Conformation and Dynamics of 18-Crown-6, Cryptand 222, and Their Cation Complexes in Acetonitrile Studied by Molecular Dynamics Simulations

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Abstract: We have performed MD simulations on 18-crown-6 and cryptand 222 and their metal cation complexes in a solution of acetonitrile in order to gain insight into the conformational preferences of the free ligands and into the solvation patterns of the host–guest complexes in a nonaqueous solvent. In contrast to what was observed in water, the interactions between the free hosts and acetonitrile are not markedly dependent on the conformation of the solute. For uncomplexed 18C6, conformational sampling is performed for 2 ns. The D_{3d} form is the most populated, followed by the C_i form observed in the solid state for the free crown. All structures are compared with those previously reported in the solid state and with those most populated *in vacuo* or in water. Upon complexation of cationic guests (Li^+–Cs^+, Ca^{2+}, and Eu^{3+}), the first solvation shells reorganize and some MeCN molecules are coordinated to the encapsulated ion. The coordination numbers of the free and complexed cations are computed. Computer experiments also give insights into the nature of ion pairs in acetonitrile. 18C6/K^+,Cl^- and 18C6/Li^+,Cl^- remain as intimate ion pairs for at least 50 ps, while 222/K^+,Cl^- dissociates rapidly. The complexes of 18C6 with Na^+, Ca^{2+}, and Eu^{3+} dissociate in acetonitrile but have lifetimes larger than 150 ps when Cl^- counterions forming intimate ion pairs are included in the simulation. Finally, we report the first free energy simulations for the complexation of alkali cations in acetonitrile. A qualitative agreement is found with experiment concerning the relative orders of stabilities and the "recognition" by 222 of K^+ among Li^+, Na^+, Rb^+, and Cs^+ cations.

Introduction

Solvation plays a major role in molecular recognition processes by influencing the stability and nature of host–guest complexes.[1,2] Since the pioneering synthesis of macrocyclic receptors by Pedersen,[3] Lehn,[4] and Cram,[5] a wealth of thermodynamic data demonstrated how solvation determines their stability,[6,7] but detailed explanation in terms of enthalpic and entropic components and their interpretation in terms of precise structures in solution remain to be done.[8,9] In particular, microscopic pictures of solvation pattern and their influence on the preferred conformation cannot be assessed on experimental grounds. For instance, it is not clear whether the symmetrical pictures of 18-crown-6 ("18C6") and cryptand 222 (222) obtained by NMR correspond to a time-average of unsymmetrical structures or to real energy minima.[10,11] The relevance of solid-state structures[12] for representing structures in solution is not clear either.[13] In terms of recognition, it would be desirable to identify the degree of preorganization of the receptors, *i.e.* to what extent the free form is conformationally close to the complexed one. Another important issue concerns the solvation of complexes and particularly the shielding of encapsulated cations from the solvent and environment. Comparison of aqueous with nonaqueous solutions is also of importance in order to understand the extraction and transport processes.

Computer simulations using molecular dynamics or Monte Carlo simulations provide valuable insights into these problems.[14] Previous studies of 18C6[15,16] and 222 uncomplexed[17] in water led to the conclusion that dissolution of the crystal should lead to conformational changes. 18C6 changes from C_i to D_{3d} and 222 from an elongated "II" form to a "K" form (Figure 1). We showed that some water molecules firmly hydrogen bonded to specific conformers of these solutes behave indeed as components of a "supermolecule". For the K^+ complex of 18C6, the minimum free energy structure calculated by Dang and Kollman[18] turned out to be very different from the D_{3d} inclusion type complex observed in the solid state[12] or simulated *in vacuo*.[19,20] From these studies, it was clear that the granularity of the solvent, *i.e.* its precise interactions with hydrophilic sites of the solute, determines the conformations in aqueous solution. It was stressed, therefore, that water is unique because of its hydrogen bonding features which allow stable bridging situations.

Encapsulation of a cation inside the cavity of these macrocyclic receptors was shown to induce a restructuring of the first shells

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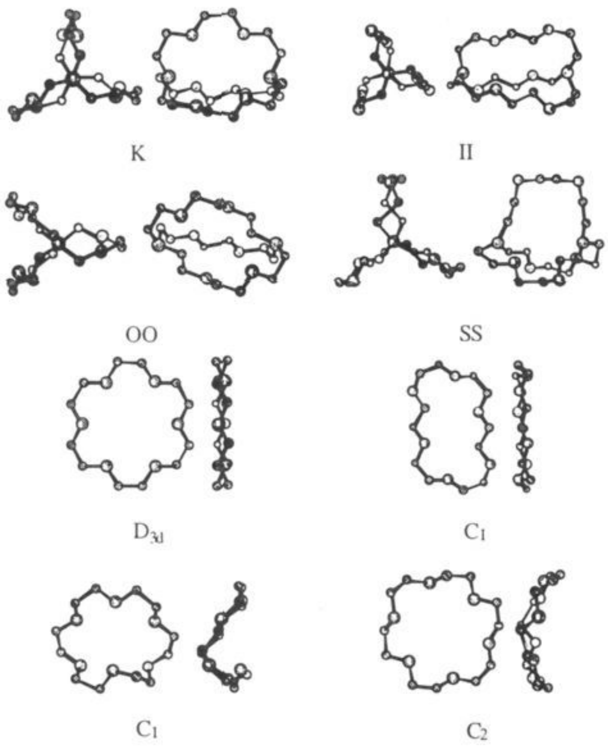

Figure 1. D_{3d}, C_i, C_1, and C_2 forms of 18-crown-6 (top) and K, II, OO, and SS forms of cryptand 222 (bottom) (orthogonal views).

of water due to a disruption of hydrogen bonds and reorientation of water dipoles induced by the cation.[17] The hypothesis had been made that like charged cryptates have similar solvation energies and behave like a big cation,[21] however, computations demonstrated that the shielding of M^{n+} from water provided by the macrocycle, an important feature of ionophores,[4,22] is not very effective, especially as the cationic charge increases.[17] During the transport process through hydrophobic membranes, the interactions between the complexed cations and the environment, expected to be weaker than in water, are not well characterized. The nature of ions pairs in nonaqueous media and the effect of counterions on the complex stability are other important issues related to the ionophoric behavior.

Our aim is to computationally elucidate several features concerning the structure of typical ionophores such as 18C6 and cryptand 222 in an aprotic nonaqueous solvent, acetonitrile.

The first concerns the conformation of the free receptors in acetonitrile. For the related dicyclohexano-18-crown-6, an isomer-dependent complexation of malononitrile has been demonstrated.[23] In solution, the conformational space can be sampled in principle by long MD simulations. After molecular mechanics calculations on 18C6[19,24-27] and 222[28,29] intensive conformational searches have been performed first in the gas phase.[26,30-32] However, the statistical pictures obtained *in vacuo* may not be relevant in solution. In particular, the D_{3d} form of 18C6 and the K form of 222, which are the most relevant in terms of "receptor design", are weakly sampled *in vacuo*. In water, very long simulations are required to provide adequate sampling because of the viscosity of the solvent and the need to keep rather low temperatures. Straatsma and McCammon showed that a 1.5-ns simulation on 18C6 was still too short to provide an adequate sampling.[16] Here, we follow an approach where representative forms are simulated in solution for short times (about 50 ps) to test the conformational (in)stability and to compare their solvation energies (solute–solvent interaction energies). In earlier calculations, such an approach allowed us to predict that the D_{3d} form of 18C6, of comparable intrinsic stability as the C_i form, was significantly better hydrated and should, therefore, display the highest population in water,[15] in agreement with subsequent theoretical studies[16,33,34] and consistent with several experimental observations.[35-37] We consider conformers of 18C6 and 222 extracted from solid-state structures[12] and solvated in acetonitrile. For 18C6, the simulation is run for 2 ns, which is the longest simulation reported so far to our knowledge for 18C6 in solution.

Crown ethers and cryptands display the extraordinary property of dissolving/extracting metal ions, including alkali cations, into nonaqueous and even nonpolar solvents.[38] It is therefore crucial to determine to what extent the complexed cation still interacts with the solvent. We therefore address the question of solvation of the complexes of 18C6 (with Li^+, Na^+, K^+, Ca^{2+}, and Eu^{3+}) and of cryptand 222 (with Li^+–Cs^+, Ca^{2+}, and Eu^{3+}) in acetonitrile. The possible interactions between the encapsulated cation with an anion Cl^- are also investigated by simulating the evolution of intimate ion pairs $18C6/M^{n+},nCl^-$ ($M^{n+} = Li^+$, Na^+, K^+, Ca^{2+}, and Eu^{3+}) and $222/K^+,Cl^-$ in acetonitrile solution.

Finally, we investigate the question of the binding selectivity of cryptand 222 for alkali cations, a quantitative measure of the recognition process.[39-43] Following the Cl^-/Br^- FEP study of a macrocyclic ionophore in water,[44] there have been several theoretical studies concerning the relative cation binding selectivities for 18C6 in water[45] or in methanol[46,47] for valinomycine[48,49] and calixarenes.[50,51] MD mapping of the process of complexation of Cl^- into the SC24,4H$^+$ cage in water,[52,53] as well as potentials of the mean force of $18C6/K^+$ in water[18,54] and a $Na^+\cdots$nonactine

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in methanol,[55] gave important insights into the (de)complexation processes in solution and the solvent reorganization concommitant to host–guest binding.

For cryptand 222, we showed that FEP simulations in water and in methanol could reproduce the selective binding for K^+ among the Na^+ and Rb^+ cations.[89] In acetonitrile, 222 forms more stable complexes with alkali cations than in water and also binds K^+ selectively,[38,56,57] but to our knowledge, no related computational work has been reported. The relative solubility of free and complexed cations in water, compared to acetonitrile, is measured by the relative free energies of transfer, which will also be calculated and compared to experimental values. From a computational point of view, we feel it is important to test FEP calculations in nonaqueous solvents, using standard potentials, in order to assess their predictive capability for other systems (*e.g.* calixarenes[58,127]) which are water insoluble.

