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Monte Carlo Simulation of a 1,4,7,10-Tetraazacyclododecane/Lithium Complex in Aqueous Solution

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Monte Carlo simulations have been carried out for the system consisting of a 1,4,7,10-tetraazacyclododecane (cyclen)–lithium complex in 201 water molecules. The volume of the periodic cube was calculated using the experimental density of pure water at 298 K and 1 atm of 1 g·cm^{-3}, plus additional space occupied by the complex. The geometry of the complex is the alternated form, where the ion is located at the center of the cyclen. The complex–water interaction was represented by the cyclen–water and lithium–water pair potentials, both of which were developed on the basis of ab initio calculations. The results show two layers of solvation shells consisting of 2 and 6.9 water molecules. Two water molecules in the first solvation shell (O_1 and O_2) bind directly to the ion in which the ion–oxygen distance is 2.38 Å, the dipole vector points to the ion, and rotation takes place around the ion–oxygen axis. In the next layer, 4 water molecules coordinate simultaneously to the first 2 water molecules in the first shell and the NH functional groups of cyclen. The remaining 2.9 water molecules in the second layer are also coordinated to be in the first half-hydration shell of O_1 and O_2.

1. Introduction

Intense interest in the reaction between metal ions and tetraazacycloalkanes[1] is partly attributed to the fact that the complexes formed can be regarded as simple models for naturally occurring structure found in proteins[2−4] as well as their usefulness in new processes of organic synthesis. The greater thermodynamic stability of macrocyclic complexes in aqueous solution compared with those of analogous acyclic tetraamines, known as the macrocyclic effect, has been extensively studied and variously attributed to either an entropic or enthalpic effect or a combination of both.[5−11] The solvation effect[7,11] was suggested since 1969 to be one of the factors contributing to such extra stability. Here, the 1,4,8,11-tetraazacyclotetradecane ligand, as well as the ligands of similar sizes, and its open-chain analogues are expected to be solvated by 2 and 4 water molecules, respectively. In addition, complexes of both types of ligands are expected to be solvated by 4 water molecules.[7,11] Consequencely, more energy would be needed to break hydrogen bonds between water molecules and the open-chain ligand than in the cyclic one during complexation. To understand such phenomena, solvation and desolvation of the ligands and their complexes in various solvents are primarily required. However, very few data on the solvation of these types of ligands and complexes have been reported in the literature because of their kinetic inertness, regarding both the complex formation and decomposition, and low solubility in aqueous solution.[11−13] These, as well as the presence of a large number of very similar atoms and atomic distances in solutions, make diffraction studies and other spectroscopic techniques for evaluation of the solvation structure of the solutions impossible.[14]

The solvation of 1,4,7,10-tetraazacyclododecane in aqueous[15,16] and aqueous ammonia solutions[17] has been previously studied by means of the Monte Carlo method. Here, clear

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pictures of cyclen's solvation have been monitored in terms of the precise location and orientation of solvent molecules.

To ascertain, on the basis of existing and available tools, data on the solvation of the complex of a macrocyclic ligand, Monte Carlo simulation of the cyclen−lithium ion complex has been undertaken. The reason for choosing this complex is the match between the size of the cyclen cavity and the lithium ion;[9,10,18] i.e., the cyclen molecule is in the configuration suitable for complexation and need not adjust its conformation much during such a process. In addition, the size of the system under consideration is within the limit of possible theoretical investigation.

2. Details of the Calculations

2.1 Monte Carlo Simulations. With the volume of 201 water molecules, calculated using the experimental density at 298 K and 1 atm of 1 g·cm^{-3} and the volume of the 1,4,7,10-tetraazacyclododecane (cyclen)−lithium complex, calculated from the hydration sphere of the cyclen molecule in aqueous solution,[15,16] the volume of the periodic cube of side length 18.28 Å was yielded. Simulation has been performed using the Metropolis Monte Carlo scheme[17] for the above system where the cyclen−lithium complex was fixed at the center of the cube. The conformation of the complex is the alternated form, in which the N−C−C−N torsion angle is 60° and the lithium ion lies at the center of the cyclen cavity. This geometry was obtained from the ab initio optimizations using DZP (double ζ (zeta) plus polarization function) basis sets, which confirm those found for the complexes of cyclen with alkali and alkaline earth ions using different basis sets.[9,10,18] This geometry was used and kept constant throughout the calculations. In addition, this conformation is rationalized in terms of an analogy with the square antiprismatic geometry found in many complexes of cyclen, cyclen−M where M denotes Bi(II)[19] and Zn(II),[20] and of its derivatives with Co(II),[21] Bi(II),[22] and La(III).[23] This indicates that geometry of the cyclen−M complexes is not sensitive to the ions used. A spherical cutoff of the pair potentials was applied at half of the box length. The starting configuration was generated randomly. With these conditions, the reject/accept ratio for the simulated system of 50:50 was yielded. All properties reported here were evaluated from 10 million configurations of the system after equilibration.

