} mol dm^{-3}. During the simulations dealing with the complexation of the calixarene with the metal cations, two Cl^- ions were included to neutralize the box. These chloride counterions were kept fixed at the box periphery to prevent their interaction with the metal−calixarene complex positioned at the box center. This mimics the situation prevailing in the experimental solution where conductometric measurements rule out appreciable cation−anion association.[5] In all simulations we performed an energy minimization procedure followed by a 0.5 ns simulation with time steps of 1 fs, keeping frozen the calixarene molecule (or the metal complex) with the aim of relaxing the solvent around the solute. Subsequently, we carried out a 2 ns long simulation for data acquisition where the above constraint on the macrocycle was removed. We applied a cutoff radius of 18 Å for nonbonded van der Waals and short-range Coulomb interactions. Long-range Coulomb interactions were treated by the Ewald method as implemented in the PME (Particle Mesh Ewald) procedure.[11,12] Simulation temperature and pressure were kept at 300 K and 1 bar by Berendsen's algorithms[13] employing time constants of 1.0 and 0.1 ps, respectively. All covalent bonds involving a hydrogen atom were constrained to their equilibrium length with the SHAKE algorithm.[14] The results of the simulations were analyzed on the basis of structural and energetic considerations.

Results and Discussion

MD Simulation of Tetraethyl Ester *p-tert*-Butylcalix[4]arene (1) in Acetonitrile Solution. A description of the main events occurring in this simulation is depicted in Figure 2.

All along the 2 ns simulation, the calixarene moiety kept the initial squashed cone conformation with a pair of opposite phenyl rings nearly parallel to each other while the other pair approaches mutual perpendicularity, and therefore no solvent could go into the hydrophobic cavity. To investigate the possibility of a later complexation with a MeCN molecule, we extended to 20 ns the simulation time. Three different solvent molecules were observed entering the upper calix with its methyl group pointing inward, changing in all cases the calixarene conformation from squashed to a nearly square cone, as can be seen in Figure 3. The stabilization potential energy of the **1**(MeCN) adduct is about −53 kJ/mol in all cases. These results show that relatively unstable **1**(MeCN) adducts could form in solution, as suggested previously,[5,15] in agreement with the observations of different solid state forms of **1** recrystallized from acetonitrile, the one reported in refs 6 and 16 showing the uncomplexed **1** calixarene, the other one reported in ref 17 showing the **1**(MeCN) adduct.

Figure 3, A and B, shows, respectively, the time evolution of the distance between opposite apical carbons and phenol oxygen atoms of the calixarene during the 20 ns simulation.

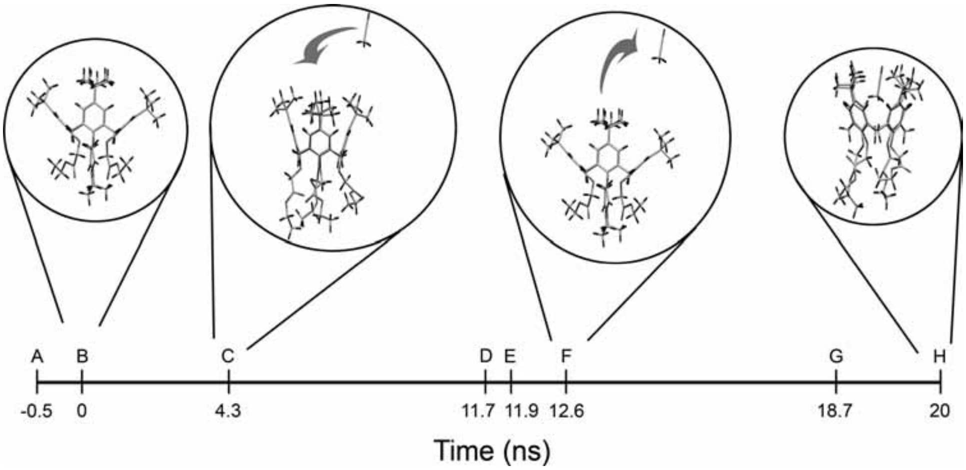

Figure 2. Timeline representation of the main events during the 20 ns simulation of **1** in MeCN solution. (A) Start of equilibration. (B) Start of data collection simulation. The calixarene assumes the squashed cone conformation. (C) A first acetonitrile molecule enters into the upper cavity, which changes to square cone conformation. (D) The MeCN molecule is pulled out from the hydrophobic cavity, which returns to the squashed cone conformation. (E) 0.2 ns after the exiting of the first MeCN, a second solvent molecule is captured by the upper cavity. (F) The second trapped MeCN molecule leaves the hydrophobic cavity. The calixarene ligand assumes the squashed cone conformation. (G) A third MeCN molecule enters into the upper cavity, remaining there until the end of the simulation (H).

The strong correlation between these distances can be traced to the lever-like rotations of the macrocycle monomer units around the linking CH_2 groups. From Figure 3 it can also be appreciated that the upper calix executes sharp transitions from a slightly distorted cone conformation when filled with the MeCN guest, to a strongly squashed cone shape when empty.

The average cross distances and rms deviations obtained from Figure 3 are shown in Table 1. In the absence of a complexed MeCN molecule, the hydrophobic cavity presents a rigid structure as indicated by a small deviation of the cross distances from their average values (Table 1). In contrast, the hydrophilic cavity has a larger mobility as shown by the cross distances values between carbonylic oxygens (rms of about 1 Å) given in Figure 3C. This fluctuation is similar to the corresponding one observed during in vacuo simulations.[6] This can be ascribed to the polar nature of the hydrophilic cavity (charged oxygen atoms) and to relatively unhindered rotations of the pendant groups around their σ-bonds along with the presence acetonitrile solvent molecules which strongly interact with the ester groups. The complexation of MeCN in the upper calix brings it to a nearly square cone conformation which is characterized by larger rms fluctuations of perpendicular cross distances around the near-average values (see Table 1).

MD Simulation of Lower Bore 1(Cd^{2+}) Complex in Acetonitrile Solution. As mentioned in the Methodology and Computational Details section, the initial **1**(Cd^{2+}) conformation was taken from in vacuo calculation in which the bonded ion in the hydrophilic cavity induces the calixararene to adopt a square conformation.[6] During the 0.5 ns solvent relaxing simulation we observed the inclusion of a MeCN molecule in the calix with its N-atom pointing inward to form a MeCN ion strong attractive interaction with average strength of −238 kJ/mol. This bond remains stable during the ensuing unrestrained 2 ns simulation. All along the simulation the cadmium ion is in a capped Archimedean antiprism, 9-fold coordinated, with the phenol and carbonyl oxygen atoms lying on the two distinct squares antiprism bases sandwiching the Cd^{2+} ion and the N-atom at the capping site. This calculated conformation in solution nicely agrees with the solid-state X-ray diffraction results.[5] The orientation of the acetonitrile molecule is opposite to that found in the crystalline **1**(MeCN) adduct,[17] in the (Pb^{2+})**1**(MeCN) complex,[5] and in most related X-ray structures reported in the literature.[18−22] This fact strongly suggests that the interaction of the metal ion with the hydrophilic cavity preorganizes the upper calix as to host a MeCN molecule oriented in such a way as to optimize its binding to the complex (allosteric effect). This MeCN−Cd bond helps in keeping the metal ion encapsulated deep inside the hydrophilic cavity (and therefore shielded against large solvation effects by acetonitrile molecules swarming at the lower bore), resulting in an endo complex (Figure 4). The ion−host interaction, which is naturally high due to the strong character of ionic forces, is increased by the stabilization effect of the adduct formed with the MeCN molecule, resulting in an average value for the **1**−Cd^{2+} interaction energy of −1023 kJ/mol, clearly indicating that the complex is stable in solution.

