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A Monte Carlo Study on the Hydration of a Macrocyclic Magnesium Complex

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Abstract

The magnesium complex of 1,4,7,10-tetraazacyclododecane (cyclen) has been studied in water at 25 °C and 1 atm by means of a Monte Carlo simulation including 200 H_2O molecules. The potential function for the water magnesium/cyclen complex was derived under the assumption of additivity of the potentials obtained from *ab initio* calculations for H_2O/Mg^{2+}–, H_2O/cyclen– and water–water interactions. The results of the calculations have been analysed in terms of energy, radial distribution functions and distribution of coordination numbers of water molecules around the various sites of the magnesium/cyclen complex. Two water molecules pointing with the oxygen atom towards the magnesium ion in the center are located above and below the plane of the complex at 2.2 Å in the *z* axis, a further 8 water molecules directed towards Mg^{2+} are located in a sphere of 3.3–4.5 Å radius, and 8 water molecules are located near to the main plane of the ligand and coordinated to the N atoms (N...O = 2.6 Å, O...center = 5.4 Å).

Introduction

One of the key problems concerning the peculiar stability of metal complexes with macrocyclic ligands compared to their open-chain analogues has been the question whether it is mainly enthalpic reasons or solvation related entropic reasons which cause this specific 'macrocyclic effect' [1–4]. The contribution of strain energy necessary to alter the conformation of the open-chain ligand to the form suitable for complexation has been recently dealt with successfully by means of *ab initio* MO calculations [5]. As a main contribution to entropic effects it was postulated that the metal ion would lose most of its solvation shell upon binding by the macrocyclic ligand, hence releasing numerous solvent molecules into the bulk [4]. This hypothesis has since been discussed in the literature on macrocyclic complex compounds without final conclusion, due to the lack of experimental possibilities for verification.

It is still almost impossible to investigate structural details of solvated macrocyclic compounds such as 1,4,7,10-tetraazacyclododecane (cyclen) and its complexes in aqueous solution experimentally by methods such as X-ray or neutron diffraction. Theoretical calculations based on *ab initio* potentials and MC or MD simulations have been successfully used, however, in order to evaluate such data for electrolyte solutions [6, 7], and also recently the solvation structure of the cyclen ligand [9–12]. In this work, a Monte Carlo simulation has been performed for the Mg^{2+} complex of cyclen in water.

The potential function used for the water/magnesium/cyclen complex in this Monte Carlo simulation was assumed to be of additive character, *i.e.* a sum of the water–cyclen potential function, the water–magnesium ion potential function and that of the water–water interaction [13–16]. The location of the Mg^{2+} ion inside the ligand was kept constant at its energy optimized position [5], due to the strong stability of the complex compared to the binding energy of the water molecules. The geometry of the ligand was also assumed, therefore, to remain in its metal-adapted, energy optimized form [5].

The final form of the used analytical potentials is:

$$\begin{aligned}\Delta E(\mathrm{W,W}) = {} & q^2\left(\frac{1}{r_{13}}+\frac{1}{r_{14}}+\frac{1}{r_{23}}+\frac{1}{r_{24}}\right)+\frac{4q^2}{r_{78}} \\ & -2q^2\left(\frac{1}{r_{18}}+\frac{1}{r_{28}}+\frac{1}{r_{37}}+\frac{1}{r_{47}}\right) \\ & + a_1\exp(-b_1r_{56})+a_2[\exp(-b_2r_{13}) \\ & +\exp(-b_2r_{14})+\exp(-b_2r_{23}) \\ & +\exp(-b_2r_{24})]+a_3[\exp(-b_3r_{16}) \\ & +\exp(-b_3r_{26})+\exp(-b_3r_{35}) \\ & +\exp(-b_3r_{45})]-a_4[\exp(-b_4r_{16}) \\ & +\exp(-b_4r_{26})+\exp(-b_4r_{35}) \\ & +\exp(-b_4r_{45})] \qquad (1)\end{aligned}$$

for the water–water interactions (MCY potential, [15]);