Methods

We used the AMBER software[28] for MM and MD simulations, with the following representation of the potential energy:

$$E_T = \sum_{\text{bonds}} K_r(r - r_{eq})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} V_n(1 + \cos n\phi) + \sum_{i<j} (\epsilon(R^*/R_{ij})^{12} - 2\epsilon(R^*/R_{ij})^6 + q_iq_j/R_{ij})$$

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 222 and for 18C6, described with explicit CH_2 groups, are the same as in refs 17 and 59, respectively. The atomic charges are derived from ab initio 6-31G* electrostatic potentials, without a special scaling factor for 1⋯4 interactions. For the cations, we used integer charges and the same ϵ, R^*, and charge parameters as in ref 17 for all simulations. We refer to this set as the "Amber" parameters. In order to check the sensitivity of the results on the cation's representation, we repeated the simulations on free alkali cations and those complexed by 222 by using the Aqvist's parameters, derived from free energy calculations in SPC water.[119] Both sets of parameters are included in Table 7. For Cl^-, ϵ and R^* are taken from ref 44.

The MeCN solvent is represented explicitly as a cubic box of about 30 Å in length. The initial equilibrated solvent configuration was obtained from Guillot *et al.*[60] 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. For MeCN, we used a three-point model, with OPLS parameters[61] (united atom representation of the Me group), constrained to be linear with SHAKE.

After a conjugate gradient energy minimization (RMS < 0.5 $\text{kcal}\cdot\text{mol}^{-1}\cdot\text{Å}^{-1}$), the MD simulations were run for at least 30 ps at constant volume and temperature (300 K) by using the Verlet algorithm (Δt = 1 fs) and starting with random velocities. A residue based cutoff of 10 Å was used for nonbonded interactions, taking the solute(s) as a single residue.

The "FEP" (free energy perturbation) calculations were performed with the windowing technique, changing the ϵ and R^* parameters of M^+ linearly with λ: $\epsilon_\lambda = \lambda\epsilon_{M_1^+} + (1 - \lambda)\epsilon_{M_2^+}$ and $R^*_\lambda = \lambda R^*_{M_1^+} + (1 - \lambda)R^*_{M_2^+}$. The mutation of cation M_1^+ (free or complexed) into M_2^+ was achieved in 20 windows. At each window, 0.5 ps of equilibration was followed by 5 ps of data collection, and the change of free energy ΔG was averaged from the forward and backward cumulated values.

Choice of Starting Structures. For cryptand 222, the four conformers II, OO, K, and SS which we simulated previously in water were considered in acetonitrile (Figure 1).[12] Conformer II, which corresponds to the uncomplexed form of 222, is elongated, has no cavity, and is calculated to be the most stable *in vacuo*.[32,62] The K form, extracted from the K^+ complex, displays a spherical cavity with converging binding sites and diverging CH_2 groups. The SS and OO forms look more hydrophilic since their respective oxygen and nitrogen binding sites are diverging. They are expected, therefore, to be better solvated in polar solvents.

For 18C6, we consider the forms D_{3d} (from the K^+ complex), C_1 (from its Na^+,H_2O complex), C_2 (built from the dibenzo-18C6 derivative[12]), and C_i (free form in the solid state[63] and intrinsically the most stable[19]).

The starting structures of complexes were D_{3d} for 18C6 and the K form for 222, with the cation set at the center of the cavity, assuming a 1:1 stoichiometry.

Analysis of the Results. The coordinates were saved every 0.1 ps; the time evolution and averages of structural and energy parameters, as well as a graphical display of the dynamics structures, were obtained using our MDS software.[64] In the following, we will refer for simplicity to the calculated solute–solvent interaction energy as the "solvation energy", as it is the major contribution to the enthalpy component of the solvation energy.

Results

I. 18C6 and Cryptand 222 Uncomplexed in Acetonitrile. (a) Comparison of the Four Conformers of 18C6 for 50 ps. In acetonitrile, 18C6 appears to be quite flexible and displays a conformational equilibrium between several forms. This is suggested from the comparison of the original four conformers. In contrast to what is observed in water on the same time scale,[65] three conformers evolve to others during 50 ps. The C_1 and C_2 forms are unstable and retain their structure for less than 1 ps. In comparison, the D_{3d} form has the longest lifetime (larger than 50 ps). The C_i form is more mobile, and after 7 ps, *gauche–trans* conversions take place. After 200 ps, it becomes D_{3d}.

In water, the relative "hydration energies" for the D_{3d}, C_2, C_1, and C_i forms were 0.0, 2.0, 1.0, and 20.0 ± 0.5 kcal/mol, respectively,[65] calculated with the solute free of constraints. Constraining these forms to fixed geometries led to almost identical values of 18C6/water interaction energies. In acetonitrile, because three structures are conformationally labile, we put constraints on the initial coordinates to fix them and determine their relative solvation energies. For the D_{3d}, C_2, C_1, and C_i forms, it amounts to 0.0, 5.6, 2.2, and 10.1 ± 0.4 kcal/mol, respectively. The difference between the D_{3d} and C_i values is 50% smaller in acetonitrile than in water, but larger than the intrinsic relative stabilities ($\Delta E_{\text{opt}} = -1.7$ kcal/mol and $\langle \Delta E \rangle_{\text{acetonitrile}} = -1.6$ kcal/mol, respectively), which suggests that dissolution of the crystal (C_i form) in acetonitrile should lead, as in water, to other conformers with D_{3d} being more populated than C_i. This is confirmed by the subsequent sampling simulation described in the next section. In acetonitrile, the C_1 and C_2 forms are not viable because of their poor solvation energy (ΔE = 2.2 and 4.4 kcal/mol, respectively, relative to C_i) and instability compared to D_{3d} (ΔE_{opt} = 9.6 and 4.4 kcal/mol, respectively) (Table 1).

(b) Conformational Sampling of 18C6 for 2 ns. We paid particular attention to the D_{3d} form and calculated the dynamics up to 2 ns. As found in water,[16] new forms appear continuously along the trajectories, and no convergence is obtained (Figure 2). The time evolution of the six OC–CO dihedral angles (Figure 3) indicates a clear preference for *gauche* and *trans* arrangements, but all torsional angles are required to characterize the structural

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Table 1. The **18C6** Crown and the **222** Cryptand in Acetonitrile[a]

solutes	E_{tot}, solute	E_{tot}, solute/solvent	E_{tot}, solvent
18C6 D_{3d}	0.0[b]	–37.2	–967
18C6 C_i	1.5	–29.7	–945[c]
18C6 C_1	3.5	–28.8	–980[c]
18C6 C_2	2.7	–25.6	–959[c]
222 K	0.0[d]	–74.1	–1185
222 OO	0.5	–68.5	–1186[e]
222 II	–3.0	–67.1	–1158[e]
222 SS	–1.3	–69.9	–1291[e]

[a] Average energy (kcal/mol) of the solute, average solute–acetonitrile interaction energy, and average energy of the solvent. Fluctuations are less 0.3 kcal/mol. [b] Total energy is 142.3 kcal/mol. [c] Normalized to 316 solvent molecules. [d] Total energy is 25.6 kcal/mol. [e] Normalized to 270 solvent molecules.

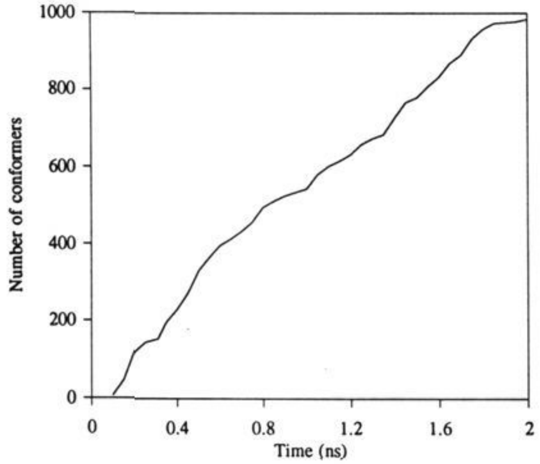

Figure 2. 18C6 in acetonitrile. Total number of conformers as a function of the simulation time.

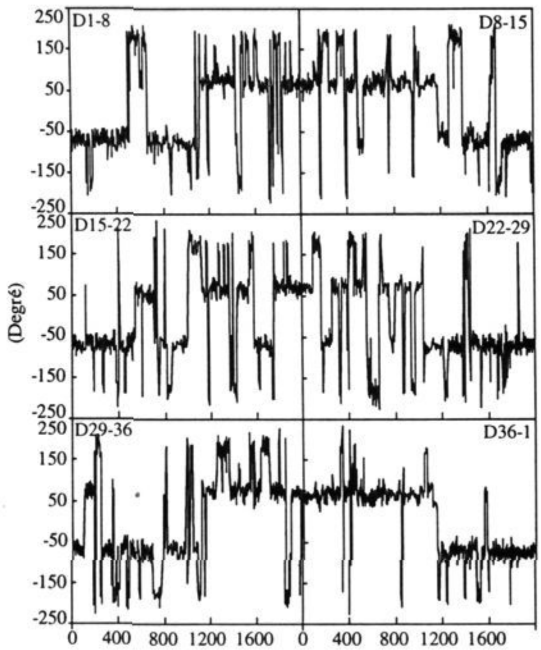

Figure 3. Time evolution of the six OC–CO didedral angles of 18C6 in acetonitrile for 2 ns.

diversity simulated in acetonitrile. We define each dihedral angle as g^+ (60° ± 60°), g^- (–60° ± 60°), or t (180° ± 60°) and each structure by the sequence of its 18 dihedral angles, either clockwise or counterclockwise, with the six possible origins. Thus symmetry equivalent or mirror images are counted as one single conformer. This led to a total of 1936 interconversions and 984 different structures. The 30 most populated forms (Table 8 in the supplementary material) contribute 51% of the total population in acetonitrile, which is comparable to their contribution in water (56%).[16] Interestingly, the D_{3d} starting form first disappears (after 96 ps), but reappears seven times before the end of the 2-ns simulation, and displays the largest occurrence (14.3%). Removal of the first D_{3d} sequence in the statistics still leaves this conformer as the most populated (10.4%). This large occurrence does not result therefore from being trapped for a long time (96 ps) in the starting structure but from its relatively low internal energy and from its solvation pattern (see the next section). C_i has the largest population after D_{3d} and appears/disappears 21 different times. As a result, D_{3d} has a much longer lifetime than C_i (35.7 and 5.5 ps, respectively) in acetonitrile. In many of the other dominant forms, moieties of the D_{3d} or C_i forms can be recognized (Figure 4).