2.2 Intermolecular Pair Potentials. The water−water interaction was described by the MCY model.[24] The pair approximation is used to model the complex−water interaction; i.e., the complex−water potential was represented by the two pair potentials, cyclen−water[16,17] and lithium−water[25]

$$\Delta E_{\text{complex-water}} = \Delta E_{\text{cyclen-water}} + \Delta E_{\text{lithium-water}} \qquad (1)$$

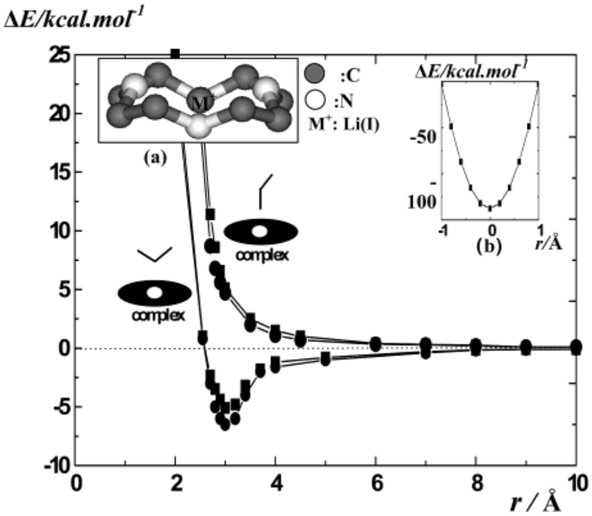

Figure 1. As a function of the lithium−oxygen distance (*r*), sum of the lithium−water and cyclen−water interaction energies (right side of eq 1) in the configuration given in the inset which are used in this simulation (●) compared to complex−water interaction energies calculated from ab initio method using the DZP basis set (■). Three-dimensional structure of cyclen is shown in inset a. Cyclen−Li(I) interaction energies as a function Cg−Li(I) distances, where Cg denotes center of the cyclen and Li(I) moves along the line perpendicular to the ligand's plane, are given in inset b.

To examine this approximation, the complex−water interactions (with the lithium ion at the center of the cyclen) in certain configurations have been calculated. For each configuration, three pairs of interactions, cyclen−water, lithium−water, and complex−water, have been evaluated using an ab initio method. The sum of the interactions obtained from the first two pairs (right side of eq 1) was compared to the third one (left side of eq 1) and plotted in Figure 1.

3. Results and Discussion

3.1 Complex−Water Pair Potential. Good agreement of the interaction energies obtained from the two sources as shown in Figure 1 indicates reliability of the pair approximation which describes the complex−water interaction by the sum of the cyclen−water and lithium−water pair potentials. Note that the detailed development of the lithium−water potential and its applications was given in ref 25. The cyclen−water function was developed from more than 1000 ab initio data points.[16] The basis set dependence as well as the error due to an unbalance in the basis set, basis set superposition error (BSSE), were also examined. The results show that the BSSE lies within fluctuation due to thermal effects at room temperature. In addition, the calculated dipole moment of 1.73 D is comparable to the experimental velue of 1.85 D.[26] The analytical functional form of the complex−water potential is

$$\Delta E(L,W) = \sum_{i=1}^{3}\sum_{j=1}^{32} \frac{A_{ij}^{ab}}{r_{ij}^{\;6}} + \frac{B_{ij}^{ab}}{r_{ij}^{\;12}} + \frac{C_{ij}^{ab}}{r_{ij}^{\;4}} + q_i q_j\left[\frac{1}{r_{ij}} + \frac{1}{r_{ij}^{\;2}}\right] \qquad (2)$$

where 3 and 32 are the numbers of atoms in water and cyclen molecules, respectively, A_{ij}, B_{ij}, and C_{ij} are fitting constants, r_{ij} is the distance between an atom i of a water molecule