$$\Delta E(\mathrm{L},\mathrm{W}) = \sum_{i=1}^{3}\sum_{j=1}^{32}\left[-\frac{|A_{ij}|}{r_{ij}^{6}} + \frac{|B_{ij}|}{r_{ij}^{12}} + \frac{q_i q_j}{r_{ij}}\left(|C_{ij}| + \frac{|D_{ij}|}{r_{ij}}\right)\right] \tag{2}$$

for the cyclen–water interaction [8]; and

$$\Delta E(\mathrm{Mg}^{2+},\mathrm{W}) = \sum_{i=1}^{3}\left[\frac{A_{i1}}{r_{i1}} + \frac{B_{i1}}{r_{i1}^{2}} + C_{i1}\exp(-D_{i1}r_{i1})\right] \tag{3}$$

for the magnesium–water interaction [14]. This potential takes into account the polarization of water molecules by the divalent metal through the parameters fitted to *ab initio* calculations. Equations (2) and (3) have been combined assuming additivity of both potentials. It has been shown that this assumption is not completely justified, but that the resulting potential functions will lead to qualitatively correct structures in the simulation [13].

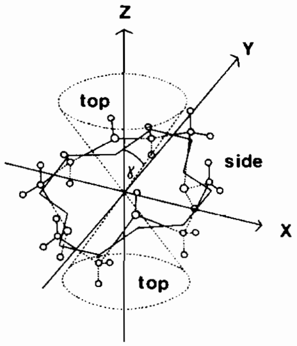

Fig. 1. Definition of the top, side and plane regions (γ = 45°).

Calculations

The Monte Carlo simulation modified according to Metropolis *et al.* [16] has been performed for a system consisting of 201 particles (1 magnesium/cyclen complex and 200 water molecules), at 25 °C, 1 atm and density of 1 g cm^{-3}, corresponding to a basic box sidelength of 18.34 Å. Half of this sidelength was chosen to be the radius of the spherical cut-off.

For the evaluation of results, the space around the magnesium/cyclen complex was divided into three regions: top (T), side (S) and plane (P), similar to ref. 12 and as illustrated in Fig. 1.

A total of 3.0 × 10^6 configurations for the rigid magnesium–cyclen complex in its *ab initio* optimized geometry [5] in water were generated, and the configurations obtained after reaching equilibrium at 1.5 × 10^6 steps have been used for evaluation of data (Fig. 2). Probability distribution plots have been used to illustrate the water distribution in three different planes (0.0 ± 0.2, 2.0 ± 0.2, and 3.0 ± 0.2 Å distant from the ion in the z axis).

Results and Discussion

After 1.5 × 10^6 configurations, the energy of the system has converged, although the fluctuations are still considerable in absolute terms (575 ± 25 kcal/mol). In relative terms, this fluctuation (± 4%) is not higher than that of the cyclen/water system (± 7%, 55 ± 4 kcal/mol). The average hydration energy of the complex is higher than the sum of the calculated [18] hydration energies for the metal ion and the cyclen ligand (494 kcal/mol), and also considerably higher than the experimental hydration energy of the ion (477 kcal/mol [19]).