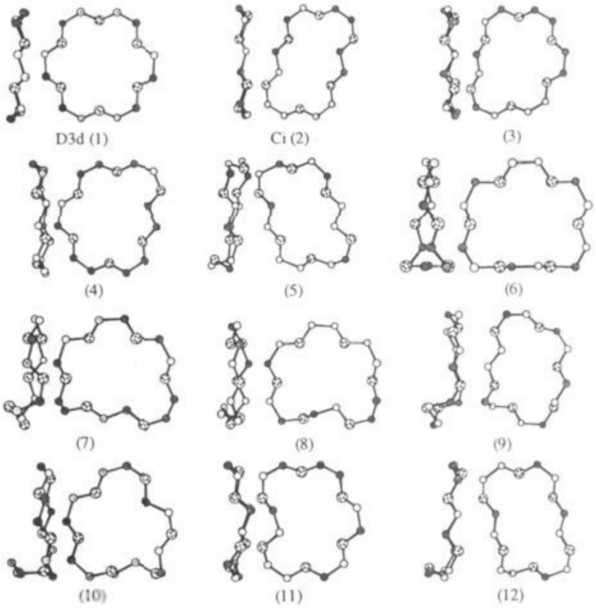

Figure 4. Twelve conformers of 18C6 with the largest occurrence after a 2-ns MD simulation in acetonitrile (see Table 8 in the supplementary material). The next 18 conformers are given as supplement material.

After energy minimization of the 30 dominant forms, the most stable is C_i, but there are other relatively unstable forms, like forms 5 and 10, which are at least 3 kcal/mol higher in energy (Table 8). No correlation is found between the total population of one form and its intrinsic stability. Although to a smaller extent than in water, there is a significant modulation of populations by the solvation energy, in addition to the internal energy of the solute. We have represented in Figure 5 the time evolution of the potential energy of 18C6, its interaction energy with the solvent, and its dipole moment. No clear pattern emerges concerning the fluctuations of the two energies. Interestingly, the most negative solute–solvent interaction energy (<–40 kcal/mol) often corresponds to a nearly zero dipole moment of the crown. As previously pointed out in water,[15] there is no correlation between the dipole moment of the solute and its interaction energy with the acetonitrile solvent. The reason is that an important contribution comes from the centrosymmetrical C_i and D_{3d} forms, the latter one being particularly well solvated by acetonitrile (and water). The average dipole moment calculated results from other unsymmetrical forms and amounts to 2.1 D (the mean square deviation of the distribution is 1.2 D). This value is intermediate between the experimental value of 2.6 D in cyclohexane[24,66] and that of 1.9 D calculated by Ha *et al.* in CCl_4.[34] Ha used a united atom force field and q_0 charges of –0.30, which differs from ours

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(66) Caswell, L. R.; Savannut, D. S. *J. Heterocycl. Chem.* **1988**, *25*, 73.

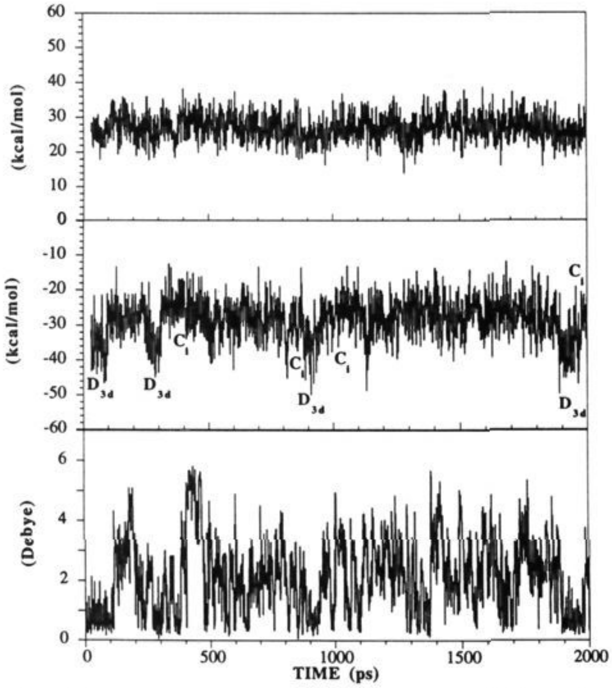

Figure 5. Internal energy of 18C6 (top), 18C6/acetonitrile interaction energy (middle), and dipole moment of 18C6 (bottom) during the 2-ns MD simulation.

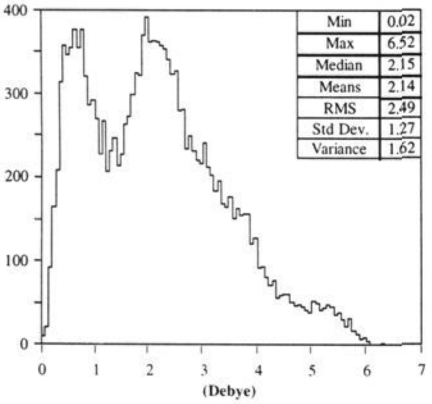

Figure 6. Statistics of the dipole moment of 18C6 in acetonitrile.

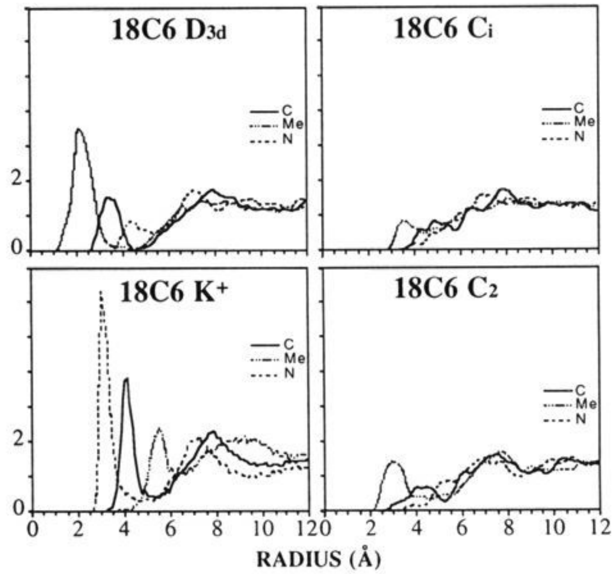

Figure 7. 18C6 in acetonitrile: rdf's of the Me, C, and N atoms around the center of mass of the D_{3d}, C_i, and C_2 uncomplexed forms and of the D_{3d} K$^+$ complex.

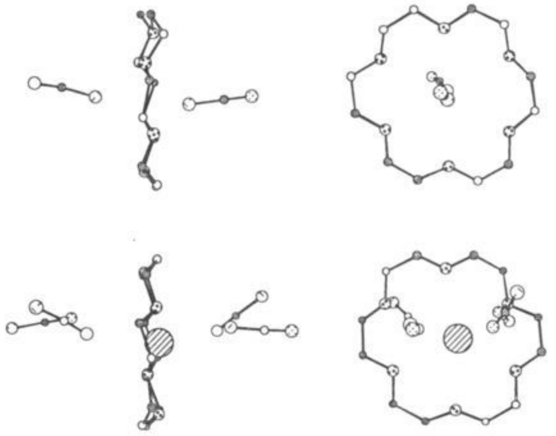

Figure 8. Snapshot of a typical solvation pattern of 18C6 D_{3d} and of its K$^+$ complex (orthogonal views).

($q_0 = -0.404$). Using the same charges would lead to $\mu = 1.6$ D. We have displayed in Figure 6 the statistics of all μ values. Interestingly, there are two peaks (at 0.7 and 2.1 D), indicative of nonregular distribution of the dipole moments and of the structural diversity of 18C6 in solution.

(c) Solvation of 18C6 D_{3d}. The rdf's of Me, C, and N around the center of mass of the solute show a first peak (Figure 7) which integrates to exactly two MeCN molecules, consistent with the instant structure displayed in Figure 8. Each acetonitrile molecule is perched over the crown, with its Me at 2.2 Å from the center. In fact, instantaneous coordination may be also 2 + 1 or 2 + 2, but the 1 + 1 coordination is found most frequently and has by far the longest lifetime. In many snapshots, the MeCN axis is close to the C_3 symmetry axis of the crown. Such a coordination is very similar to solid-state structures of the 2MeCN·18C6 adduct[67-69] and consistent with structures of neutral complexes with 18C6 and related macrocycles.[70,71] It can relate to the long lifetime of the D_{3d} form. In these structures, however, like in the molecular mechanics minimized MeCN·18C6 complex,[72,73] MeCN is more tilted from the symmetry axis of the crown. For other forms of 18C6, similar patterns are found, with the MeCN dipole more or less perpendicular to the average plane of the crown, pointing its positive end to the center. For the C_i form, the closest MeCN molecules are lying more or less parallel over the ring, giving good van der Waals contacts.

(d) Comparison of the Four Forms of Cryptand 222 for 100 ps. For the cryptand, the situation is more simple to describe, since the four starting structures are conformationally stable for 100 ps. It is therefore more meaningful to compare their solvation energies and stabilities in acetonitrile than those for 18C6. Table 1 shows, indeed, that the 222/solvent interaction energy is similar for the II, OO, and SS forms (within 2 kcal/mol) and most attractive for the K form (−74 kcal/mol), *i.e.* 5–6 kcal/mol better

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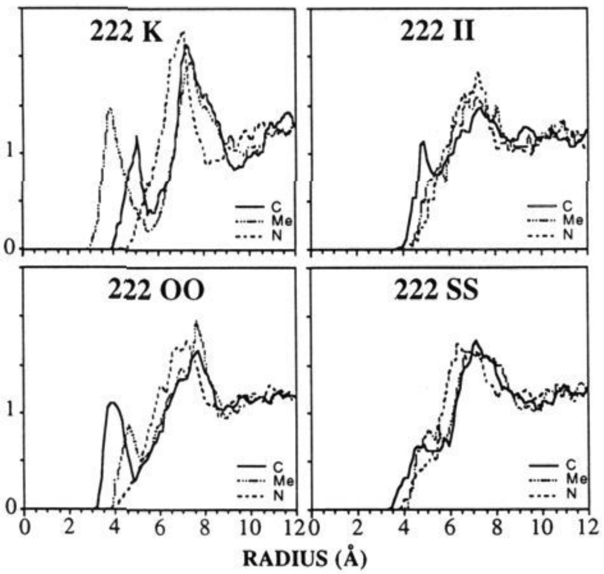

Figure 9. Cryptand 222 in acetonitrile: rdf's of the Me, C, and N atoms around the center of mass of the K, II, OO, and SS forms.