Average values and rms deviation of relevant cross-atomic distances obtained from 2 ns simulation of (Cd^{2+})**1**(NCMe) complex are given in Table 2. The results show that the calixarene adopts a slightly distorted cone conformation as observed in gas-phase MD simulations of the **1**(Cd^{2+}) complex but now without the transitions between the two mutually perpendicular rectangular conformations present in these latter calculations.[6] The different behavior can be traced to the steric restrain imposed by the MeCN molecule included in the calix of the (Cd^{2+})**1**(NCMe) complex. The rectangular cone conformation arises because steric repulsion prevents the relatively small Cd^{2+} ion to be coordinated at Cd−O contact distances with all four carbonyl oxygens. In fact, these ligands are arranged in opposite pairs, one pair at a short Cd−O contact distances (O12−O32 mean distance of 2.71 Å) while the other one at longer distances (O22−O42 mean distance of 5.41 Å) from the ion, as displayed in Table 2.

MD Simulation of Lower Bore 1(Pb^{2+}) Complex in Acetonitrile Solution. In the 2 ns simulations of the **1**(Pb^{2+}) complex in acetonitrile we observed that the strong interactions between the lead ion and phenol and carbonyl oxygens in the hydrophilic cavity maintain the calixarene in the square cone conformation. This keeps the entrance of the upper calix wide opened, helping the inclusion of a solvent molecules. After about 0.3 ns of simulation, a MeCN molecule enters the calix and remains stable there until the end of the calculation. The MeCN-calixarene interaction is around −51 kJ/mol, nearly the same as in the **1**(MeCN) adduct. These acetonitrile−host interactions

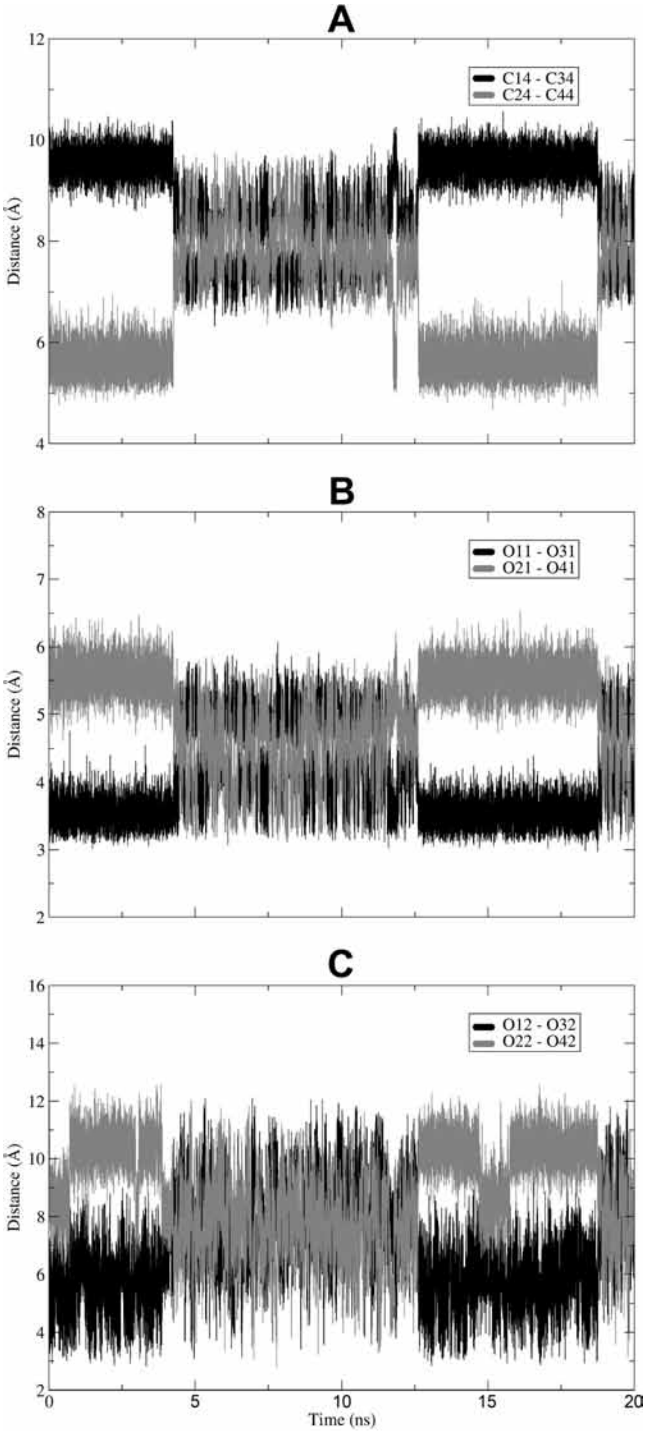

Figure 3. Cross distances between apical carbons (A) and phenol (B) and carbonyl (C) oxygen atoms of **1** in acetonitrile solution from 20 ns simulation.

TABLE 1: Average Values and Rms Deviation of Cross Distances for Apical Carbons and Phenol and Carbonyl Oxygen Atoms Obtained from 20 ns Simulation of 1 in Acetonitrile Solution

	uncomplexed MeCN[a]		complexed MeCN[a]	
	mean (Å)	rms (Å)	mean (Å)	rms (Å)
C14−C34	9.57	0.27	8.10	0.69
C24−C44	5.66	0.34	7.78	0.76
O11−O31	3.53	0.19	4.42	0.58
O21−O41	5.55	0.23	4.59	0.56
O12−O32	5.75	1.08	7.92	1.43
O22−O42	10.03	0.99	7.75	1.37

[a] Uncomplexed MeCN and complexed MeCN refer to conformation of calixarene without and with acetonitrile molecules included in the hydrophobic cavity, respectively.