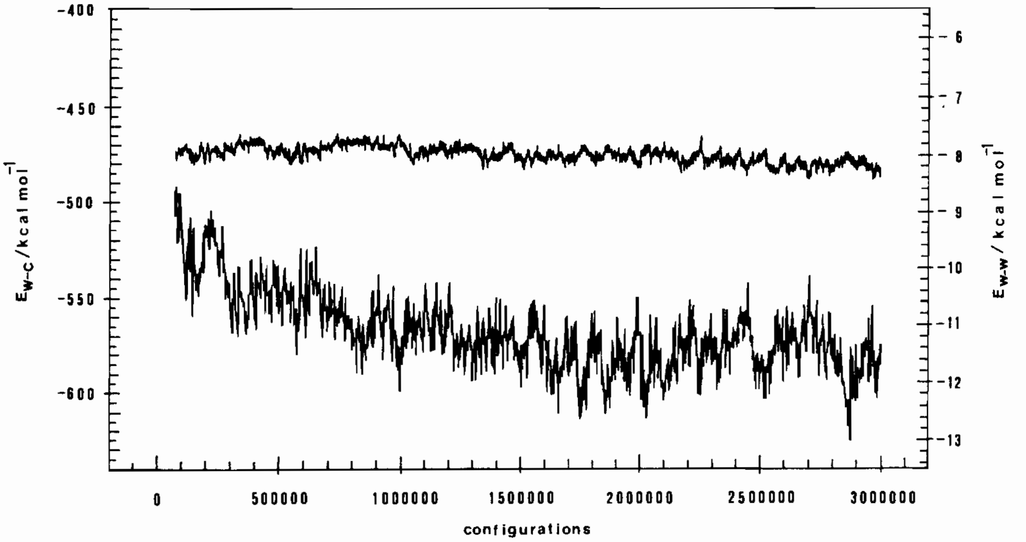

Fig. 2. Convergence and fluctuation characteristics for simulation of dilute aqueous solution of the magnesium cyclen complex.

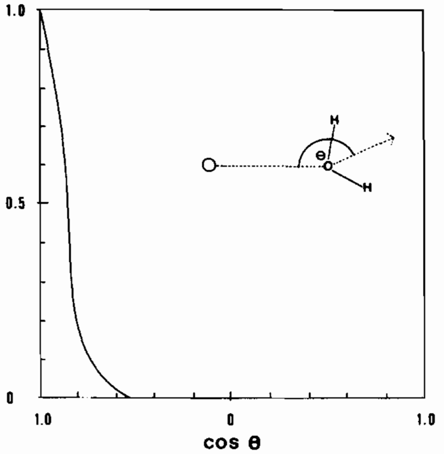

Fig. 3. Cosine distribution of the angle θ for the top region (r_m = 2.5 Å).

These energy data already indicate that hydration might enhance the stabilization of the macrocyclic complex due to enthalpic effects. In order to answer the question whether metal plus ligand or the complex bind more water molecules – related to possible entropic contributions – it will be necessary to evaluate the structure of the hydration shell(s).

The solute–solvent radial distribution functions and the corresponding average coordination numbers of various sites of the solute have been considered as well as the distribution of coordination numbers, K_n, and the angular orientation of water molecules (cos θ, Fig. 3) for obtaining information about the solvation structure. The radial distribution functions, given in Fig. 4 will be first discussed for the water molecules in the three defined regions (top = T, side = S and plane = P) and compared to that of the entire molecule (M). The first peak of the distribution function, $g_{TO}(r)$ (Fig. 4a), being equivalent to the first peak of $g_{MO}(r)$ (Fig. 4d) is located at 2.2 Å, with a corresponding integration number of two up to the minimum reached after this first peak, r_m = 2.5 Å. The first peak of the function $g_{TH}(r)$ (dashed line in Fig. 4a), at 2.8 Å gives the running integration number $K = 4$ corresponding to four hydrogen atoms. The peak distance between function $g_{TO}(r)$ and $g_{TH}(r)$ (Fig. 4a) being 0.6 Å indicates that these two water molecules point with their oxygen atoms towards the magnesium ion with the angular distribution illustrated in Fig. 3 ($\theta = 180$ dominates this distribution). Thus, we can conclude that there are two water molecules directly bound to Mg^{2+} at the distance of ~2.2 Å with C_{2v} symmetry, one above and one below the *xy* plane of the complex. The distribution of coordination numbers around the magnesium ion either evaluated from oxygen distribution (Fig. 6e), $K_O = 2$ (at r_m = 2.5 Å) or from hydrogen distribution (Fig. 6f), $K_H = 2$ (at r_m = 2.2 Å) confirm the well-defined binding of these two water molecules in the *z* axis of the complex.