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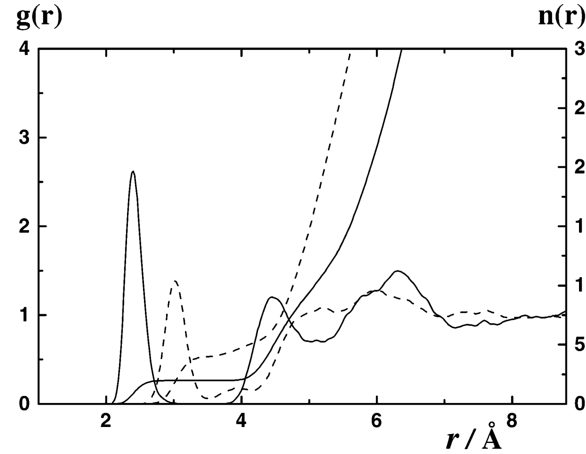

Figure 2. Radial distribution functions and corresponding running integration numbers from O (—) and H (- - -) of water molecules to the lithium ion which lies at the center of mass of cyclen.

and an atom *j* of cyclen, and q_i and q_j are the net atomic charges of atoms *i* and *j*, respectively, in atomic units as obtained from the population analysis[27] of the isolated molecules. Superscripts a and b on the fitting parameters have been used to classify atoms of cyclen of equal atomic number but different environment condition. The second Coulombic term[15,16,28−31] leads to a distance-dependent product of q_i and q_j. The development of the cyclen−water pair potential and the fitting parameters was given in detail in ref 15. In addition, this function was successfully used to evaluate the solvation structure of the cyclen molecule in aqueous[15] and in aqueous ammonia solutions.[16]

It is suggested from these data, as far as the molecular dipole moment, the stabilization energies, the corresponding distances, and the BSSE are concerned, that the simulated model should be a reliable basis for the system under consideration and should not influence the simulated results.

3.2 The Entire Solvation Shell of the Complex. The entire solvation shell of the cyclen−lithium complex was monitored in terms of lithium−water radial distribution functions, RDFs (Figure 2). The Li(I)−O RDF displays a first, sharp maximum at 2.38 Å and second and third broad peaks centered at 4.44 and 6.28 Å, respectively. The average numbers of water molecules lying under those three peaks, calculated from the integration of the Li(I)−O RDF up to the minima beyond the maxima, are 2, 6.9, and 37.6, respectively. The corresponding Li(I)−H RDF shows its first maximum at 3.06 Å, accumulating the 4 hydrogen atoms of the 2 water molecules located under the first peak of the Li(I)−O RDF. Due to the disklike structure of the cyclen−lithium complex as well as our experience in evaluation of the solvation structure of the cyclen molecule in water[16] and aqueous ammonia[17] solution, the 2 and 37.6 water molecules in the first and third maxima of the Li(I)−O RDF can be tentatively assigned as the nearest neighbors lying above or below the ligand plane around the lithium ion and as the outer solvation shell lying around the hydrophilic CH_3 functional groups of cyclen, respectively. The appearance of the first peak of the Li(I)−H RDF at a longer distance than the Li(I)−O peak indicates an orientation of the two nearest neighbors to point their dipole vectors toward the lithium ion. Then, the 6.9 water molecules under the second peak can be considered as sandwichlike solvation in which half of them are located above and the other half below the ligand plane.

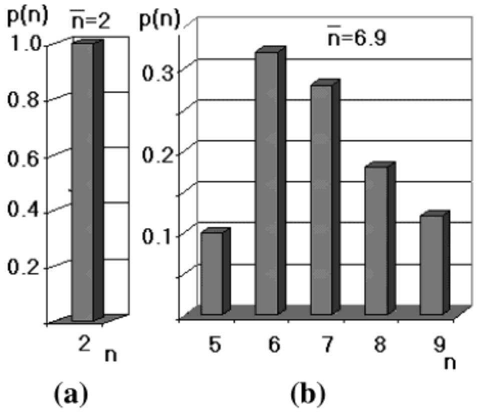

Figure 3. Distribution of integer coordination numbers (*n*'s) around the Li(I) for the water molecules situated under (a) the first and (b) the second peaks of the Li(I)−O RDF, leading to the average coordination numbers of 2 and 6.9, respectively.

