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THE ROLE OF SOLVATION FOR THE MACROCYCLIC EFFECT

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Abstract

The role of solvation in the complex formation of macrocyclic compounds is discussed on the basis of comparative Monte Carlo Simulation studies of the ligand 1, 4, 7, 10-tetraazacyclododecane (Cyclen) and its magnesium complex. Both compounds have characteristic and strongly different hydration structures, with that of the complex being by far the more ordered. According to the results, it has to be expected that it will be enthalpic rather than entropic effects of hydration, which influence the stability of macrocyclic complexes and that substitutions at the macrocyclic's nitrogen atoms may have a considerable influence on solvation contributions to the macrocyclic effect.

Introduction

The peculiar stability of metal complexes with macrocyclic ligands, usually referred to as macrocyclic effect, has been attributed to both enthalpic and entropic effects in the past[1-6] and the dispute regarding which effect is dominant is still going on. Entropic contributions should arise from solvation/desolvation effects and have been suggested to be dominant by some authors[5], whereas others believe, that they have been much overestimated[6].

One of the reasons that this dispute has not been resolved so far is that no experimental method can, for the time being, reveal the structure of the hydration shell of either the macrocyclic ligand or the corresponding complex. Due to the many atoms of the system and the numerous very similar atomic distances in it, X-ray or neutron diffraction patterns can not be resolved, especially at the comparatively small concentration of solutions of these compounds.

Data obtained by computational methods like Monte Carlo or Molecular Dynamic have given much more insight into the structure of complicated hydrated systems and thus allow one to deal with problems hardly accessible experimentally. Monte Carlo simulation has also been applied recently to the hydration of macrocyclic compounds[7] and complexes[8]. This approach could be utilized, therefore, to deal with

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the question of solvation influence on the macrocyclic complex stability, and the result of these investigations, presented in this paper, should be helpful to answer some of the open questions in the above-mentioned dispute.

Method

Monte Carlo simulations have been performed for the solvated ligand cyclen (1 cyclen + 200 water molecules) and the corresponding magnesium complex (1 Mg(II)/cyclen + 200 water molecules), at the density of 1g/cm^3. The ligand and complex have been taken in their ab-initio optimized geometries[9]. Half of the basic box sidelength has been taken as cut-off for the evaluation of interactions, obtained from the previously published water-water[10], water-magnesium[11], water-cyclen[12] and water-Mg(II)/cyclen[13] pair potentials. The Monte Carlo simulations were performed using the Metropolis method[14] and after having reached equilibrium after 1.5×10^6 configurations, one more million configurations have been used for data collection. Computation was performed on the CDC Cyber 835 Computer of the University of Innsbruck and the IBM 3031/08 Computer of Chulalongkorn University.

For the presentation of the results, we have chosen probability plots, showing the distribution of water molecules around the ligand and the complex in selected planes. Each of these slices locates at various distances in the z-axis (perpendicular to the plane of paper in Figures 1 and 2). The number of water molecules is the hydration spheres has been evaluated by integration of the radial distribution functions published previously[7, 8].

Results and Discussion

To evaluate the directional difference of water structure coordinated to the ligand and its complex, the spaces around them were divided into three regions, top, side and plane. Top corresponds to the conical volumes enclosed by rotating a 45° vector, starting from the molecular centre, around the + and − z-axis and side corresponds to the volumes below the vector. Inside this side region, a cylinder of height 1 Å in the z-axis was defined as the plane region.

As there exist different types of hydration water molecules within the solvation sphere of both the ligand and its magnesium complex, they have been evaluated separately and listed in Table 1. Water type 1 is located in the z-axis above and below the molecular plane (xy-plane) while types 2a, 2b and 3 are in the top, side and plane regions, respectively. Secondary solvation shells have not been evaluated, due to the large size of the central molecular systems compared to the dimension of the basic box. They can be expected to exist, however, from the structure displayed by the water distribution plots (Fig. 1-3), but can be assumed to have only a smaller influence on the stabilization of the system.

Considering the total coordination numbers of the primary solvation shells of

Table 1 CHARACTERISTIC DATA FOR THE HYDRATION SPHERES OF CYCLEN AND ITS MAGNESIUM COMPLEX.