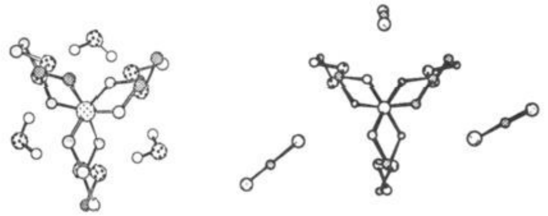

Figure 10. Snapshot of cryptand 222 (K conformer) in water and in acetonitrile.

than for the other forms. On the other hand, the average energy of the solute is comparable for the four forms. This is very suggestive of a conformational equilibrium in acetonitrile, with a higher population of the K form.

Concerning the relative contributions of the van der Waals and electrostatic components to the interaction energy with acetonitrile, it is interesting to find that both components are attractive, but the first one is clearly dominant (81–88%) in contrast with the situation in water.[17,32]

In contrast to what was calculated in water,[17] no clear solvation pattern is found for cryptand 222. The first peak of the rdf around the center of the cavity (Figure 9) is sharpest for the K form. *The closest solvent atoms are C(Me) > C > N, which* indicates that the dipoles point with the positive end toward the cavity. A typical structure is shown in Figure 10. First of all, the cavity of the cryptand is empty, like in water. The converging C–O dipoles of 222 induce some dipole–dipole interactions with MeCN, when the Me group points to the center of cavity, reminiscent of the three bridging water molecules characterized in aqueous solution (Figure 10). However, the absence of hydrogen bonding in acetonitrile leads to a somewhat weaker coordination of acetonitrile (about 8.5–9.5 kcal/mol per MeCN) compared to water (about 12 kcal/mol per bridging H_2O[17]). Other first shell solvent molecules lie in the groove delimited by two bridges of 222 (Figure 10), accounting for the relatively weak electrostatic and strong van der Waals interactions calculated above.

For the other forms II, OO, and SS of 222, no clear pattern is found due to the lower symmetry of the solute and the absence of strong interactions. In particular, the diverging oxygen atoms of the SS form, or the solvent accessible nitrogen atoms of the OO form, are not better solvated than in the II or K forms, where the heteroatoms are less accessible to the solvent.

Table 2. The Cation Complexes of **18C6** and of **222**: Characteristics of the First Peak in the Cation MeCN *rdf*'s (Calculated with Amber Parameters for the Cations)

complexes		CH_3	C	N
18C6/Li^+	*a*	4.5/8.3	3.1/7.4	2.0
	b	2.1	1.9	1.9
18C6/K^+	*a*	*5.5/9.2*	*4.1/7.8*	*3.1/7.2*
	b	4.7	3.5	3.3
222/Li^+	*a*	4.6/8.5	3.2/7.8	2.1
	b	1.8	1.7	1.8
222/Na^+	*a*	5.4/8.0	3.9/7.8	2.7/7.3
	b	1.7	1.2	1.3
222/K^+	*a*	5.6/8.0	4.2/7.8	3.3/7.3
	b	3.1	2.1	2.2
222/Cs^+	*a*	6.1/7.5	4.6/7.8	3.6/7.5
	b	3.7	2.6	2.6
222/Ca^{2+}	*a*	5.1/8.6	3.6/7.8	2.5/7.1
	b	3.0	3.0	3.0
222/Eu^{3+} [c]	*a*	5.1/8.5	3.6/7.5	2.4/6.5
	b	4.0	4.0	4.0
222/Eu^{3+} [d]	*a*	5.0/8.6	3.6/7.7	2.4/6.8
	b	3.4	3.4	3.4

[a] Maxima positions (Å). [b] Coordination number. [c] Average from the first to 20th ps. [d] Average from the 23rd to the 30th ps.

II. Cation Complexes of 18C6 and of 222 in Acetonitrile. Complexation of a cation by 18C6 or by 222 induces a reorganization of the solvent, whose structure is determined by the electrostatic field of the cation and by the structure of the complex. We have reported in Table 2 the characteristics of the rdf's around the complexed cations of increasing size (Li^+–Cs^+) and charge (Na^+, Ca^{2+}, and Eu^{3+}) obtained with Amber parameters. For the Na^+, Ca^{2+}, and Eu^{3+} "complexes" of 18C6, no values are reported since decomplexation occurred after 47, 19, and 40 ps, respectively. In subsequent simulations, included Cl^- counterions formed intimate ion pairs with the complexed cation; the resultant complex remained stable and of inclusive type.

In the K^+ complex of 18C6, the cation is poorly shielded from the solvent and coordinated, on the average, to 3.3 MeCN molecules by their nitrogen atom. In fact, K^+ oscillates by about 0.8 Å from the center of the crown, and its motion is coupled to a dynamic coordination of solvent molecules, of types 3 + 1, 2 + 2, and 2 + 1.

Although the bicyclic topology of 222 provides more shielding than the monocyclic 18C6, the cation encapsulated in 222 is still in direct contact with acetonitrile. The coordination numbers are 1.3 for Na^+, 2.2 for K^+, and 2.6 for Cs^+. In this series, the *interaction energy between the cation and the solvent decreases* slightly (from −66 to −60 kcal/mol), like the cation–host interaction energies (from −77 to −56 kcal/mol), due to the weaker cation-binding site interactions (Table 3). The first peaks of the cation–nitrogen rdf are at 2.7, 3.1, and 3.5 Å, respectively.

As the charge of the cation increases, the interactions with the first shell acetonitrile molecules increase, the coordination numbers increase (from 1.3 for Na^+ to 3.0 for Ca^{2+} and 3.0–4.0 for Eu^{3+}), and the mobility of acetonitrile molecules around the solute is reduced. The first peaks of the rdf's are sharper for Ca^{2+} and Eu^{3+}, and more separated from the next ones, than for monovalent ion complexes, indicating the absence of first shell–second shell diffusion (Figure 11).

For all cryptates, the interaction energy between the complexed cage and acetonitrile, although attractive, is weaker than for the uncomplexed cage, as the electrostatic component is repulsive (Table 3). The van der Waals energy component is comparable in both cases. This is consistent with the electrostatic field effect of the complexed cation on the solvent. For hard cations such as Ca^{2+} and Eu^{3+}, long-range structuring of the solvent is observed,

Table 3. The Cation Complexes of **18C6** and of **222** in Acetonitrile

complexes	ligand/solvent	M^{n+}/solvent	M^{n+}/ligand	solvent
18C6/Li^+	−8.5 ± 4.9	−94.3 ± 10.7	−64.5 ± 5.4	−1367 ± 18.5[b]
18C6/K^+	−10.4 ± 4.4	−67.7 ± 9.8	−47.9 ± 2.7	1364 ± 17.8[b]
222/Li^+	−34.8 ± 0.4	−75.0 ± 1	−77.0 ± 0.1	−1138 ± 1[c]
222/Na^+	−59.0 ± 0.4	−66.2 ± 0.6	−76.7 ± 0.1	−1158 ± 3[c]
222/K^+	−59.9 ± 0.3	−64.5 ± 0.5	−72.3 ± 0.1	−1155 ± 2[c]
222/Cs^+	−61.9 ± 0.3	−60.4 ± 0.6	−56.4 ± 0.1	−1171 ± 4[c]
222/Ca^{2+}	−35.6 ± 0.3	−312.0 ± 1	−154.9 ± 0.2	−1095 ± 3[c]
222/Eu^{3+} [d]	−16.4 ± 0.5	−663.0 ± 2	−236.2 ± 0.5	−993 ± 4[c]
222/Eu^{3+} [e]	−24.3 ± 0.4	−621.0 ± 2	−239.7 ± 0.3	−1015 ± 3[c]

[a] Average energy component analysis and statistic fluctuations after 100 and 30 ps, respectively, of MD (calculated with Amber parameters for the cation) [b] Normalized to 281 solvent molecules. [c] Normalized to 315 solvent molecules. [d] Average from the first to 20th ps. [e] Average from the 23rd to 30th ps.

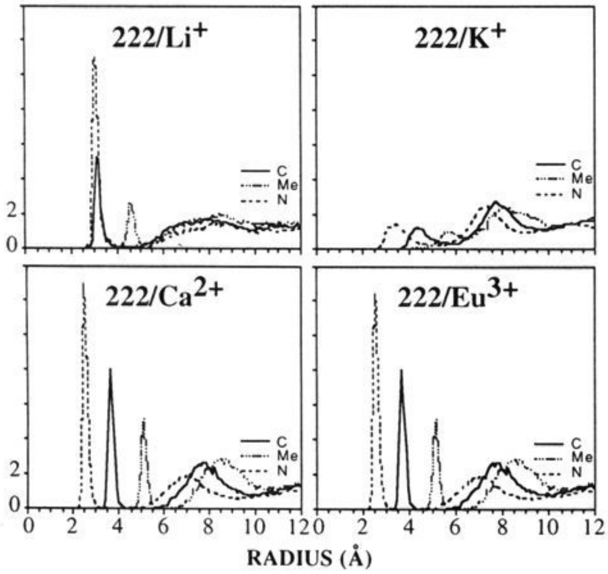

Figure 11. 222 cryptates in acetonitrile: rdf's of the Me, C, and N atoms around the Li^+, K^+, Ca^{2+}, and Eu^{3+} complexed ions.

leading to a higher energy of the solvent itself within the simulation box (Table 3). The 222/Eu^{3+} cryptate provides a nice example of solvent relaxation within the first shell. During the first 20 ps of the dynamics, Eu^{3+} is coordinated to four MeCN molecules, two of them being "squeezed" between two bridges and repelling each other. One of them then diffuses into the second solvation shell, and the loss in cation–solvent attraction energy is more than compensated by the relaxation energy of the solvent.