The average coordination numbers of 2 and 6.9 can be analyzed in terms of distribution of integer coordination numbers. The results are plotted in Figure 3, showing that only the integer value of 2 contributes to the average coordination number within the first minimum of the Li(I)−O RDF (Figure 3a). This, as expected, indicates that 2 water molecules are tightly bound to the lithium ion. For the second peak of the Li(I)−O RDF, the distribution lies between 5 and 9 with a maximum of 6 water molecules (Figure 3b). A large fluctuation range means that solvent exchange from and to this solvation shell can easily take place. A snapshot (1 out of 10 million configurations) of the entire solvation of the cyclen−lithium complex, accumulated within the second minimum of 4.94 Å of the Li(I)−O RDF, contains 8 water molecules. The result was plotted in Figure 4. A detailed investigation of the precise location and orientation of water molecules in the first two peaks of the Li(I)−O RDF is presented in the following sections.

Note that no significant difference is observed between the water−water RDFs obtained from this study and those of pure water.[30]

Some comments could be made concerning rigidity of the cyclen−Li(I) complex; this may affect solvation structure and its characters around the ligand. To clarify this assumption, the complexation energies have been calculated and inserted in Figure 1. The most stable cyclen−Li(I) stabilization energy of -137 kcal·mol^{-1} is many order of magnitudes lower than those of -6.8 kcal·mol^{-1} and -5.7 kcal·mol^{-1} representing complex−water and water−water interactions, respectively. A sharp, deep, and steep energy profile (inset

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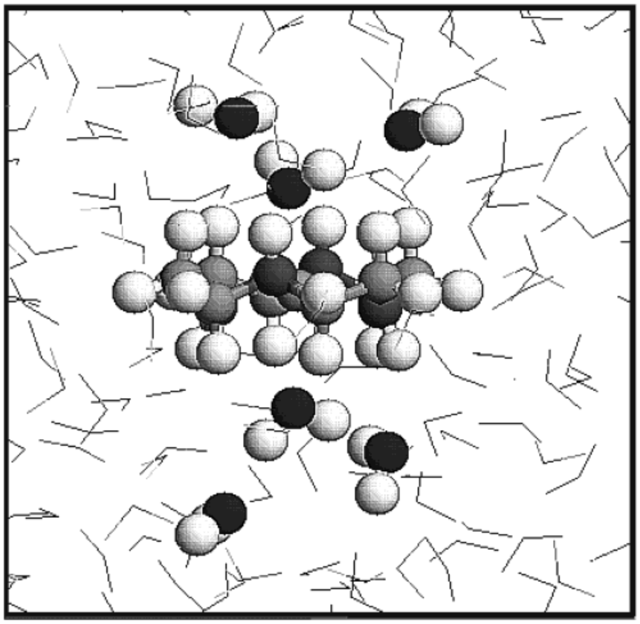

Figure 4. Snapshot (1 out of 10 million configurations) of the solvation shell of cyclen−lithium complex, labeling water molecules within the second minimum of the Li(I)−O RDF (Figure 2) of 4.94 Å.

b of Figure 1) means that very high energy is required in changing, even very slightly, the ion position (from the center of cyclen) and hence the average structure of the complex. This leads directly to the conclusion that the hydration structure of the complex could not be disturbed by thermal fluctuation, which is approximately 0.6 kcal·mol^{-1} at room temperature (estimate from kT where k denotes Boltzmann's factor).

3.3 The Nearest Solvation Shell of the Complex. To monitor the orientation of the two water molecules in the nearest solvation shell of the complex, the distribution of the cosine of an angle θ, which is defined as the angle between the dipole vector of water molecules lying under the first Li(I)−O RDF and the vector pointing from the oxygen atom of water to the lithium ion, has been calculated and displayed in Figure 5. The plot shows a sharp peak at $\theta = 0°$. This demonstrates clearly that the two water molecules bind to the complex by pointing their dipole moment vectors toward the lithium ion. The tight binding of these water molecules to the cyclen−lithium complex is indicated by the narrow distribution of the plot.