	Number		Distance from the centre of mass Å	
	L	ML	L	ML
Centre coordinated	2	2	2.6	2.2
2a Above 45° vector	12	4	4.1	3.9
2b Below 45° vector	-	4	-	3.9
3 N-H/N-coordinated	-	8	-	5.4
TOTAL NUMBER	14	18	-	-

ligand and complex, one can immediately rule out the simple model that complexation of the metal should set free four of the six water molecules of the metal's first hydration shell into bulk, thus increasing the entropy of the system[5]. Although the structure of the coordination changes considerably, there are still 8 water molecules beside the two in the z-axis, that are coordinated directly to the metal ion. Including the newly bound hydration-water coordinated to the nitrogen atoms of the ligand, the total number of the water molecules in the primary hydration sphere of the complex is larger than that of the free ligand by six. Taking the number of the primary solvation sphere of the metal ion in water as 6, the number of water molecules coordinated to the complex is therefore identical to the sum of coordinated waters for ion and ligand together. This situation can be expected to change, however, with substituents introduced at the nitrogen atoms, as they could prevent hydration by waters of the type 3 (cf. Table 1). Without having performed simulations for such systems, this question cannot be answered conclusively yet, but for systems like the cyclen ligand discussed here, one can not expect specific entropic effect due to the desolvation of ion. The fact, that within the given series of macrocyclic ligands, the stability seems to depend strongly on the enthalpy of hydration of the complex[15], and the results obtained by our simulations seem to lead to the conclusion that it is mainly enthalpic contributions that make up the solvation influence on the macrocyclic effect. The energy level reached in the simulation of the hydrated complex[9] also shows, that the primary hydrated shell is bound quite strongly and thus stabilizes well the system.

More details of the difference between the solvated ligand and the solvated complex are revealed by the comparison of the distribution plots. Figure 1 illustrates hydration near the main plane of the macrocycle, and Figure 2 displays water structures at larger distances from the plane. Figure 3 demonstrates especially well the hydration structure above and below the complex, showing clearly, that solvation of such compounds has been quite underestimated in the past. It should be mentioned at this point, that the specific pair potential being used for the water-Mg(II)/cyclen interactions, based on the assumption of potential additivities, might lead to certain errors for the exact distances between central ion and water[13], due to somewhat overestimated interaction energies near the minimum of the potential curves. The general feature should not change, however, and for the comparison performed in this work, the use of identically derived potential functions may be even of some methodical advantage.

Comparing all the graphs in Figure 1 and 2, one of the most visible differences is the much higher degree of order observed in the case of the complex. In the plane at z = 0 Å, the ligand itself does not show significant structural elements in the surrounding water, except for the cavity created by the large molecules. The hydration structure of the complex, however, is well ordered. At z = 2.5 (2.0) Å, the two z-axis located water molecules can be seen clearly, coordinated to the molecular centre of the ligand and the metal ion, respectively (the orientation of these two water molecules differs, however). Whereas the ligand does not show much further hydration structure in this plane, water of type 3 and associated secondary water molecules can be recognized for the complex. At z = 3 Å, both ligand and complex show their distinct hydration structures, that of the complex being much more separated into small areas. The same features are found still at z = 3.5 Å. Here, as well as in the previous planes, the higher degree of order in the complex hydration sphere is quite evident from the fewer points in the plots, indicating that the probability for water location is restricted to sharply localized areas.

Striking differences occur for the planes of z = 5 and z = 6 Å . Whereas the plots for the ligand show a rather random water distribution, hardly described as secondary sphere, the complex displays clearly a specific and well-defined order of arrangement for all water molecules, up to the limits investigated. This result can be visualized even more clearly from the xz-plane plot shown in Fig. 3. The formation of the secondary solvation sphere around the complex will also surely have consequences for the entropic contributions to the complex stability, but rather in the positive sense as assumed by the simple model of desolvation of the metal ion. It is believed, however, that these entropic effects will not have too large an effect on the free energy of solvation and thus the stability constant, but rather that it will be the enthalpic effects associated with the formation of the well-ordered solvation sphere(s) of the complex, which can enhance further the stabilization of the complex.