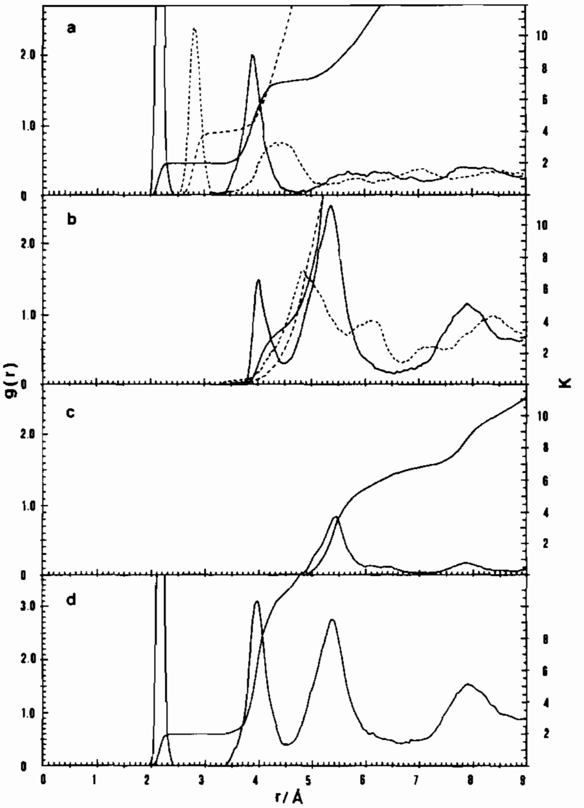

Fig. 4. Calculated atom-oxygen (——) and atom-hydrogen (– – –) radial distribution functions and running integration numbers for the top (a), side (b), plane (c) and entire system (d) regions of the magnesium cyclen complex as defined in Fig. 1.

The second peak of $g_{MO}(r)$ (Fig. 4d) corresponds to eight water molecules and is reflected by the second peak of $g_{SO}(r)$ and the second peak of $g_{TO}(r)$, corresponding to four water molecules each in the side and the top region, respectively. Therefore, another eight water molecules should be coordinated to the magnesium ion, four above and four below the *xy* plane of the complex (water type 2a and 2b in Fig. 5), at a distance of ~3.9 Å from Mg^{2+} and about 3.0 Å above/below the *xy* plane. The geometrical arrangement of these water molecules is still dominated by the ion, as they point with their oxygen atoms towards magnesium. The orientation is confirmed by the functions $g_{TH}(r)$ (maximum at 4.4 Å) and $g_{SH}(r)$ (maximum at 4.9 Å). The appearance of another broad peak $g_O(r)$ at 7.9 Å (Fig. 4) indicates, that there are still numerous water molecules located in a more or less ordered configuration around the complex, which can be interpreted as a second solvation sphere. The ordered water molecules in the plane of cyclen appearing in the probability distribution plot (Fig. 8a) within about 5.5–8.0 Å could be considered also a part of this second solvation sphere. The probability distribution plot of Fig. 8b confirms the existence of the two water molecules at 2.2 Å in the *z*

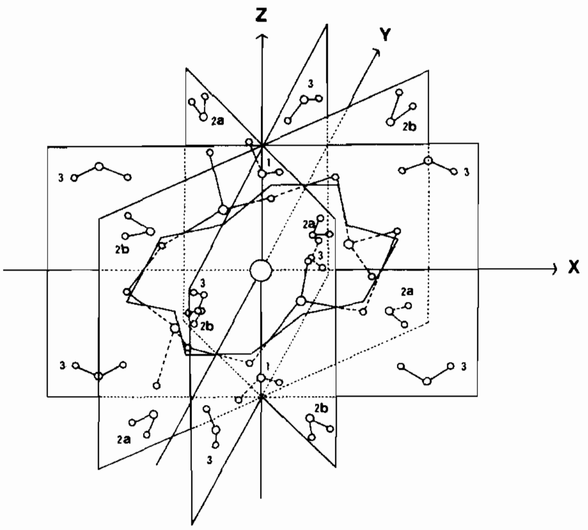

Fig. 5. Solvation model for water molecules in the first hydration shell of the magnesium cyclen complex.

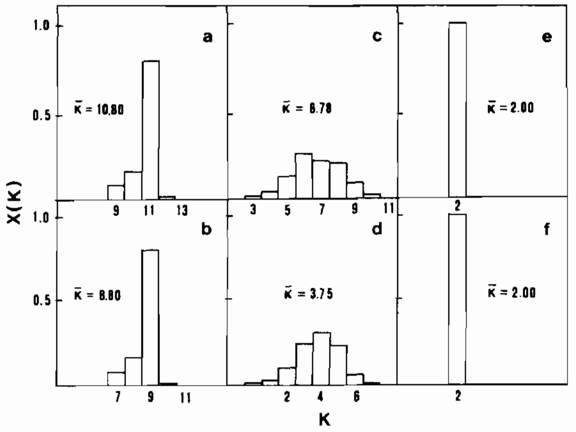

Fig. 6. Distribution of coordination numbers (K) around the magnesium ion (center of mass of magnesium cyclen complex) for the following regions: (a) entire (r_m = 4.5 Å), (b) entire (r_m = 3.3–4.5 Å), (c) plane (r_m = 7.0 Å), (d) side (r_m = 4.5 Å), (e) top (r_m = 2.5 Å) and (f) distribution of H atoms of water for the top region (r_m = 3.2 Å).