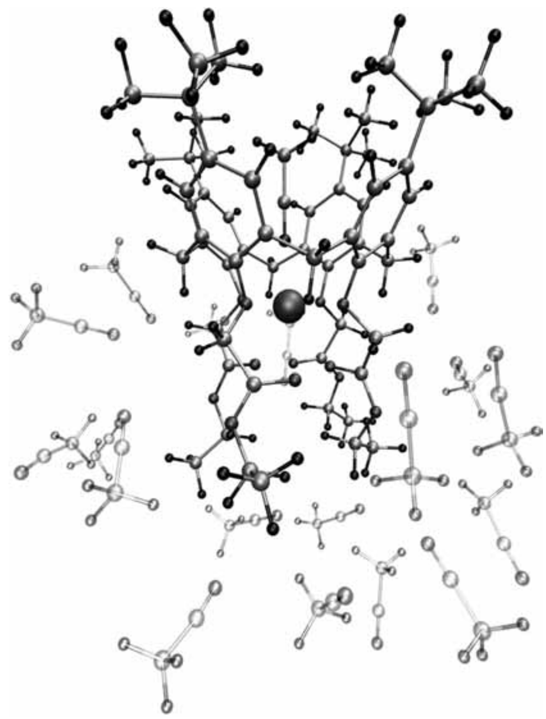

Figure 4. Side view of the (Cd^{2+})**1**(NCMe) complex (dark lines) showing the final endo conformation in the acetonitrile solution after 2 ns MD simulation. The Cd^{2+}−NCMe bond avoids close interactions of bulk solvent molecules (light lines) with the encapsulated metal ion.

though favoring complexation are, as expected, much weaker than ion−calixarene binding (see Figure 6). Interestingly, the orientation of the entering MeCN molecule, namely with its CH_3 end pointing inward (Figure 5), agrees with the experimentally observed structure in the solid state[5] and is opposite to both the calculated (see above) and experimental one found for the (Cd^{2+})**1**(NCMe) complex, where the acetonitrile enters the calix with its N-atom pointing inward to form a strong MeCN−Cd^{2+} bond. Thus, in the (Pb^{2+})**1**(MeCN) complex, the attractive hydrophobic interaction of the acetonitrile methyl group with the phenyl rings is privileged over the destabilization arising from the electrostatic repulsion between the MeCN molecule and the Pb^{2+} ion (+13.5 kJ/mol).

During the whole simulation, the Pb^{2+} ion is retained in the hydrophilic cavity keeping a stable endo complex. This stability is evidenced by the strong nonbonded interaction between the lead ion and the calixarene presented in Figure 6.

The interaction energy, which initially attains a value of −870 kJ/mol, rapidly drops to −780 kJ/mol because the solvent molecules at the lower bore interact with the metal ion, shifting it from its initial position, and also with the pendant groups displacing them laterally. When compared with the (Cd^{2+})**1**(NCMe) complex it turns out that the Pb^{2+}−host bond is about 240 kJ/mol weaker than the corresponding Cd^{2+}−calixarene bond, in qualitative agreement with the corresponding experimental value of $\Delta H = 287$ kJ/mol for the $M^{2+}(vac) + \mathbf{L}(MeCN) \rightarrow (M^{2+})\mathbf{L}(MeCN)$ process derived from the thermodynamic data reported in ref 5 In the 1.7−1.95 ns interval it can be appreciated that the metal ion becomes again

TABLE 2: Average Values and Rms Deviation of Cross Distances for Apical Carbons and Phenol and Carbonyl Oxygen Atoms Obtained from 2 ns Simulations of 1−M^{2+} Complexes in Acetonitrile Solution[a]

	1(Cd^{2+})		**1**(Pb^{2+})[b]		**1**(Pb^{2+})(MeCN)[b]	
	mean	rms	mean	rms	mean	rms
C14−C34	8.12	0.25	7.64	0.52	7.78	0.25
C24−C44	7.69	0.25	7.68	0.52	7.76	0.25
O11−O31	4.32	0.10	4.89	0.14	4.84	0.16
O21−O41	4.55	0.13	4.86	0.14	4.82	0.16
O12−O32	2.71	0.11	4.64	0.18	4.68	0.16
O22−O42	5.41	0.28	4.64	0.19	4.67	0.16

[a] All distances and deviations are in Å. [b] These results refer to the calixarene conformation before and after the inclusion of a solvent molecule within the hydrophobic cavity.

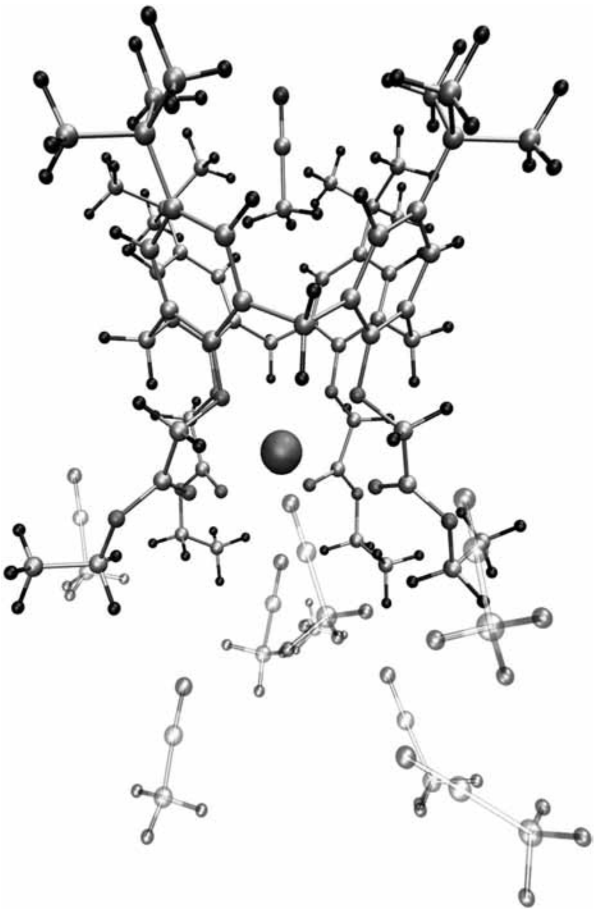

Figure 5. Side view showing the final endo conformation of the (Pb^{2+})**1**(MeCN) complex (dark lines) in the acetonitrile solution after 2 ns MD simulation. Note the two solvent molecules close to the hydrophilic cavity interacting with the lead ion.

more stable as a consequence of an “intruding” MeCN molecule exiting the lower bore and hence affording the closing up of the cavity. After 1.95 ns another acetonitrile molecule interacts laterally with the ion weakening its binding to the hydrophilic cavity for the rest of the simulation. These results show that the metal ion remains stable within the hydrophilic cavity despite the solvent molecules’ competition with the bidentate pendant groups for its binding, a process that accounts for the fluctuation in the ion−calixarene interaction energy of about 30 kJ/mol depicted in the Figure 6.

Structural changes on **1** and the effects produced on the macrocycle by the complexation of a solvent molecule by the hydrophobic cavity are shown in Table 2. These data indicate that the calixarene keeps the square cone conformation all along the simulation. We also observe that the inclusion of the MeCN molecule in the hydrophobic cavity at 0.3 ns mainly affects the breathing motion amplitude of the calix upper rim. This can be inferred by comparing data from Table 2, where the rms deviation of the phenyl apical cross distances (C14−C34 and C24−C44) around their mean values drops from 0.52 to 0.25 Å upon MeCN complexation.