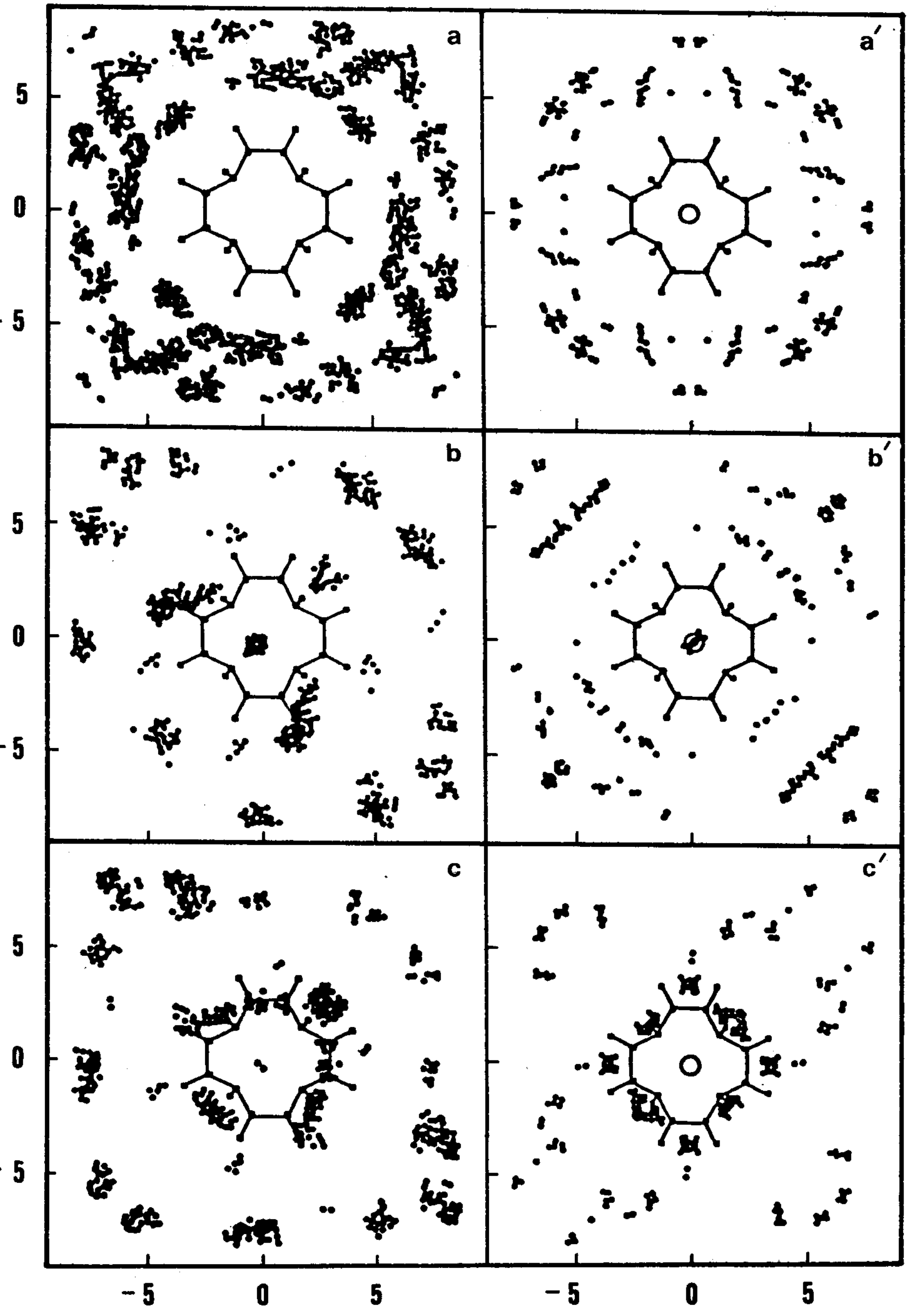

Figure 1 Distribution of water in the xy-plane at various distances z from the molecular center : a, a′ : z = 0.0 Å , b : z = 2.5 Å, b′ : z = 2.0 Å , c, c′ : z = 3.0 Å .