axis and also shows parts of the first and the second solvation sphere. The probability distribution plot of Fig. 8c shows besides the water molecules representing water of type 2a and 2b mapped near the N atoms of the molecules, another 4 accumulations representing water molecules located in the side region (mapped between C–C bonds of cyclen), corresponding to the second peak of $g_{SO}(r)$ (Fig. 4b) at 5.4 Å. These eight water molecules, four above and four below the xy plane of the complex are coordinated only to the N atoms of cyclen via their hydrogen atoms or via oxygen and the N_H hydrogen atoms. The peak of the function $g_{FO}(r)$ (Fig. 4c) at 5.4 Å gives a running integration number of eight, corresponding to the assumed existence of eight water molecules of this coordination type.

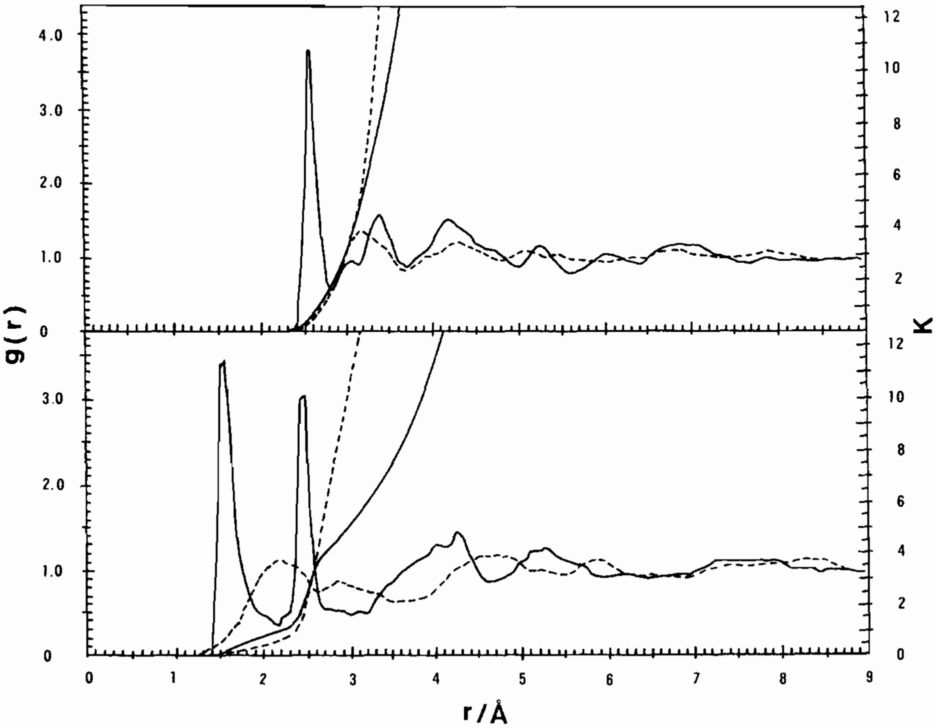

Fig. 7. Calculated atom-oxygen (——) and atom-hydrogen (– – –) radial distribution functions and running coordination numbers for the N (a) and H_N (b) atoms of cyclen.

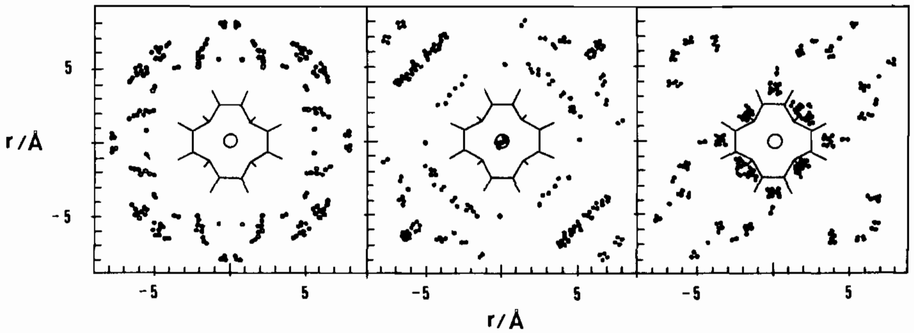

Fig. 8. Water distribution in and above the *xy* plane of the magnesium cyclen complex within ±0.2 Å of the selected value of the *z* axis (a) $z = 0.0$ Å, (b) $z = 2.0$ Å and (c) $z = 3.0$ Å.