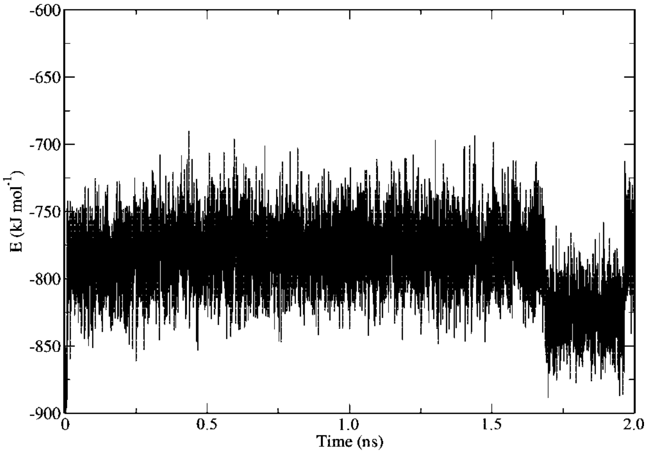

Figure 6. Lead−calixarene nonbonded interaction energy in the (Pb^{2+})**1**(MeCN) complex during the 2 ns simulation.

The phenol and carbonyl oxygen atoms are mainly influenced by its interaction with the enclosed metal ion and the solvent molecules around the lower rim. During the simulation, the behavior of the hydrophilic cavity does not change after complexation of the MeCN molecule in the upper calix. In contrast, the frequent inclusion and exclusion of bulk solvent molecules in the coordination sphere of the Pb^{2+} does affect the interaction metal−ligand energy (see Figure 6) but has no influence in the hydrophilic cavity conformation. These facts are confirmed by the small rms deviations of oxygen cross distances over the entire simulation presented in Table 2. These results, along with the ones obtained in other simulations involving the ester calixarene, allow us to conclude that the inclusion of the MeCN molecule in **1** is favored by the symmetric opening of the calix upon ion−hydrophilic cavity bond formation (allosteric effect). It can be appreciated that despite the solvation effects in the lower bore the (Pb^{2+})**1**(MeCN) bifunctional complex constitutes a stable endo association in the solution. Therefore, it comes as no surprise that this complex survives the crystallization that follows a slow evaporation of the solvent, as suggested by the X-ray diffraction structure.[5]

MD Simulation of Tetramethyl Ketone *p-tert*-Butylcalix[4]arene (2) in Acetonitrile Solution. The starting box of the 2 ns simulation includes a **2** calixarene ligand in a squashed cone conformation in acetonitrile solution stabilized by a 0.5 ns constrained simulation. After 0.5 ns of the unconstrained simulation a MeCN solvent molecule enters the hydrophobic cavity, with its methyl group pointing inward, driven by a potential energy of about −53 kJ/mol to conform a stable **2**(MeCN) adduct until the end of simulation. The adduct remained stable when the simulation was extended to 20 ns. This agrees both with the crystal X-ray diffraction structure and the calculated in vacuo MD equilibrium conformation[6] and lends support to previous suggestions on the existence of the adduct in acetonitrile solution.[5]

The structural changes on **2** due to the formation of the **2**(MeCN) adduct are shown in Figure 7. From Figure 7A we

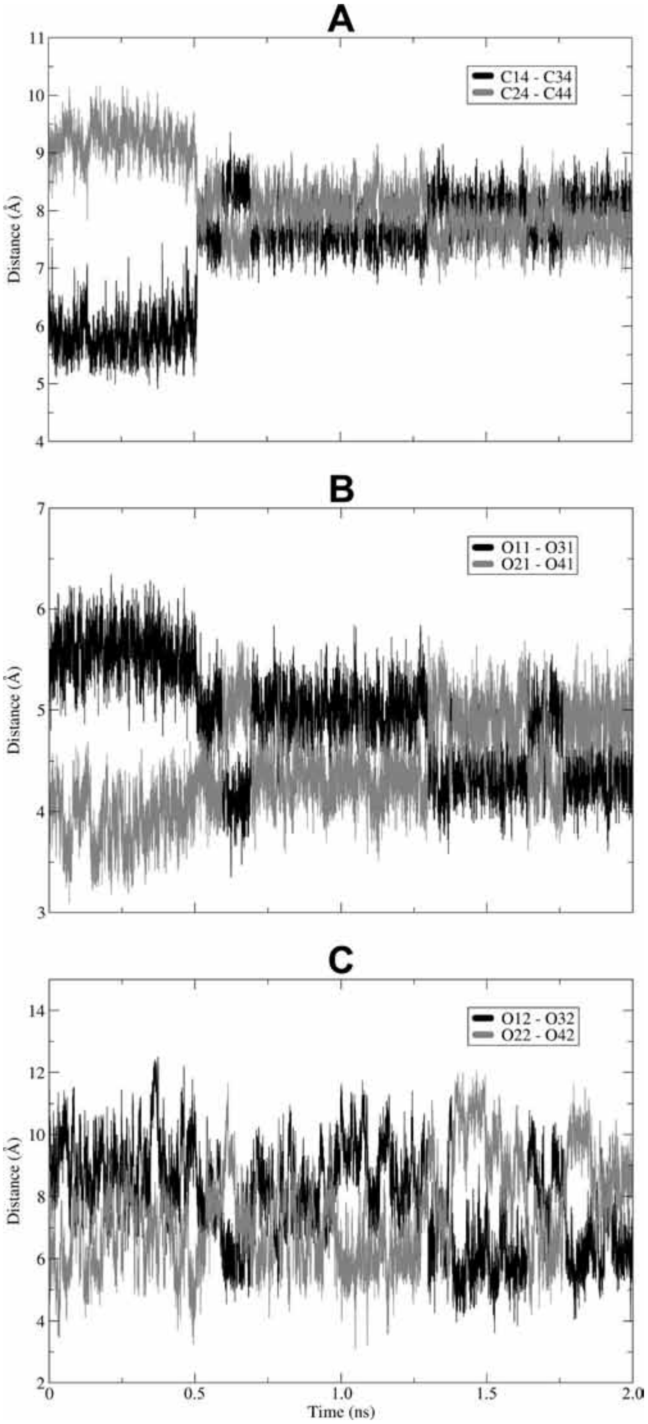

Figure 7. Atomic cross distances from 2 ns simulation of tetramethyl ketone *p-tert*-butyl calix[4]arene in acetonitrile solution. The complexation of a MeCN molecule by the upper calix at around 0.5 ns is clearly observed.

can infer that upon the inclusion of the MeCN molecule, the calix adopts a less distorted cone conformation. By comparison with Figure 7B, we notice a strong correlation between O(ph)···O(ph) and corresponding phenyl C(ap)···C(ap) cross distances (correlation coefficient of −0.73). This can be traced to the above-mentioned hinge-like rotations of the macrocycle monomer units around the linking CH_2 groups. In contrast, the lower bore O(carb)···O(carb) cross distances (Figure 7C) are only weakly influenced by the inclusion of the MeCN in the upper bore. In fact, the correlation coefficient between O(carb)···O(carb) and C(ap)···C(ap) cross distances increases from a nearly null value to about −0.44 upon MeCN complexation. This is an important result: the inclusion of the acetonitrile molecule within the calix does not preorganize significantly this cavity beyond the phenol oxygens. We may also observe that the **2** molecule is more flexible than **1**, a property that can be traced to the shorter $-CH_2-(C{=}O)-CH_3$ pendant groups of **2** carrying fewer negatively charged oxygen atoms as compared with the $-CH_2-(C{=}O)-O-CH_2-CH_3$ arms of **1**.