The Li^+ complexes present a structure different from those of the other alkali complexes, since Li^+ is too small for the cavity of 18C6 or of 222. In fact, in the 18C6/Li^+ complex, the ion moves from the center to an asymmetrical position (Figure 18 in the supplementary material). The crown remains in a conformation close to D_{3d}, but Li^+ displays instant coordination to two ether binding sites of the crown and to two MeCN molecules. Along the dynamics, Li^+ exchanges between several ether sites. In the 222/Li^+ cryptate, a similar pattern is found at the beginning of the simulation: Li^+ moves off the center of the cage to one bridge and coordinates to two ether oxygens of the host and to one MeCN at each side (Figure 12). Later on, more asymmetrical forms are observed, in which Li^+ is coordinated to one MeCN only. In water, we found that one H_2O molecule was co-complexed with Li^+ inside the cavity, by a three-point anchoring scheme consistent with the X-ray structure of the 18C6/Li^+/H_2O complex[74] (see Figure 10 of ref 17). In acetonitrile, no solvent molecule is co-complexed with Li^+, due to the steric hindrance and the weakness of hydrogen bonds between ether oxygens and the Me group of MeCN[75] compared to the $O_{ether}\cdots H_{water}$ hydrogen bonds.

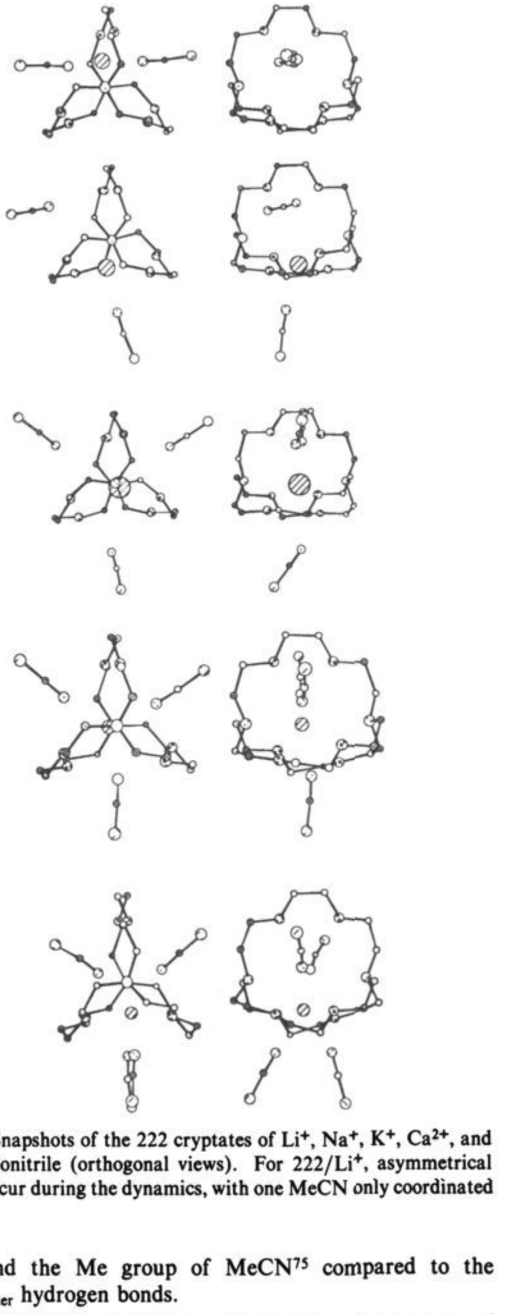

Figure 12. Snapshots of the 222 cryptates of Li^+, Na^+, K^+, Ca^{2+}, and Eu^{3+} in acetonitrile (orthogonal views). For 222/Li^+, asymmetrical structures occur during the dynamics, with one MeCN only coordinated to Li^+.

III. Investigation of Possible Ion-Pairing. Importance of Counterions on the Lifetime of the Na^+, Ca^{2+}, and Eu^{3+} 18C6 Complexes. The nature of ion pairs in solution results from cation–anion interactions, and of the solvation effects, with both enthalpic and entropic components. The nature of the anion is known to influence the stability of the alkali cation complexes,[76–80] as well as the selectivity of metal extraction and transport. Since factors like the anion radius, hydration enthalpy, or softness parameter have not been sufficient,[81] the explanation at the molecular level

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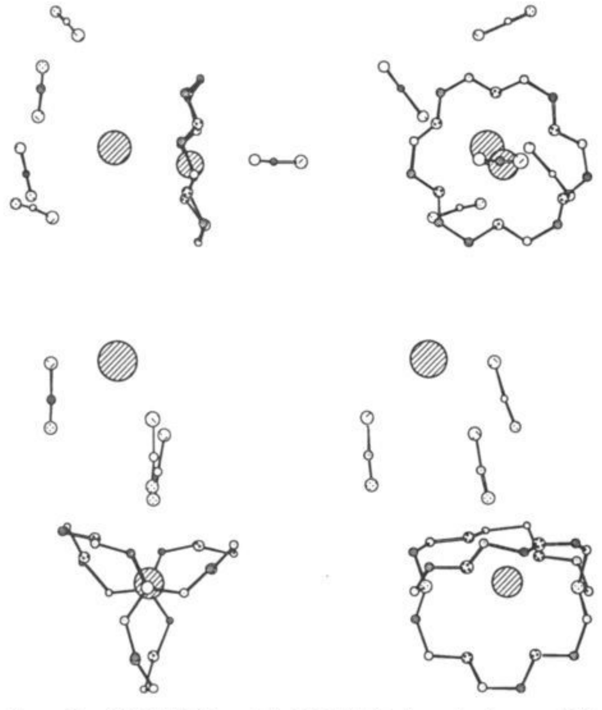

Figure 13. 18C6/K^+,Cl^- and the 222/K^+,Cl^- ion pairs in acetonitrile (snapshot of first shell solvent molecules around the ions, see text).

remains to be found. In the case of cryptates, cation complexation is generally considered to induce a separation of ions.[82] Small-angle neutron scattering measurements on the K^+ and Ba^+ 222 cryptates in acetonitrile, with ClO_4^- as the counter ion, suggest that the ions can come in close contact even when the cation is complexed.[84] Quantitative insights into the nature of ion pairs can be obtained by the calculation of the potential of mean force, *i.e.* the change of free energy as a function of their separation,[85] which is a very time consuming task. We recently performed computer experiments on the time evolution of intimate ion pairs of 222/Mn^+ cryptates and Cl^- anions in water.[86] Interestingly, Cl^- dissociated from the K^+ and Cs^+ complexes within the first picosecond of the MD, while for Na^+, Ca^{2+}, and Eu^{3+} cryptates, ion pairs remained intimate for the 50 ps of the simulation. We *therefore decided to repeat such simulations in acetonitrile, which* provides in principle a poorer solvation of the partners and should lead to less dissociation. The 18C6/M^{n+},nCl^- (M^{n+} = Li^+, Na^+, K^+, Ca^{2+}, and Eu^{3+}) and 222/K^+, Cl^- complexes were simulated in acetonitrile, using the same protocol as we used in water.[86] After energy minimization, we ran 5 ps of MD, keeping the solute rigid, in order to allow for optimal positioning of the solvent. This was followed by at least 50 ps of MD simulation.

The results for the 18C6 complexes differed from those for the 222 complexes. In all 18C6 complexes, the cation and Cl^- ion pairs remained intimate for at least 150 ps, with the cation close to the center of the crown. This is in contrast with the 222/K^+,Cl^- cryptate, where dissociation of the intimate ion pair took place rapidly (after 10 ps), to form first a solvent-separated ion pair (Figure 13). Typically, two MeCN molecules built up a network between K^+ and Cl^-: K^+···NCMe···Cl^-. This is likely related to the hindrance imposed by the bridges of 222, which prevent solvation of the anion when it forms intimate contacts with the cryptate. In the 18C6 complex, the Cl^- anion can still enjoy coordination to some acetonitrile molecules and remains in contact with K^+. The lifetime of this 222/K^+···Cl^- solvent-separated ion pair was about 20 ps, after which it dissociates completely.

Table 4. Relative Free Energies of Mutation of Alkali Cations and Relative Binding Affinities for Cryptand **222** (kcal/mol)

		Na^+/Li^+	K^+/Na^+	K^+/Rb^+	Rb^+/Cs^+
ΔG_3 for free ions	"Amber"	−25.0	−13.3	5.6	5.3
	"Aqvist"	−17.5	−13.5	4.5	6.7
	exptl[a]	−18.9	−16.2	4.9	7.2
ΔG_4 for 222 cryptates	"Amber"	−11.4	−8.6	8.7	14.1
	"Aqvist"	−7.3	−8.9	5.1	12.0
binding affinities, $\Delta\Delta G_c$	"Amber"	−13.6	−4.7	−3.1	−8.9
	"Aqvist"	−10.2	−4.6	−0.6	−5.3
	exptl[b]	−3.6	−2.3	−2.4	−6.8

[a] Reference 87. [b] References 38 and 56.

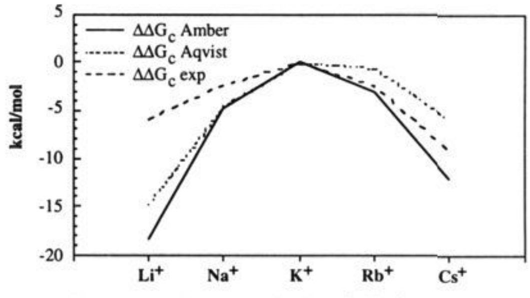

Figure 14. Relative binding selectivities of alkali cations for 222 in acetonitrile: calculated with Amber and Aqvist cation parameters and experimental $\Delta\Delta G_c$'s.