To ascertain more information concerning the two water molecules, their hydrogen coordinates have been projected onto the cyclen's molecular plane and plotted in Figure 6. The cyclen−lithium complex was represented by the disklike structure where the two opposite NH functional groups of cyclen located at the xy-coordinates {+,+} and {−,−} are above and the other two groups are below the ligand's molecular plane. The density represents the probability of finding hydrogen atoms of the two water molecules on the xy-plane, or molecular plane. The density plot shows two maxima. This indicates clearly that the favorite orientation of the two water molecules, which point their dipole moments to the ion in the nearest shell around the complex, is to turn their molecular plane (defined by all three atoms of water) perpendicular to the plane defined by the two vectors along the opposite NH groups of cyclen in order to avoid repulsion with the NH groups. Interest is focused on the appearance of nonzero densities in all quadrants, which indicates that rotation of the water molecules around the Li(I)−O axis has been detected. This phenomena did not take place for the free ligand, cyclen, in aqueous solution;[16] i.e., the two water molecules which lie in the nearest solvation shell, one above and the other one below the ligand plane, and point one O−H bond to the cyclen's cavity were not able to rotate through the energy barrier due to repulsion with the NH functional groups.

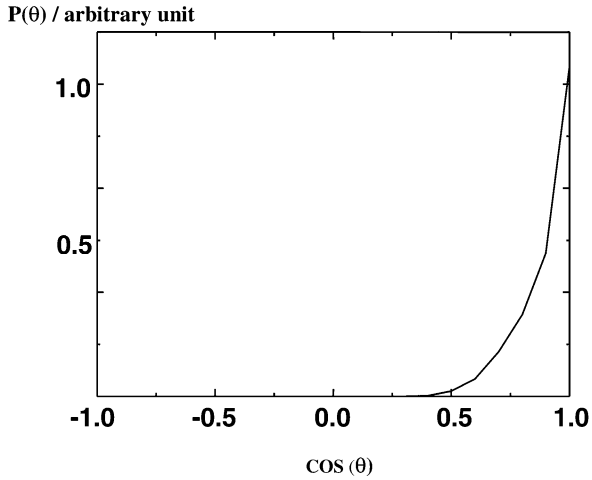

Figure 5. Distribution of cos(θ) for the two water molecules in the nearest solvation shell of the cyclen−lithium complex where θ is defined as the angle between the dipole vector of a water molecule lying under the first Li(I)−O RDF (Figure 2) and the vector pointing from the oxygen atom of water to the lithium ion.

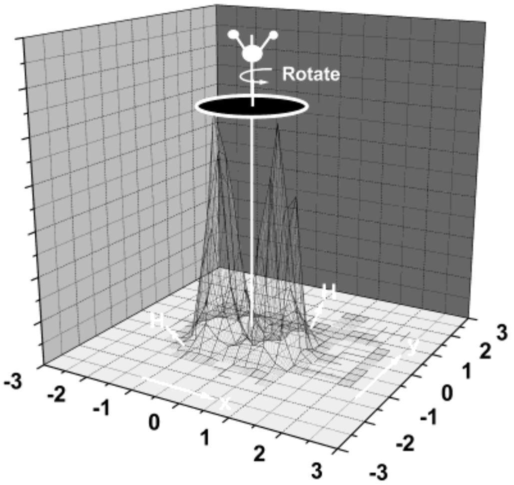

Figure 6. Projection of the hydrogen coordinates of one of the water molecules in the nearest solvation shell of the cyclen−lithium complex above (or below) the ligand plane onto the xy-plane (see text for more details).

3.4 Characteristics of the Complex−Water Hydrogen Bond. Comprehensive evaluations are turned now to the 6.9 water molecules lying under the second peak of the Li(I)−O RDF in order to demonstrate the precise location and orientation of these molecules. RDFs with respect to

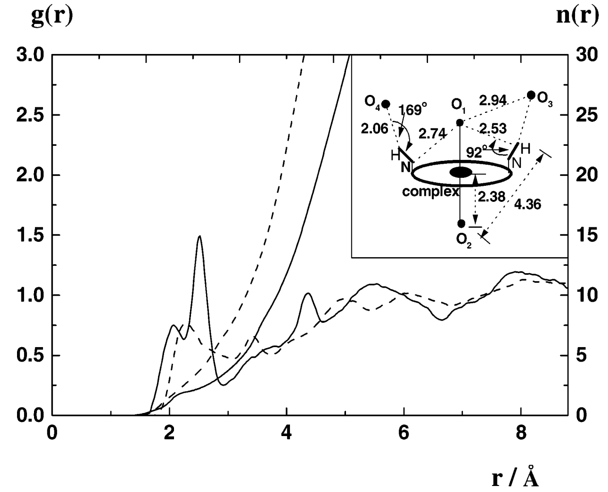

Figure 7. Radial distribution functions and corresponding running integration numbers from O (—) and H (- - -) of water molecules to hydrogen atoms of the NH functional groups of cyclen. Estimated distances (Å) and angles (deg) between the related atoms are given in the inset.