MD Simulation of Lower Bore 2(Cd^{2+}) Complex in Acetonitrile Solution. The main events of the performed simulations of the **2**−Cd^{2+} complex in acetonitrile solution are depicted in Figure 8.

The final simulation's snapshot shows the calixarene with a MeCN molecule included in its upper calix and the Cd^{2+} ion positioned at the lower bore of the hydrophilic cavity, coordinated by the four carbonyl oxygens and competing acetonitrile solvent molecules in an exo conformation (Figure 9).

The structural changes on **2** during the 2 ns simulation are displayed in Figure 10. Figure 10, A and 10B, show, respectively, the C(ap)···C(ap) and O(ph)···O(ph) cross distances. From these results we can infer that the initial square calix changes to a rectangular cone conformation when the metal moves to the lower bore, breaking its bonds with the phenol oxygen atoms in the beginning of the simulation. Upon inclusion of the MeCN molecule (around 0.95 ns), it is observed that the calix adopts a nearly square conical shape executing interconversions between two mutually perpendicular conformers.

The dynamics of the carbonyl oxygen atoms is depicted in Figure 10C, where the above-mentioned breaking of the Cd−O(carb) bond is indicated by the increase in O12−O32 distance in the first picoseconds of simulation. The conformational changes brought about by the inclusion of the acetonitrile molecule in the calix extend down to the hydrophilic cavity affording the reforming of the ion−O(carb) bond which, in turn, produces the strengthening of the ion−cavity attractive interaction. The O(carb)···O(carb) cross distances execute correlated fluctuations (when a pair approaches the ion, the other one moves apart) with amplitudes in the range from 3 to 5 Å, a kinematics which is reflected in the ion−cavity energy fluctuations discussed below. The results uncover the key role played by the MeCN molecule included in the upper calix in stabilizing the lower bore **2**(Cd^{2+}) exo complex. If it were not for that MeCN inclusion, it could be possible that the competition with solvation effects in the hydrophilic cavity may disassemble the metal−calixarene complex. In this respect, the formation of the **2**(Cd^{2+}) association shows the strongest dependence upon solvent effects as compared with the other complexes studied in this work. Despite this, we can safety rule out any allosteric effects by which the prior formation of the **2**(MeCN) adduct could preorganize the hydrophilic cavity to favor the ensuing formation of the ion−cavity bond. This is sustained by the results of previous section showing that the formation of the **2**(MeCN) adduct in absence of the metal ion does not influence appreciably the conformation of the hydrophilic cavity. Interestingly, during the simulation that leads to the exo **2**(Cd^{2+}) complex, the acetonitrile molecule enters the calix oriented opposite to that observed in the solid state, in which the acetonitrile N-atom points inward to form an N−Cd^{2+} bond that pulls the metal ion deep inside the hydrophilic cavity hence forming an stable **2**(Cd^{2+}) endo complex.[5] Though this could also be observed in solution (as already observed during the **1**(Cd^{2+}) simulations) provided we could run longer simulations, we can envisage that during the usual process of recrystallization by slow evaporation from a saturated acetonitrile solution, the

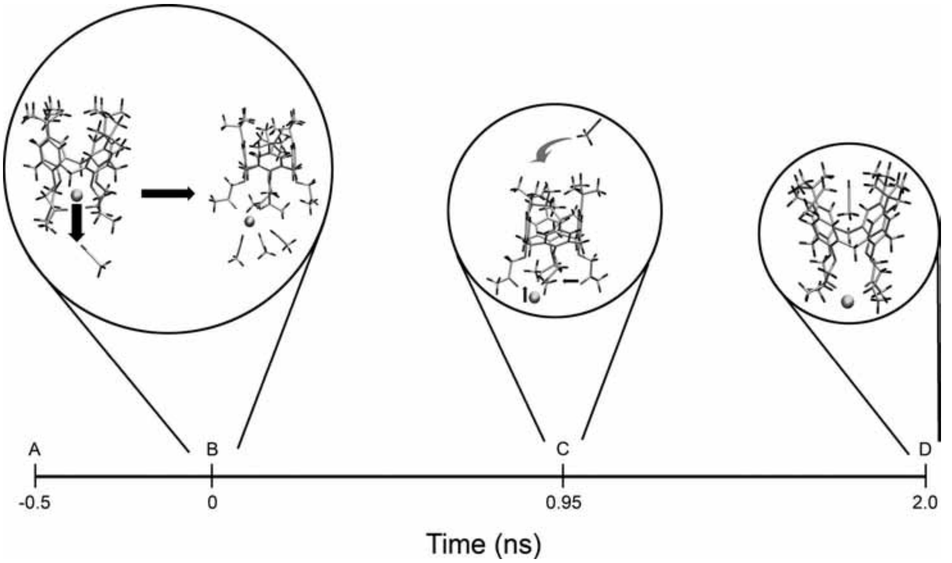

Figure 8. Timeline representation of the main events during the simulation of **2**−Cd2+ complex in acetonitrile solution. (A) Start of equilibration. (A → B) One solvent molecule sites at the lower opening of the hydrophilic cavity with the nitrogen end pointing toward the metal ion, which forms an endo complex. (B) Start of data collection. (B → C) The solvent molecules displace the methyl ends of the pendant groups to form a MeCN−Cd^{2+} bond, dragging the ion toward the cavity external border. This results in a change in the calixarene conformation from squared to rectangular. The metal ion bonds to three carbonyl oxygen atoms as the fourth one moves away from the ion coordination sphere. (C) Complexation of a MeCN molecule into hydrophobic cavity with its methyl group pointing inward. This MeCN−calixarene binding of about −54 kJ/mol (as expected, close to the value calculated for the **2**(MeCN) adduct) symmetrizes the calix to a near square conformation. These effects extend down to the lower bore where the uncoordinated carbonyl oxygen resumes its contact with the ion. This conformational rearrangement stabilizes the complex, which thereafter remains essentially unchanged until the end of the simulation (D).

competing solvent molecules are depleted from the calixarene lower bore thus favoring the ion being swallowed within the hydrophilic cavity to privilege the bonding with the phenol oxygen and the N-atom of an upside down MeCN included molecule. In short, the crystallization process may turn the calculated in solution (Cd^{2+})**2**(MeCN) exo complex into the observed solid state (Cd^{2+})**2**(NCMe) endo one.