IV. The Binding Selectivity of 222 for K^+ in Acetonitrile: Free Energy Simulations. The relative binding affinity in solution of the receptor R for the ions M_1^+ and M_2^+, measured experimentally by the difference of free energies of complexation $\Delta\Delta G_c = \Delta G_1 - \Delta G_2$, is equal to the difference of free energies $\Delta G_3 - \Delta G_4$. The ΔG_3 and ΔG_4 free energies correspond respectively to the mutation of the free ions and of their complexes in solution, which can be calculated with small statistical uncertainties (about 0.5 kcal/mol) compared to the direct calculation of ΔG_1 or ΔG_2.

$$\begin{tikzcd} M_1^+ + R \arrow[r] \arrow[d, "\Delta G_3"] & M_1/R^+ \arrow[d, "\Delta G_4"] & \Delta G_1 \\ M_2^+ + R \arrow[r] & M_2/R^+ & \Delta G_2 \end{tikzcd}$$

There is no direct experimental determination of ΔG_4, but the calculated ΔG_3 values can be compared with experimental relative free energies of solvation. These values are reported in Table 4 together with the results calculated with the two sets of cation parameters; the $\Delta\Delta G_c$'s are plotted in Figure 14. Experimental ΔG_3 energies are deduced from the relative free energies of transfer ΔG_t from water to acetonitrile,[87] corrected by the relative free energies of hydration.[88] For Li^+, no data are available, and ΔG_t has been extrapolated from data on the Li^+/Na^+ difference involving other solvents.[87]

The simulations have been performed in the directions $K^+ \rightarrow Na^+ \rightarrow Li^+$ and $K^+ \rightarrow Rb^+ \rightarrow Cs^+$ for the free and complexed ions, with two sets of cation parameters. As observed experimentally, ΔG_3 increases as the size of the ion increases, and ΔG_4 follows the same trend. If one assumes that the Li^+ extrapolated ΔG_3 energy is correct, the calculated ΔG_3 would be slightly underestimated for the small ions (by 6.1 kcal/mol for Li^+ and

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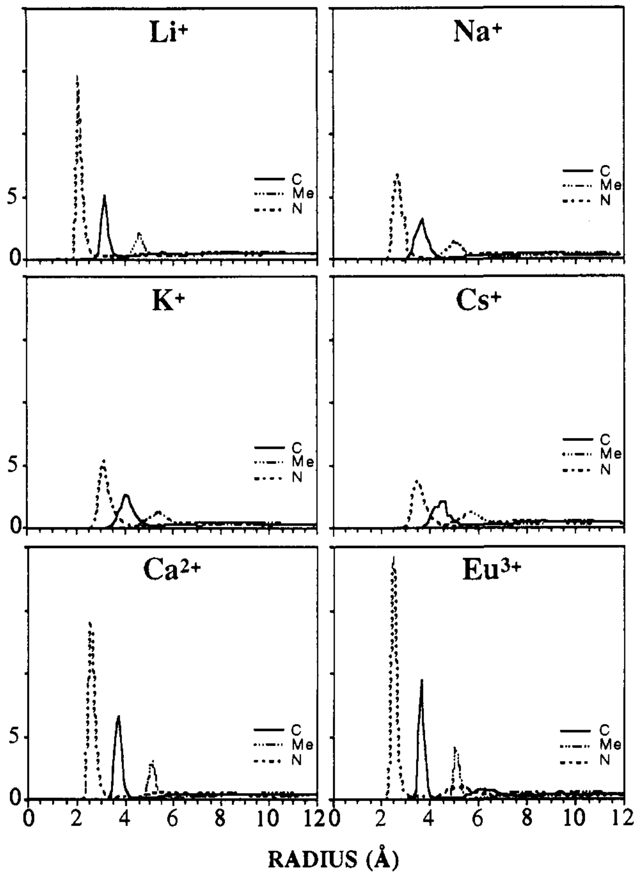

Figure 15. rdf's of the free cations Li^+–Cs^+, Ca^{2+}, and Eu^{3+} in acetonitrile.

2.9 kcal/mol for Na^+) and slightly overestimated for Cs^+ (by 1.9 kcal/mol) with the Amber parameters. The Aqvist parameters give ΔG_3 values similar to the Amber parameters, except for the Na^+/Li^+ mutations, which become closer to the "experimental" values.

As far as binding selectivities in acetonitrile are concerned (Table 4 and Figure 14), the calculations with both sets of cation parameters are successful in reproducing the peak for K^+, as well as qualitative preference for each cation compared to the next one in the series Li^+–Cs^+. The agreement is not quantitative, however, likely because of the lack of an explicit polarization term for acetonitrile. Counterion effects on relative affinities cannot be ruled out,[76] especially for hard cations such as Li^+, which displays the largest discrepancy (Table 4).

V. The Solvation of Li^+–Cs^+, Ca^{2+}, and Eu^{3+} Free Cations in Acetonitrile. The MD equilibrated configurations of the free cations in acetonitrile, performed to initiate the free energy simulations, allow one to calculate the rdf of the N, C, and Me atoms of the solvent around each ion. Figure 15 shows that coordination takes place, as expected, by the N terminus of acetonitrile. The peaks broaden from Li^+ to Cs^+ but sharpen as the charge of the cation increases. We have summarized in Table 5 the characteristics of the first peaks in the rdf's obtained with the two sets of cation parameters. From the integration of the peak of the N atom of the solvent, the calculated coordination numbers with Amber parameters are 4.5 for Li^+, 6.8 for Na^+, 7.8 for K^+, and 9.3 for Cs^+. With the Aqvist parameters, coordination numbers are nearly identical for Na^+–Cs^+ within statistical uncertainties. The only difference concerns Li^+ (6.0 MeCN molecules). Integration of the C atom's rdf gives a value very close to the N atom's rdf, whereas the Me rdf's integrate to larger, although less precise, values. This reflects the decrease of $M^+\cdots NCMe$ charge–dipole attractions as the size of the cation increases.

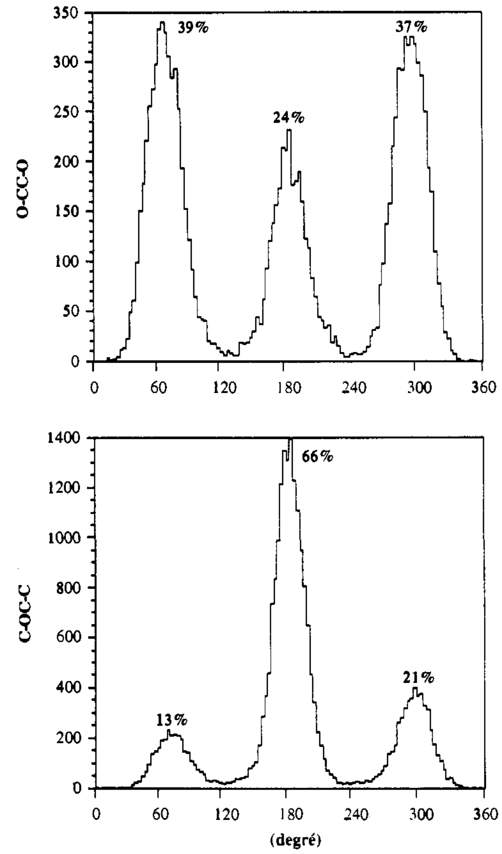

Figure 16. 18C6 in acetonitrile: distribution of the OC–CO (top) and CO–CC (bottom) torsion angles after 2 ns of MD. Compare with Figures 7–10 of Ha *et al.*[34]

Table 5. The Free Cations Li^+–Cs^+, Ca^{2+}, and Eu^{3+} in Acetonitrile: Characteristics of the First Peak of the *rdf*'s

		CH_3		C		N	
cations		Amber	Aqvist	Amber	Aqvist	Amber	Aqvist
Li^+	*a*	4.6	4.7	3.1	3.3	2.0	2.2
	b	6.0	10.5	4.5	6.2	4.5	6.0
Na^+	*a*	5.1	5.1	3.7	3.7	2.7	2.7
	b	9.9	9.8	6.7	7.0	6.8	6.7
K^+	*a*	5.4	5.5	4.1	4.0	3.1	3.1
	b	12.7	12.5	8.3	7.8	7.8	7.4
Rb^+	*a*	5.5	5.4	4.2	4.0	3.2	3.0
	b	12.2	12.0	8.0	7.6	7.8	7.7
Cs^+	*a*	5.7	5.8	4.4	4.4	3.5	3.5
	b	14.7	14.4	9.8	9.2	9.3	9.0
Ca^{2+}	*a*	5.1		3.7		2.6	
	b	9.1		8.7		8.1	
Eu^{3+}	*a*	5.0		3.6		2.5	
	b	8.5		8.8		8.6	

[a] Maxima positions (Å) [b] Coordination number.