hydrogen atoms of the NH functional groups of cyclen have been calculated and drawn in Figure 7. Estimated distances and angles between the related atoms where O_1 and O_2 are fixed at 2.38 Å (distance to the first maximum of the Li(I)−O RDF, Figure 2), from the ion and on an axis perpendicular to the ligand plane, are given in the inset.

The H_N−O RDF displays a first split peak centered at 2.06 and 2.52 Å, a second front-tailed-peak at 4.34 Å, and a third broad peak at 5.56 Å. Integration up to the first and the second minima at 2.94 and 4.58 Å leads to the average coordination numbers of 1.9 and 8.4 water molecules, respectively. Referring to the inset of Figure 7, it can be concluded clearly that the peaks at 2.52 and 4.34 Å are the contribution from the oxygen atoms, O_1 and O_2, of the two nearest molecules above and below the ligand plane, respectively.

For the peak at 2.06 Å which accumulates 1 water molecule, this water can be tentatively assigned to coordinate to the NH functional group of cyclen via a hydrogen bond. Further confirmation of this conclusion is exhibited by the distribution plot shown in Figure 8, where the angle α is defined by the H−N bond and the vector pointing from the nitrogen atom of the cyclen toward the oxygen atom of water lying within the first minimum of the H_N−O RDF at 2.94 Å. The plot shows two maxima at $\alpha = 92°$ and 169°. It is clear from this plot that the central water molecule O_1 which is located at 2.52 Å of the H_N−O RDF leads to $\alpha = 92°$. The other water is approximately placed to form a hydrogen bond with the NH group where the distance from H_N to O is 2.06 Å and the N−H_N-O angle is 169°. Stronger binding of the central water to the lithium ion than the other one to the NH group yields a narrower second peak at $\alpha = 92°$ than the first one at $\alpha = 169°$ as well as a higher H_N−O RDF at 2.52 Å than that at 2.06 Å. For easier monitoring, the 4 water molecules which form hydrogen bonds with the 4 NH groups are named O_3−O_6. According to the geometrical parameters and related distances given in the inset of Figure 7, O_3 and O_4 (or O_5 and O_6) are also considered to be in the first coordination shell of O_1 (or O_2) as the $O_1 \cdots O_3$ and $O_1 \cdots O_4$ (or $O_2 \cdots O_5$ and $O_2 \cdots O_6$) distances of 2.94 Å are within the hydrogen bond distance.[32] Deviation from the linear N−H⋯O hydrogen bond ($\alpha = 169°$) is also a consequence from the simultaneous binding.

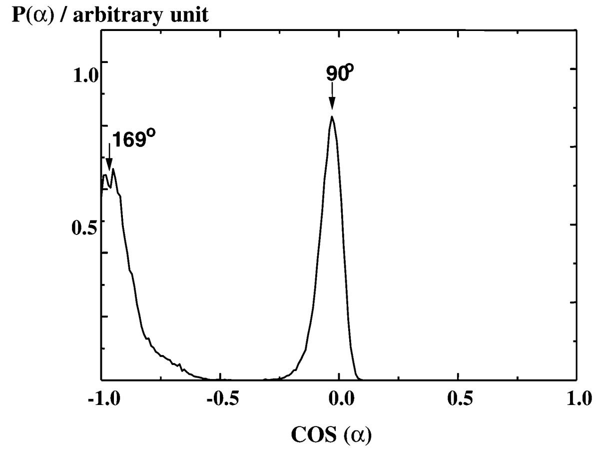

Figure 8. Distribution of the cosine of α, the angle between the N−H bond and the vector pointing from the nitrogen atom of cyclen toward the oxygen atom of water which lies within the first minimum of 2.94 Å of the H_N−O RDF (Figure 7).