The ion−calixarene interaction energy is about −1000 kJ/mol at the beginning of the simulation because the initial endo conformation used as starting point. The shifting of the ion (described above) due to the bulk acetonitrile influence results in an exo conformation complex, with cadmium coordinating three of the four carbonyl oxygen atoms, thus diminishing the ion−host interaction to −670 kJ/mol. After the inclusion of the MeCN molecule into the calix at 0.95 ns, it is observed an increase in the strength of the ion−calixarene interactions to a value of about −770 kJ/mol due to the above-mentioned reforming of a ion−O(carb) contact. After 0.95 ns and until the end of the simulation the ion−host interaction energy fluctuates in the range from −900 to −650 kJ/mol mirroring the above-mentioned conformational transitions of the carbonyl oxygens.

MD Simulation of Lower Bore 2(Pb^{2+}) Complex in Acetonitrile Solution. The initial configuration for the 2 ns solution simulation has the **2**(Pb^{2+}) complex in the square cone conformation. The Pb^{2+} ion is 8-fold coordinated to the four phenol and four carbonyl oxygen atoms which are at the corners of a squashed cube, and the hydrophobic cavity is empty. During the simulation, bulk solvent acetonitrile molecules pull the lead ion from its initial position to the cavity lower border hence conforming an exo complex, which persists until the end of simulation as displayed in Figure 11. A detailed description of the main events observed during the simulation of **2**−Pb^{2+} complex in acetonitrile solution is illustrated in Figure 12.

The lead−host coordination in solution obtained from the simulation differs from the one observed in the solid state where

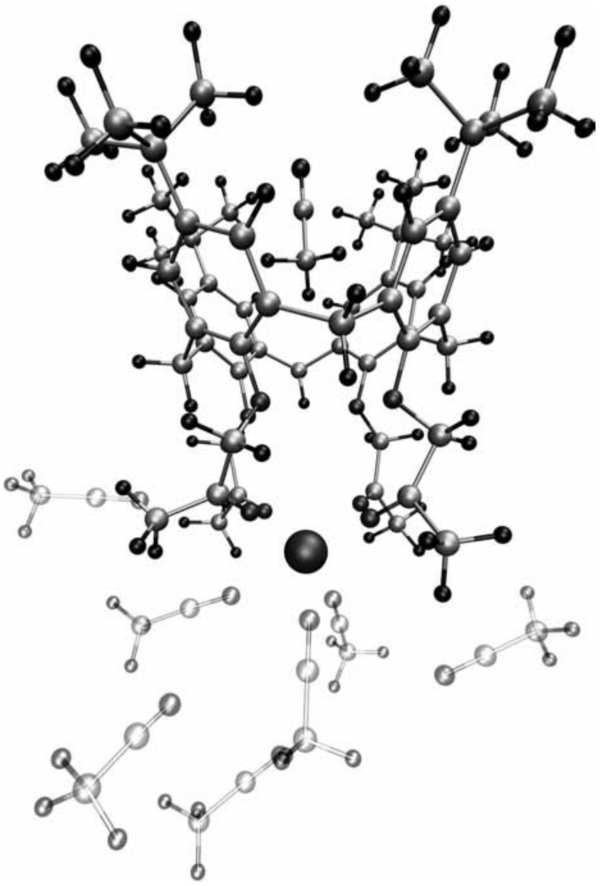

Figure 9. Side view showing the final conformation of the (Cd^{2+})**2**(MeCN) complex (dark lines) in the acetonitrile solution after 2 ns of unconstrained simulation. Note the inclusion of a MeCN molecule in the calix and the Cd^{2+} ion in the lower opening of the hydrophilic cavity characterizing an exo complex.

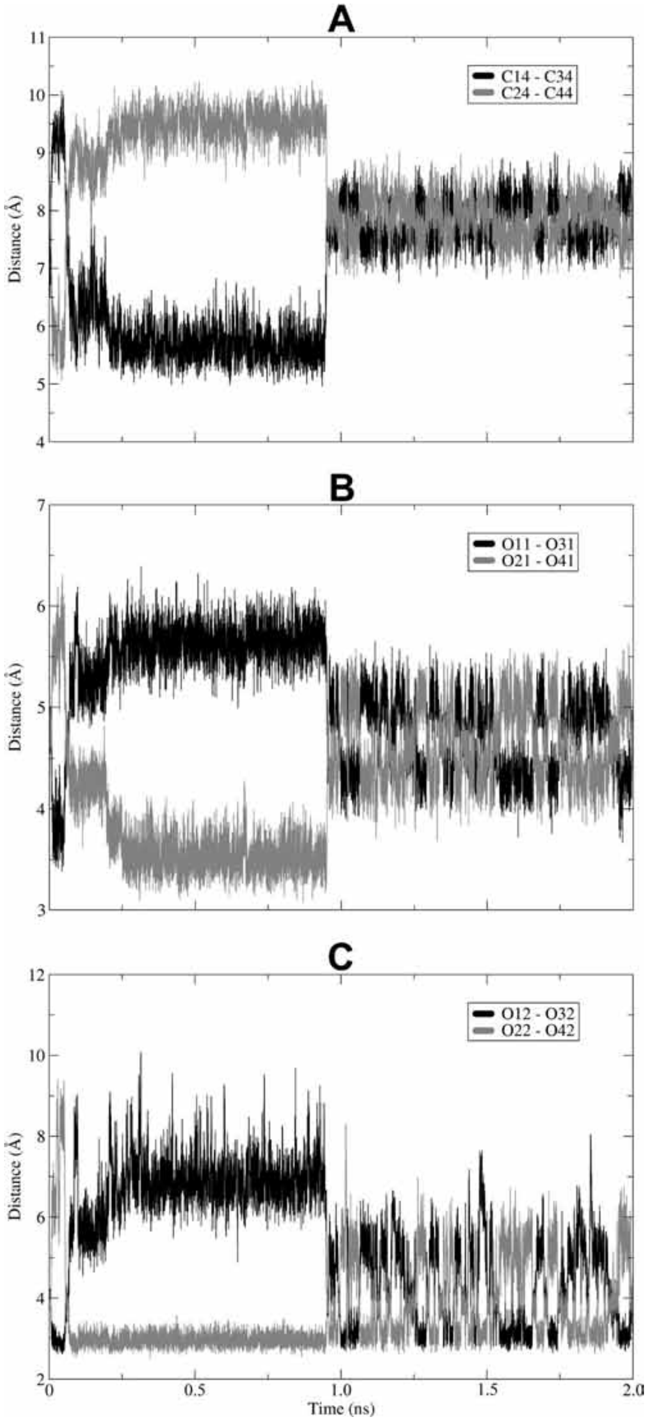

Figure 10. Atomic cross distances from 2 ns simulation of $\mathbf{2}(\mathrm{Cd}^{2+})$ complex in acetonitrile solution. Notice the squashed cone conformation assumed by the calixarene due to the change from endo to exo complex at the beginning of simulation and the inclusion of a MeCN molecule within the calix at about 0.95 ns.

an endo complex is found. To trace the origin of this difference, we monitored the ion−calixarene interaction. The structural effects on **2** induced by the change of the ion complexation mode from endo to exo and the complexation of a MeCN solvent molecule by the hydrophobic cavity are discussed in terms of the atomic cross distances and their rms deviations quoted in Table 3.