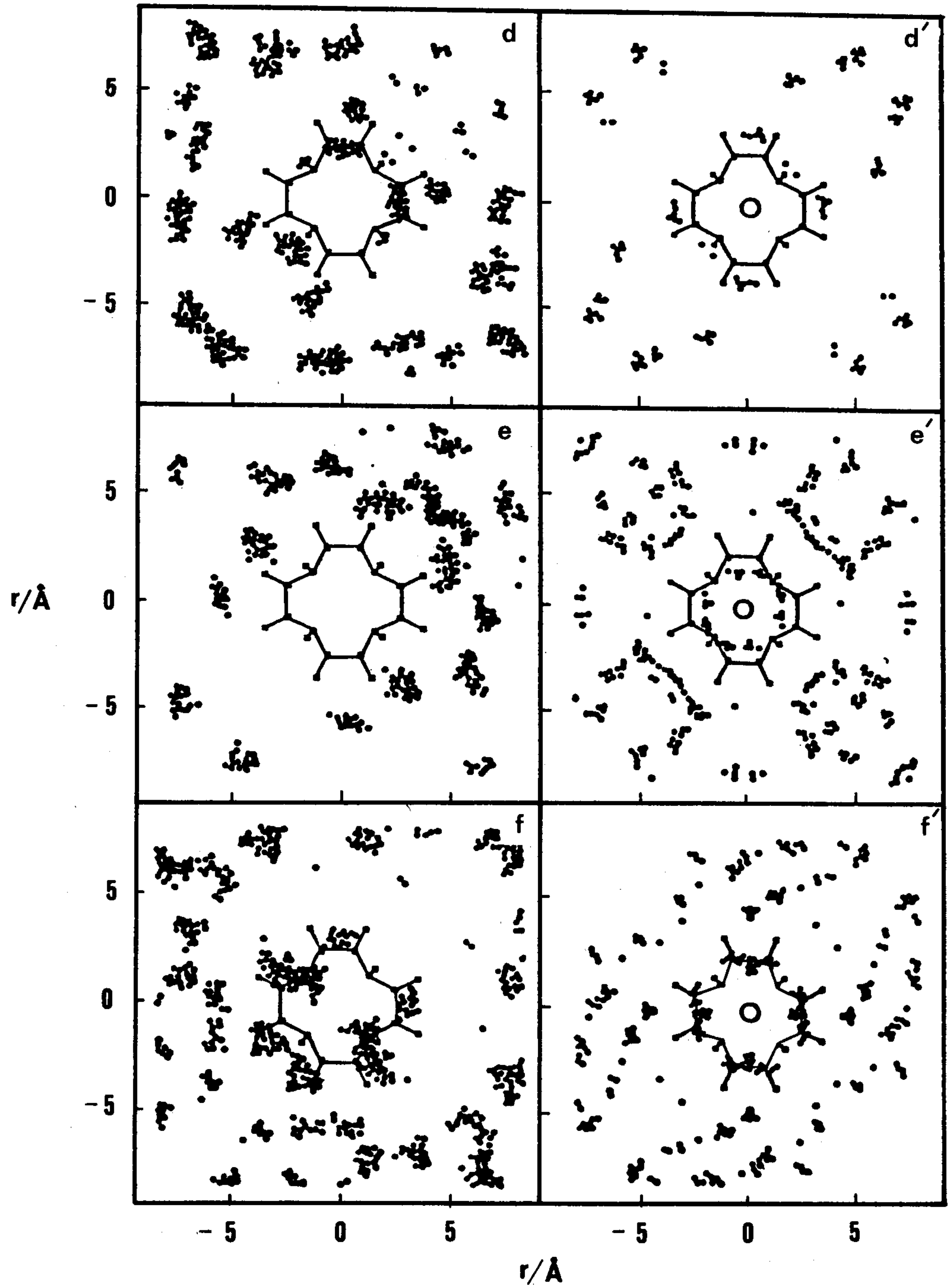

Figure 2 Distribution of water in the xy-plane at various distances z from the molecular center : d,d″ : z = 3.5 Å , e, e′ : z = 5.0 Å , f, f′ : z = 6.0 Å .