The solvation numbers already mentioned, which consist of 2 nearest neighbors bound to the lithium ion and the other 4 molecules coordinated to the NH groups via hydrogen bonds, are not yet consistent with the numbers of 2 and 6.9 under the first and the second peaks of the Li(I)−O RDF (Figure 2), respectively. To search for the remaining 2.9 water molecules under the second peak (subtracting 6.9 water molecules under the second peak of the Li(I)−O RDF by the 4 water molecules, O_3−O_6, which are coordinated to the four NH function groups), the coordinates of oxygen atoms which lie above the ligand plane and within $2.95 \leq R_{\mathrm{LI(I)-O}} \leq 4.94$ Å (distances to the first two minima of the Li(I)−O RDF) have been projected into the ligand plane. The result is shown in Figure 9. The two NH groups above (or below) the ligand plane are represented by arrows. Among the three maxima, two sharp peaks which lie close to the NH groups are the projections of O_3 and O_4 (or O_5 and O_6). The other broad peak is one of the three water molecules which are considered to be in the first half-hydration shell of O_1 (or O_2). Simultaneous binding of O_3 or O_4 to O_1 (or O_5 or O_6 to O_2) and NH groups, both via hydrogen bonds, leads to less flexibility of these water molecules and hence is more pronounced for the two maxima than the other one. In addition, nonzero densities around the three maxima are the contribution of the remaining 0.9 water molecule (subtracting 2.9 water molecules under the second peak of the Li(I)−O RDF by the 2 water molecules which are the third nearest neighbor of O_1 and O_2) which is not in the first hydration shell of O_1 and O_2. However, the running coordination number of 0.9 is the integration of the Li(I)−O RDF within $4.80 \leq R_{\mathrm{LI(I)-O}} \leq 4.94$ Å. Due to a flat minimum of the RDF in this region (Figure 2) which indicates solvent

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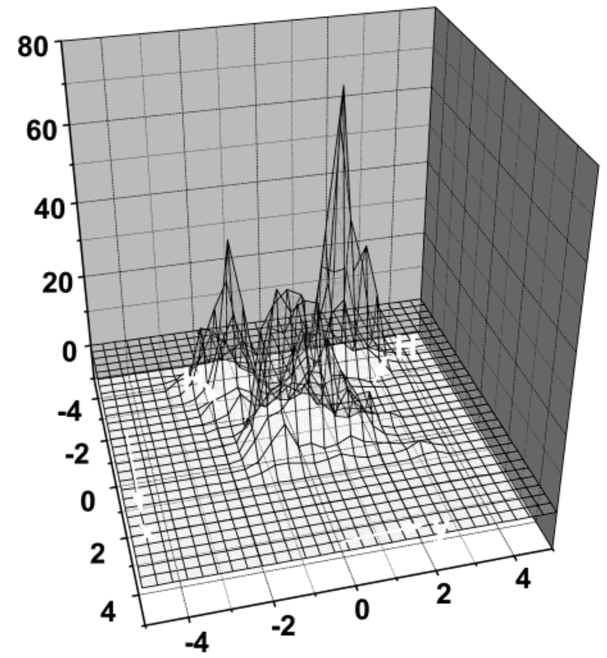

Figure 9. Projection of the oxygen coordinates of water molecules lying above the ligand plane and within $2.95 \leq R_{\mathrm{LI(I)-O}} \leq 4.94$ Å (distances to the first two minima of the Li(I)−O RDF) onto the ligand plane.

exchanges between the two shells before and after the minimum, 0.9 water can be excluded from the second peak of the Li(I)−O RDF.

Taking into account all the data given and discussed here, the cyclen−lithium complex is solvated by 6 water molecules (0.9 is excluded due to the flat minimum of the Li(I)−O RDF around 4.94 Å). Two water molecules bind directly to the lithium ion while the other 4 molecules coordinate to the 4 NH functional groups of cyclen via hydrogen bonds. These data are inconsistent with the number of 4 suggested by Cabbiness and Margerum.[7,11] In addition, the average coordination number of 2 water molecules obtained from the previous simulation of the cyclen in aqueous solution[16] agrees well with that expected by Carbbiness and Margerum.[7,11] Therefore, our suggestion on the existence of the macrocyclic effect still confirms that proposed in the previous work which states that the enthalpic contribution (solvation effect) due to the energy required for breaking some hydrogen bonds could not be the main factor influencing the macrocyclic effect.

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