Data from Table 3 show that the upper calix conformation is mainly influenced by its filling with the MeCN molecule and not for the displacement of the metal ion toward the lower bore of the hydrophilic cavity. The formation of the **2**(MeCN) adduct after 1 ns of simulation stabilizes the calix as evidenced by the reduction in the fluctuation amplitudes of the phenyl C(ap)···C(ap) cross distances around their mean values (rms from 0.49 to 0.26 Å).

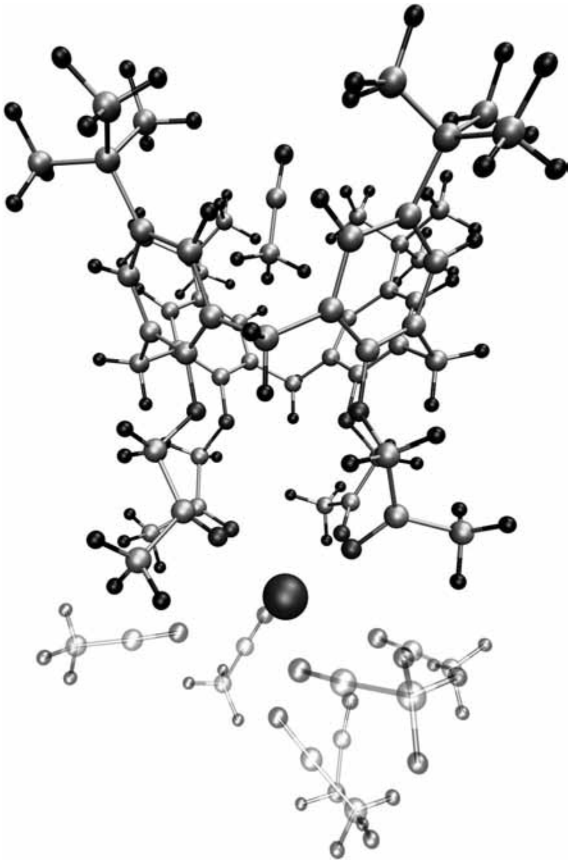

Figure 11. View showing the final conformation of the $(\mathrm{Pb}^{2+})\mathbf{2}(\mathrm{MeCN})$ complex in acetonitrile solution after 2 ns simulation. Note the inclusion of an acetonitrile molecule in the calix and the Pb^{2+} ion in the lower opening of the hydrophilic cavity (exo complex).

The behavior of the phenol and carbonyl oxygen atoms is different as they are only affected by the ion movement. In fact, as the ion is pulled out from deep inside the cavity due to solvation effects at the lower bore, the phenol and carbonyl oxygen cross distances are changed in about 0.2 and 0.5 Å, respectively, while keeping an approximate C_4 symmetry. This is due to steric restraints of the included MeCN molecule producing a square calix. This high symmetry, by the lever-like effect, extends down to the phenol oxygen atoms despite the ion movement toward the lower bore of the hydrophilic cavity.

The ligand-dependent endo/exo binding modes in solution described above are supported by thermodynamic data. In spite of the fact that the enthalpy change (ΔH_c) during the complexation process $\mathrm{M}^{2+}(\mathrm{MeCN}) + \mathbf{L}(\mathrm{MeCN}) \rightarrow (\mathrm{M}^{2+})\mathbf{L}(\mathrm{MeCN})$ for a given ion ($\mathrm{M}^{2+} = \mathrm{Cd}^{2+}, \mathrm{Pb}^{2+}$) is nearly the same for the $\mathbf{L} =$ **1** and **2** ligands, the corresponding Gibbs energies (ΔG_c) are more negative for $(\mathrm{M}^{2+})\mathbf{2}(\mathrm{MeCN})$ than for $(\mathrm{M}^{2+})\mathbf{1}(\mathrm{MeCN})$ complexes.[5] Considering that $\Delta G_c = \Delta H_c - T\Delta S_c$, we therefore conclude that the higher Gibbs energy stabilization of $(\mathrm{M}^{2+})\mathbf{2}(\mathrm{MeCN})$ relative to $(\mathrm{M}^{2+})\mathbf{1}(\mathrm{MeCN})$ complexes is due to a larger entropic change (ΔS_c) associated with the formation of the former complex as compared with the latter. This agrees with the MD results showing more disordered $(\mathrm{M}^{2+})\mathbf{2}(\mathrm{MeCN})$ exo complexes (Figure 9 and Figure 11) as compared with the $(\mathrm{M}^{2+})\mathbf{1}(\mathrm{MeCN})$ endo counterparts (Figure 4 and Figure 5).

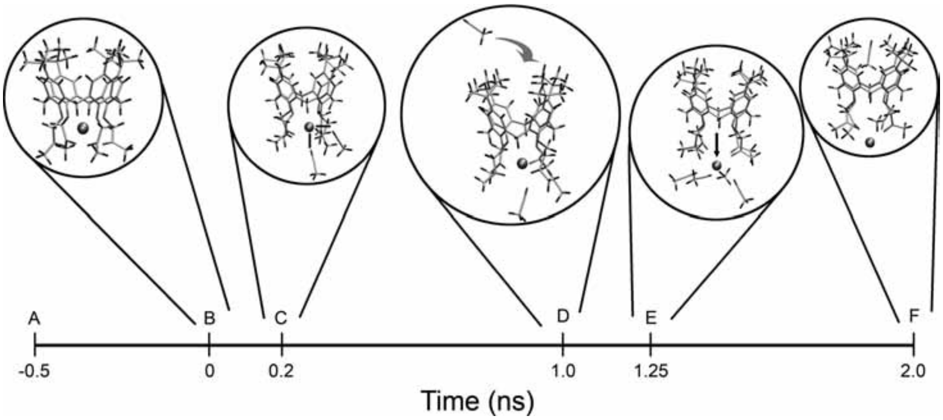

Figure 12. Timeline representation of the main events during the simulation of **2**−Pb^{2+} complex in acetonitrile solution. (A) Start of equilibration. (B) Start of the data collection simulation. The complex is in the endo conformation with the Pb^{2+} encapsulated within the hydrophilic cavity. (C) Two solvent molecules move toward the lead ion, becoming part of its coordination sphere, and start to pull the ion from the hydrophobic cavity core. This results in a drop from −890 to −840 kJ/mol in the strength of the ion−host interaction energy. (D) While the before mentioned MeCN molecules drag the ion outside, another acetonitrile molecule is captured by the hydrophobic cavity. The complexation of this solvent molecule apparently does not influence the process that takes place in the hydrophilic cavity. (E) The lead ion loses its close contacts with the phenolic oxygen atoms and is displaced to the lower border of the calixarene. This change of the complex conformation from endo to exo results in a decrease of the ion−host interaction from −840 to −590 kJ/mol. These results indicate that in solution the ion is not completely encapsulated within the hydrophilic cavity (endo complex), as observed in the solid state. (F) The (Pb^{2+})**2**(MeCN) exo complex continues stable until de end of the simulation.