VI. Relative Free Energies of Transfer from Water to Acetonitrile for the Li^+–Cs^+ Free Cations and Those Complexed by 222. Since the mutations have been carried out in acetonitrile (this study) and previously in water,[89] it is possible to calculate relative free energies of transfer from water to acetonitrile, by using the thermodynamic cycle below for the free ions M_1^+ and M_2^+ in acetonitrile:

$$\begin{tikzcd}
M_1^+ \arrow[r] \arrow[d, "\Delta G_t(M_1^+)"] & M_2^+ \arrow[d, "\Delta G_t(M_2^+)"] & \Delta G_{3\text{-wat}} \\
M_1^+ \arrow[r] & M_2^+ & \Delta G_{3\text{-acet}}
\end{tikzcd}$$

For two uncomplexed cations, the relative free energies of transfer is

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Table 6. Free Energies of Transfer (kcal/mol) of the Uncomplexed Free Na^+, K^+, and Rb^+ Cations and of Their **222** Cryptates from Water to Acetonitrile

		Na^+/K^+	K^+/Rb^+
ΔG_3-wat of free ions	"Amber"	18.7	7.2
	"Aqvist"[a]	17.6	5.4
	exptl[b]	17.5	5.5
ΔG_3-acet of free ions	"Amber"	13.3	5.6
	"Aqvist"	13.5	4.5
	exptl[c]	16.2	4.9
$\Delta\Delta G_t$[d] of free ions	"Amber"	−5.4	−1.6
	"Aqvist"	−4.1	−0.9
	exptl[e]	−1.3	−0.6
222 cryptates	$\Delta G_{4\text{-wat}}$ "Amber"	13.3	10.8
	$\Delta G_{4\text{-acet}}$ "Amber"	8.6	8.7
	$\Delta\Delta G_t$ "Amber"[f]	−4.7	−2.1
	exptl[e]	−1.5	0.2

[a] Reference 119. [b] Reference 89. [c] Reference 87. [d] $\Delta\Delta G_t = \Delta G_{3\text{-acet}} - \Delta G_{3\text{-wat}}$. [e] Reference 57. [f] $\Delta\Delta G_t = \Delta G_{4\text{-acet}} - \Delta G_{4\text{-wat}}$

$$\Delta\Delta G_t = \Delta G_t(M_1^+) - \Delta G_t(M_2^+) = \Delta G_{3\text{-wat}} - \Delta G_{3\text{-acet}}$$

Similarly, for two cation cryptates

$$\Delta\Delta G_t = \Delta G_t(222/M_1^+) - \Delta G_t(222/M_2^+) = \Delta G_{4\text{-wat}} - \Delta G_{4\text{-acet}}$$

We have reported in Table 6 the calculated and experimental values for the Na^+/K^+ and K^+/Rb^+ pairs, using the values calculated in water with the Amber parameters by Auffinger *et al.* for the Na^+, K^+, and Rb^+ free and complexed ions.[89] Calculations of ΔG_t for the free cations with Aqvist parameters are obtained from $\Delta G_{3\text{-acet}}$ (this study) and $\Delta G_{3\text{-wat}}$.[119] The experimental ΔG_t values have been reported by Danil de Namor *et al.*[57] Both sets of cation parameters give similar ΔG_t's, within less than 1 kcal/mol. The calculations give the same trend as the experiment concerning the relative free energies of transfer from water to acetonitrile, which are more negative for the larger ion than for the smaller one. Quantitatively, however, the calculations exaggerate this trend by 1–3.9 kcal/mol. The only qualitative difference concerns the $222K^+/222Rb^+$ cryptates, for which the experimental $\Delta\Delta G_t$ is nearly zero (0.2 kcal/mol) and the calculated value is negative (−2.1 kcal/mol). Previous related theoretical work dealt with neutral organic molecules[90] instead of ions and gave somewhat better quantitative agreement.

Discussion

1. Free Crown 18C6 and Cryptand 222 in Acetonitrile. (a) Conformational Equilibrium for 18C6 and 222. Although acetonitrile is aprotic and weakly polar, the simulations demonstrate that it interacts significantly with both ionophores. Among the D_{3d}, C_i, C_1, and C_2 forms of the crown, D_{3d} is best solvated. This is consistent with the observation of 18C6/MeCN adducts in the solid state where the crown is D_{3d}[67–70] and with the formation of a 1:1 18C6/MeCN adduct in CCl_4[91] or in benzene solutions.[92] Within the 18C6/2MeCN complex D_{3d} (extracted from the MD trajectory and energy minimized by molecular mechanics), we indeed find an attraction energy of 9.7 kcal/mol per MeCN with the crown, *i.e.* between the value of 10.0 kcal/mol of Grootenhuis *et al.*[72] and the 6.7–8.3 kcal/mol values of Damewood *et al.*[73] The van der Waals and electrostatic contributions are respectively −4.0 and −5.7 kcal/mol. Although the coordination pattern is consistent with C–H···O hydrogen bonds,[75] no special term was included in the force field for such bonding, as the Me group is represented in a united atom approximation. The major difference in the total solvation energy of D_{3d}, compared to the other forms, may be due to these two MeCN molecules. From this particular solvation pattern, one may stress that smaller crown ethers such as 15C5 or 14C4 should be less well solvated by acetonitrile, as suggested by dielectric relaxation and infrared experiments.[93]

Coming now to the question of which structure of 18C6 is most populated in acetonitrile, we suggest that D_{3d} has the highest proportion, as in water. A spectacular difference with water concerns the C_i form, which is the most stable one among those observed in the solid state.[19] It displays the second highest population in acetonitrile but is absent in water.[16,34] Other forms consistent with a tripod coordination of MeCN, as characterized for $R{-}NH_3^+$ complexes (see ref 94 and references cited therein), are also present in acetonitrile. Ultrasonic relaxation spectra of 18C6 and 222 in acetonitrile were interpreted as isomeric relaxations involving the solvent.[95] This is however too slow (about 10^8 s^{-1}) to relate to our simulations. For cryptand 222, there is likely an equilibrium between several forms, including the K form which is *preorganized* for complexation of the K^+ ion.

(b) Comparison of Structures of 18C6 in Acetonitrile with Structures in Vacuo, in Water, and in the Solid State. We searched among the 984 different structures of 18C6 in acetonitrile for those which have been reported for 18C6 in the solid state, in the gas phase, and in water. The solid-state structures are taken from the studies of Dobler[26] and of Fyles *et al.*[96] In the gas phase, the 11 forms Ia–Ik of Billeter *et al.*[59] and the 30 most populated forms sampled by Sun *et al.*[31] are considered. In water, the 40 most populated forms were reported by Straatsma *et al.*[16] No precise comparison can be made to the results from the Monte Carlo simulation of Ha *et al.*[34] in water and in CCl_4 solution because the explicit sequence of torsional angles is not available to us. These results are reported in Table 8, in the order of decreasing population in acetonitrile. Among the 984 forms present in acetonitrile, a total of 18 can be identified either *in vacuo* (14), in water (6), or in the solid state (4), but only three of them have a population larger than 1% in acetonitrile: D_{3d}, C_i, and the "C24" form of the gas-phase study of Sun.[31] Among them D_{3d} is present in the four environments, with similar populations in acetonitrile (14.3%) and water (16.7%). This contrasts with C_i, which is absent in water[16] and displays the highest population after D_{3d} (5.7%) in acetonitrile. As far as solid-state structures are concerned, in addition to D_{3d} and C_i, two other solid-state conformers are found, but with a very weak population. They are the "L" structure of ref 26 (from the K_2·phtalocyanin complex of 18C6) and the "C2(E-)" structure of ref 96 (from a tetramide derivative).

The distribution of the OC–CO and CO–CC torsion angles in acetonitrile peaks for *gauche* and *trans* conformations (Figure 16), as in the solid state.[97,98] Comparison with the distribution obtained in water and in CCl_4[34] suggests that the distribution in acetonitrile is intermediate between the ones in these two solvents.

(c) Comparison of Aqueous Acetonitrile Solutions of 18C6 and 222. By comparing free 222 and 18C6 in acetonitrile/water solutions, we find average solute/solvent attractions of about 74/79 kcal/mol for 222 and 36/56 kcal/mol for 18C6, indicating a somewhat poorer solvation in acetonitrile. These numbers cannot be compared directly, because the size of the solvent boxes were not identical and the solvent disruption energies are not the same, but are consistent with the fact that the enthalpy of transfer of 222 from water to acetonitrile is positive (+13.78 kcal/mol),[57] and with the loss of specific hydrogen bonds with water.[17]

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(d) The Question of "Preorganization". In acetonitrile, like in water, the most populated conformers have the right cavity size and shape to incorporate the K^+ cation with minor structural reorganization, if any. In that sense, they could be considered as "preorganized" for complexation. Taking into account the solvation effects, however, shows that the solvent molecules have to be stripped upon complexation and their dipole moments reversed in order to point the negative end, instead of the positive one, to the center. As suggested earlier,[17] the energy cost associated with the desolvation of the ligand may relate to the relatively low rates of complexation, compared to those of a purely diffusional process.[99-102]

2. Free Cations and Cation Complexes. (a) Coordination Numbers of the Free Cations. The MD simulations allow us first to determine coordination numbers of the alkali cations Li^+–Cs^+ and of Ca^{2+} and Eu^{3+} uncomplexed cations, in the absence of counterions. To our knowledge, no precise experimental data are available in acetonitrile.[88,103,104] For instance, experimental values for Li^+ range from 4 to 9, depending on the method. Our values obtained with the two sets of parameters are nearly identical, for Na^+ to Cs^+. Only Li^+ displays a smaller coordination number with the Amber (4.5) than with the Aqvist parameters (6.0). The broad range of experimental values may be related to the nature of ion pairs, which has not been considered so far in simulations. For hard cation such as Eu^{3+}, intimate ion pairs are formed in acetonitrile with a coordination number of 10.0 for the NO_3^- anion in excess.[105] A neutron scattering study showed that the Li^+, Br^- ion pair remains intimate in acetonitrile, with Li^+ coordinated with about three solvent molecules.[106] The role of the associated anion on coordination numbers of the free cations remains to be investigated.

(b) Does the Ligand Shield the Cation from the Solvent? None of the cations complexed by 18C6 or by 222 are completely shielded from the solvent, and their coordination numbers depends on the charge and atom size. Far IR and Raman spectra of Li^+ and Na^+ 222 cryptates in acetonitrile suggested that "the alkali metal ions are completely enclosed in the cryptand cavity",[107] but such techniques may not be sensitive enough to the environment of M^+. In the solid-state structure of the $Eu(ClO_4)_3$ complex with 222, one bidentate perchlorate is bound to Eu^{3+} between the two bridges.[108] NMR of the cations is a more sensitive probe, and variations in their chemical shifts are indicative of interactions between cations complexed by 18C6 or 222 and the surrounding nonaqueous solvents, including acetonitrile.[109] Proton and ^{13}C NMR studies on 221 Na^+ and K^+ cryptates also demonstrate conformational changes of the ligand, as a function of the ion–solvent coordination.[110] However, it is not possible, from these NMR studies, to determine the coordination number of M^+. Our theoretical results are in the agreement with these results and give a microscopic account. The cation–acetonitrile interaction energy is always attractive (from −75 to −60 kcal/mol, Table 3) and most likely contributes to the high solubility of their cryptates in acetonitrile.