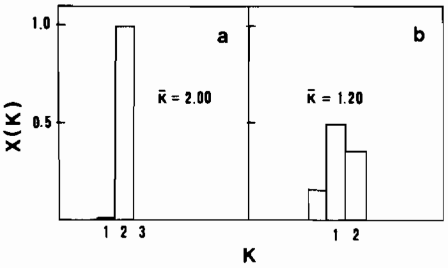

Fig. 9. Distribution of the coordination numbers around N ($r_m = 2.8$ Å) and H_N ($r_m = 2.2$ Å) atoms of cyclen.

TABLE I. Type of Water Molecules Solvating the Mg^{2+}/ Cyclen Complex in Its First Hydration Sphere

Type of water	Number	Distance from Mg^{2+} (Å)
1	2	2.2
2a	4	3.9
2b	4	3.9
3	8	5.4

The peak of the function $g_{NO}(r)$ at 2.6 Å has a running integration number of $K = 2$ (Fig. 7a). The average coordination number of water molecules for each of the 4 N atoms is therefore confirmed as 2 again. The two peaks of the function $g_{HNO}(r)$ (Fig. 7) at 1.6 and 2.4 Å have the running integration numbers of $K = 1$ and 2 respectively. The first peak ($K = 1$) corresponds to the water type 2a of Fig. 5 and the second peak ($K = 2$) to the water of type 3 in Fig. 5. The average coordination number of water molecules around the N atoms as shown in Fig. 9 is 2, confirming again the location of the water molecules of type 3 (Fig. 5) between the C–C bonds of cyclen.

We can conclude, therefore, that the first hydration sphere around the magnesium/cyclen complex consists of eighteen water molecules, which might be separated into three types as shown in Table 1 and Fig. 5. Water 1 represents the two strongly bound molecules at the ideal binding distance to Mg^{2+} (2.2 Å), in the *z* axis. Water type 2a and 2b are rather similar and their position is close to the 45° vector, so that they are counted sometimes in the top region (2a), sometimes in the side region (2b). Due to the distance of 3.9 Å from Mg^{2+}, the binding energy of these waters to Mg^{2+} should be considerably lower than for water of type 1.

The last type of solvation water is not coordinated to the ion, but to the N atoms via hydrogen bonds. The strength of these hydrogen bonds is surely increased due to the ion's indirect influence via the polarization of the ligand, induced mainly at the N atoms binding the Mg^{2+} ion. The data obtained from the simulation show, therefore, that the solvation structure of a macrocyclic complex extends far beyond the two water molecules expected in the *z* axis. Any discussion concerning the influence of solvation effects on the stability of such complexes will thus have to account for this fact.

A final question is the reliability of the analytical potential function used in this work for the prediction of the structure obtained by the simulation. A comparison of parts of the energy surface evaluated by both full *ab initio* MO calculation [17] and by assuming additivity of the *ab initio* evaluated Mg(II)/ water and cyclen/water potentials has shown, that the features of the potential surface for attractive and repulsive configurations are reflected correctly, including the position of the minima. The interaction energies at shorter distances are overestimated, however, by the addition of potentials, especially for very short distances (repulsive part). At larger distances, both types of potential curves almost converge [13]. It can be expected, therefore, that evaluated energies are not very reliable yet, whereas the structural data for the hydration sphere should be quite reliable. The most interesting problem, whether desolvation could be a main factor leading to entropic contributions, can be answered, therefore quite satisfactorily, whereas the enthalpic stabilization due to hydration (which is also easier accessible experimentally) will have to be evaluated rather on the basis of a fully *ab initio* evaluated potential surface of the complex/water system [17].

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