TABLE 3: Cross-Distance Average Values and Rms Deviation for Apical Carbons and Phenol and Carbonyl Oxygen Atoms Obtained from 2 ns Simulations of (Pb^{2+})2(MeCN) Complex in Acetonitrile Solution

	before MeCN complexation[a]		after MeCN complexation[a]		before exo[b]		after exo[b]	
	mean	rms	mean	rms	mean	rms	mean	rms
C14−C34	7.62	0.49	7.85	0.26	−	−	−	−
C24−C44	7.74	0.48	7.83	0.26	−	−	−	−
O11−O31	−	−	−	−	4.86	0.15	4.65	0.18
O21−O41	−	−	−	−	4.87	0.16	4.66	0.18
O12−O32	−	−	−	−	4.67	0.16	4.20	0.22
O22−O42	−	−	−	−	4.66	0.16	4.22	0.23

[a] Results obtained before and after the inclusion of a solvent molecule in the hydrophobic cavity. [b] Results obtained before and after change from endo to exo in the ion complexation mode.

The unexpected MD finding of exo metal ion−calixarene complexes has been also reported to occur in simulations of the chelating process involving tetraamide and phosphoryl *tert*-butylcalix[4]arene derivatives and trivalent lanthanide ions when taking into account the competition of solvent and/or counterions with the host macrocycle for metal ion binding.[10,23]

Concluding Remarks

The MD simulations in MeCN solution uncover the following main features:

(i) The ketone calix[4]arene (**2**) exhibits more flexibility and mobility than the ester derivative (**1**), forming a stable **2**(MeCN) adduct in the liquid. This association survives crystallization by solvent evaporation. Our simulations also uncovers the formation of a similar, though less stable, **1**(MeCN) adduct. The filling of the **1** and **2** chalices with acetonitrile does not significantly preorganize the corresponding hydrophilic cavities toward metal ion binding.

(ii) On the other hand, the strong metal ion−hydrophilic cavity interaction produces a wide open calix which favors the inclusion of a stabilizing MeCN solvent molecule (allosteric effect).

(iii) The calculated equilibrium conformation of the ester calix[4]arene−metal complexes closely agrees with the endo form observed in the solid state.

(iv) The theoretical structural results for the metal complexes of the ketone calix[4]arene derivative, however, are at variance with the crystallographic ones and show stronger solvation effects in the lower bore where competing MeCN solvent molecules pull the metal ion to the outer rim of the hydrophilic cavity to conform an exo complex.

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Supporting Information Available: GROMACS topology files of the calixarenes, ions, and acetonitrile molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Asfari, Z. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001.

(2) Gutsche, C. D. *Calixarenes revisited*; Royal Society of Chemistry: Cambridge, England, 1998.

(3) Vicens, J.; Asfari, Z.; Harrowfield, J. M. *Calixarenes 50th aniversary: commemorative issue*; Kluwer Academic: Dordrecht, The Netherlands, 1995.

(4) Vicens, J.; Böhmer, V. *Calixarenes: a versatile class of macrocyclic compounds*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991.

(5) Danil de Namor, A. F.; Chahine, S.; Kowalska, D.; Castellano, E. E.; Piro, O. E. *J. Am. Chem. Soc.* **2002**, *124*, 12824.

(6) de Araujo, A. S.; Piro, O. E.; Castellano, E. E.; de Namor, A. F. D. Combined Crystallographic and In Vacuum Molecular Dynamics Study of Allosteric Effects in Ester and Ketone p-tert-butyl Calix[4]arene Derivatives and their Complexes with Acetonitrile, Cd(II) and Pb(II), submitted for publication, 2008.

(7) Van der Spoel, D.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J. C. *J. Comput. Chem.* **2005**, *26*, 1701.

(8) Jorgensen, W. L.; Maxwell, D. S.; TiradoRives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225.

(9) de Araujo, A. S.; Sonoda, M. T.; Piro, O. E.; Castellano, E. E. *J. Phys. Chem. B* **2007**, *111*, 2219.

(10) Baaden, M.; Burgard, M.; Boehme, C.; Wipff, G. *Phys. Chem. Chem. Phys.* **2001**, *3*, 1317.

(11) Darden, T.; York, D.; Pedersen, L. *J. Chem. Phys.* **1993**, *98*, 10089.

(12) Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. *J. Chem. Phys.* **1995**, *103*, 8577.

(13) Berendsen, H. J. C.; Postma, J. P. M.; Vangunsteren, W. F.; Dinola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.

(14) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327.

(15) Denamor, A. F. D.; Desueros, N. A.; Mckervey, M. A.; Barrett, G.; Neu, F. A.; Schwingweill, M. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1546.

(16) Arnaudneu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; Mckervey, M. A.; Marques, E.; Ruhl, B. L.; Schwingweill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.

(17) Pitarch, N.; Walker, A.; Malone, J. F.; McGarvey, J. J.; McKervey, M. A.; Creaven, B.; Tobin, D. *Gaz. Chim. Ital.* **1997**, *127*, 717.

(18) Abidi, R.; Baker, M. V.; Harrowfield, J. M.; Ho, D. S. C.; Richmond, W. R.; Skelton, B. W.; White, A. H.; Varnek, A.; Wipff, G. *Inorg. Chim. Acta* **1996**, *246*, 275.

(19) Danil de Namor, A. F.; Castellano, E. E.; Salazar, L. E. P.; Piro, O. E.; Jafou, O. *Phys. Chem. Chem. Phys.* **1999**, *1*, 285.

(20) Danil de Namor, A. F.; Kowalska, D.; Castellano, E. E.; Piro, O. E.; Velarde, F. J. S.; Salas, J. V. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4010.

(21) Danil de Namor, A. F.; Piro, O. E.; Salazar, L. E. P.; Aguilar-Cornejo, A. F.; Al-Rawi, N.; Castellano, E. E.; Velarde, F. J. S. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 3097.

(22) Tsoucaris, G.; Atwood, J. L.; Lipkowski, J. North Atlantic Treaty Organization. Scientific Affairs Division. *Crystallography of supramolecular compounds*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1996.

(23) Guilbaud, P.; Varnek, A.; Wipff, G. *J. Am. Chem. Soc.* **1993**, *115*, 8298.

JP804198C