(c) Importance of Counterions on the Inclusive Nature of 18C6 Complexes. Surprisingly, upon simulation of the Na^+, Ca^{2+}, and Eu^{3+} complexes of the crown, the cations preferred to move to the solvent than to remain complexed inside the cavity. This seems in contradiction with the stability constants observed in acetonitrile ($\log K = 4.2$ for Na^+ and 2.6 for Eu^{3+} [7]). Recent simulations of these complexes in water under the same conditions led to the result that only the Na^+ complex remained encapsulated, whereas Ca^{2+} and UO_2^{2+} made second sphere coordination and Eu^{3+} dissociated completely.[83] Recent thermodynamics data showed that the complexation of light lanthanoid nitrates with crown ethers is enthalpy driven in acetonitrile.[111] We cannot completely rule out force field artifacts related to an unbalanced electrostatic representation of the crown and the solvent, but our computer experiments including Cl^- counterions strongly suggest that ion pairing is necessary for the stability of the inclusion complexes with 18C6 in acetonitrile. The potential of mean force calculations[86] should demonstrate this effect, supported qualitatively by the lifetime of starting intimate ion pairs, which is at least 150 ps for Na^+, Ca^{2+}, and Eu^{3+} complexes in the presence of Cl^- counterions. In the solid state, lanthanide complexes of 18C6 are in direct contact with anions as in solution.[112-114] In acetonitrile solution, conductivity measurements show that the 18C6 1:1 complexes of lanthanide nitrates are nonelectrolytes, which suggests that the anions are coordinated like in the solid state.[113,114] Recently, it was shown for the 18C6 $La(NO_3)_3$ complex that "La^{3+} is centered in the ring, with respectively two and one nitrate anions on each side of the crown ether pseudoplane. In no case do either water or solvent molecules directly coordinate to La^{3+}." [125] Our structures obtained by simulation are fully consistent with this view.

For lanthanide 222 cryptates, small anions (F^-, Cl^-, and OH^-) can interact strongly with the complexed cation in acetonitrile,[115] whereas 1:1 complexes of lanthanide perchlorate complexes are dissociated.[113,114] For mono- and divalent cation complexes, no such data are available to our knowledge, but our results suggest strongly that the nature of the anions (size, polarizability, and hardness), which is known to modulate the rate and efficiency of transport or extraction processes, determines also the precise nature of the cation complex. Further investigations on this question are in progress.[86]

3. Molecular Recognition in Nonaqueous Solvents. The complexes of alkali cations and 222 are more stable in nonaqueous solvents such as acetonitrile than in water[56,57,116] partly because of the reduced energy cost for cation desolvation upon complexation. Acetonitrile solvates the free ions or their 222 complexes less than water: the corresponding free energies of transfer from water to acetonitrile are positive.[57,87] The binding selectivity results from an interplay between enthalpy and entropy components. The complexes are enthalpy stabilized but entropy destabilized. The enthalpy of complexation, more negative in acetonitrile than in water, peaks respectively at K^+ and Rb^+, whereas the free energy is most negative for K^+ in both solvents.[57]

We used a standard procedure to calculate the relative binding affinities in acetonitrile. The parameters of the solvent were fitted on the bulk solvent properties and on MeCN···TIP4P water interaction energies,[61] and no polarization term is included in the force field. It is therefore gratifying to find the peak of selectivity for K^+ determined from calculation in agreement with experiment.

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Table 7. Interaction Energies between M^+ Cations and One Solvent Molecule (kcal/mol)

$CH_3CN{\cdots}M^+$		Li^+	Na^+	K^+	Rb^+	Cs^+
Amber's[a]	R^*	1.0	1.6	2.0	2.2	2.4
parameters	ϵ	0.01	0.05	0.08	0.095	0.12
Aqvist's[b]	R^*	1.138	1.868	2.658	2.956	3.395
parameters	ϵ	0.018 34	0.002 77	0.000 33	0.000 17	0.000 08
Amber		−30.3	−19.5	−15.6	−14.1	−12.8
Aqvist		−26.9	−20.5	−16.6	−15.4	−13.8
exptl[c]			−31	−24.4		−19.2

[a] Reference 89. [b] Reference 119. [c] Reference 118.

Upon the mutations, like along the MD runs, all cryptates remained of "inclusive" type, *i.e.* the cation lies close to the center of mass of the cryptand. Only the small Li^+ and Na^+ cations move to asymmetrical positions (Figure 12). On the basis of NMR results, "exclusive" Cs^+ complexes, which would be more open, have been postulated in nonaqueous solvents.[110,117] In fact, the picture of such "exclusive complexes"[109,110,117] is purely speculative. Even in our simulated "inclusive" complex, Cs^+ is in fact not completely shielded from acetonitrile but in direct contact with 2.6 MeCN molecules. The complexed Cs^+ might be similarly in direct contact with its counterion (*e.g.* SCN^- or octanoate), which prevents coordination to solvent molecules. The Cs^+ chemical shift would be therefore solvent independent *at low temperatures*, as observed experimentally. As the temperature increases, dynamics exchange between the anion and solvent molecules should make the Cs^+ chemical shift solvent dependent. According to the criteria of Popov *et al.*,[109,110,117] it would be considered as "exclusive". It is thus likely that the distinction between "exclusive" and "inclusive" complexes is more a question of semantics than a real structural problem. The reasonable agreement between calculated and experimental Rb^+/Cs^+ binding selectivities also suggests that the Cs^+ cryptate is "inclusive".

Concerning the relative free energies of solvation ΔG_3, the largest discrepancy is found for the Li^+/Na^+ pair with the Amber Li^+ parameters, which exaggerate the Li^+ solvation by 6.1 kcal/mol, whereas the Aqvist Li^+ gives a much better agreement ($\Delta\Delta G_3 = 1.4$ kcal/mol). Calculations on the $M^+{\cdot}MeCN$ complexes in the gas phase give similar values for Na^+–Cs^+ with the two sets of cation parameters (Table 7). Compared to the gas-phase interaction enthalpies of Kebarle *et al.*[118] for $M^+{\cdot}MeCN$, these values are underestimated from about 6 kcal/mol (for Cs^+) to 11 kcal/mol (for Na^+). A 6-31G* *ab initio* calculation on the $Na^+{\cdot}MeCN$ complex gives an interaction energy of 33.7 kcal/mol,[126] close to the Kebarle's energy (31 kcal/mol). For Li^+, no experimental values are available, but polarization should be still larger. The polarization energy estimated by Kebarle *et al.*[118] indeed accounts for most of the difference between experimental and molecular mechanics energies. Better quantitative agreement would probably require explicit representation of the polarization energy in the force field. The success of these relative free energy calculations, like those performed previously in other solvents using pair potentials, is likely related to a cancellation of errors of the polarization contributions in the free and complexed states.[119] In water, effective SPC or TIP3P potentials derived for the bulk liquid, used in conjunction with Aqvist 1-6-12 potentials for the cations led to correct absolute free energies of hydration. In acetonitrile, solvent potentials derived similarly for the bulk liquid, in conjunction with the same Aqvist or Amber cation parameters, give correct trends and *relative* free energies but should underestimate the absolute free energies of solvation.

Conclusion

We have reported the first theoretical investigation of typical ionophores 18C6, cryptand 222, and their M^{n+} complexes in a nonaqueous solvent (acetonitrile) using MD simulations. Under the same time scales (50 ps), we find that the solvation patterns in acetonitrile are markedly different from those in water. For free 18C6, a long MD simulation (2 ns) sampled 984 different conformations. Like in water, the D_{3d} form has the highest population. However, the C_i form, which is intrinsically the most stable among solid-state conformations, was poorly hydrated and absent in water.[15,16,34] In CCl_4, it was calculated to be the dominant form.[34] In acetonitrile, it is the second dominant after D_{3d}. Many other unsymmetrical forms are present and contribute to the average dipole moment of the crown.

For cryptand 222, the relative stabilities and solvation energies of selected forms suggest a conformational equilibrium similar to that described in the gas phase, involving therefore decreasing proportions of "endo–endo" > "endo–exo" > "exo–exo" conformers at the bridgehead nitrogens.[29,32] In aqueous solution, we predicted the K form (extracted from the K^+ complex) to be particularly well solvated because of firmly hydrogen bonded bridging water molecules (Figure 10). In acetonitrile solution, the interactions with the solute are somewhat weaker than those in water, and no marked conformational preference is expected for 222, leading to dynamical conformational processes[120–122] involving a high population of the K form.

For the free ions Li^+–Cs^+, Ca^{2+}, and Eu^{3+}, we report the coordination numbers in acetonitrile. When complexed by the "open" macrocycle 18C6 or by the more compact bicyclic cryptand 222, they are always more or less in direct contact with solvent molecules, consistent with experimental data. When complexed, these topologically organized ionophores are calculated to have structures in acetonitrile similar to those in water. This differs strikingly from the MD results obtained with non-preorganized pseudocavities. For instance, in calix[4]arenetetramide complexes, the amidic binding sites of the ligand wrap around the complexed cation much more in acetonitrile than in water, due to the competitive solvation of the binding sites.[127]

Computer experiments on ion pairs involving Cl^- and K^+ complexed either by 18C6 or by 222 show different behavior, namely the stability of intimate ion pairs in the first case and dissociation in the second one. This is also consistent with several experimental studies.[123,124] Comparison of complexes of **18C6** with Na^+, Ca^{2+}, and Eu^{3+} both with and without counterion demonstrates the dramatic role of anion coordination to the encapsulated cation on the complex stability in acetonitrile, and more generally in nonaqueous solvents.[128]

Finally, we have reported the first free energy perturbation calculations of alkali cation complexes in acetonitrile. Using standard potentials for the ions and for the solvent, we obtained

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the known peak of selectivity of 222 for K^+. Indeed, the latter have been developed from water/MeCN interaction energies and tested on the pure liquid.[61] We calculated recently the relative binding affinities of these ions for calix[4]arenetetramide in acetonitrile and found also the correct trend in binding selectivity (peak for Li^+).[127] These simulations provide microscopic pictures of solute/solvent interactions and of conformations in solution which contribute to a deeper understanding of solvent effects on molecular recognition.

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Supplementary Material Available: Tables 8 and 9, listing conformations of 18C6, and Figures 17 and 18, showing the next 18 conformers of 18C6 and a snapshot of the 18C6/Li^+ complex (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.