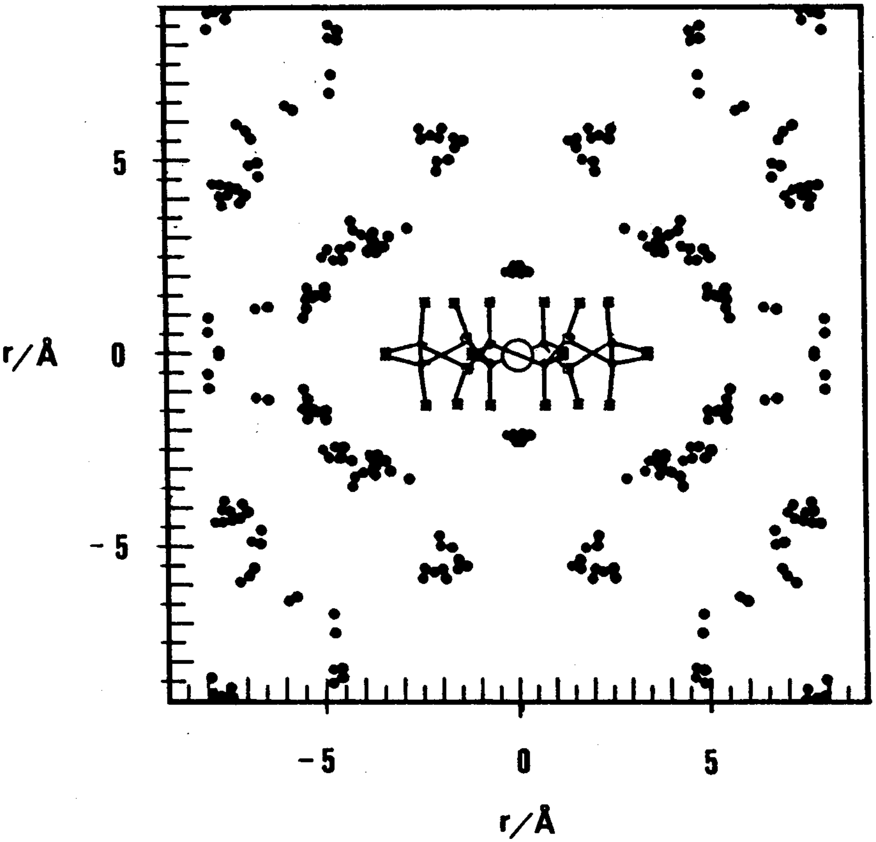

Figure 3 Distribution of water in the xz-plane for y = 0.0 Å .

The well-organized solvation sphere of the macrocyclic complex as obtained from our simulations and the comparison to that of the ligand alone also helps to rationalize the finding that the solvation enthalpy seems to be clearly related to and to determine the stability constants of a series of similar macrocyclic compounds[15].

As a final conclusion, we can point out therefore that solvation plays an important part in the specific stabilization of macrocyclic compounds, mostly through the unique possibility of building up a large hydration sphere around the cyclic compound due to the polarization of the macrocycle by the metal ion in its centre and the related enhancement of the interaction between the ligand's atoms and the water molecules. These effects will be rather of enthalpic nature, however, so that it can be concluded that the macrocyclic effect is due to enthalpic effects, due mainlv to the metal interaction with the macrocycle itself[9], with secondary effects due to the specific hydration properties of the macrocyclic complex. Entropic effects should be, therefore, of minor importance for the specific stability of macrocyclic compounds.

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บทคัดย่อ

การศึกษาผลของตัวทำละลายที่มีผลต่อการเกิดสารประกอบเชิงซ้อนของลิแกนด์วงแหวนขนาดใหญ่ โดยวิธี มอนติ คาร์โล โดยการเปรียบเทียบโครงสร้างของน้ำล้อมรอบ 1,4,7,10-tetraazacyclododecane (cyclen) และสารประกอบเชิงซ้อนของมันกับแมกนีเซียมอิออน พบว่า โครงสร้างของน้ำมีความแตกต่างกันอย่างชัดเจน กล่าวคือ น้ำล้อมรอบสารประกอบเชิงซ้อนจะมีความเป็นระเบียบสูงกว่า จากผลดังกล่าวสามารถคาดคะเนได้ว่า ความเสถียรของสารประกอบเชิงซ้อนน่าจะเป็นผลมาจากอิทธิพลของ เอนทาลบี มากกว่าที่จะมาจากอิทธิพลของ เอนโทรบี และตัวทำละลายจะมีผลมากหรือน้อยนั้นควรจะขึ้นอยู่กับชนิดของหมู่ฟังท์ชันที่ต่ออยู่กับอะตอมไนโตรเจน ของลิแกนท์วงแหวนขนาดใหญ่นั้น ๆ ด้วย