

A MONTE CARLO STUDY ON THE INFLUENCE OF MACROCYCLIC COMPOUNDS ON THE STRUCTURE OF WATER

SUPOT V. HANNONGBUA^a AND BERND - MICHAEL RODE^b

^a*Institut für Anorganische und Analytische Chemie, Universitaet Innsbruck, Austria*

^b*Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, Thailand*

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Abstract

The water structure around a 1,4,7,10 - tetraazacyclododecane molecule has been investigated by means of Monte - Carlo simulation based on ab - initio potentials. The hydration structure is visualized by water distribution plots derived from the radial distribution functions after evaluation of approximately one million configurations.

Differences between hydrophobic and hydrophilic regions of the molecule are well reflected by the simulation and a distinct hydration structure can be recognized which also allows conclusions on the role of the solvent in the complexation reaction of macrocyclic compounds.

It is known since quite some time, that solvent effects play an important part in the complex formation of macrocyclic compounds. The experimental evaluation of the hydration structure of such compounds e.g. by x - ray or neutron diffraction studies is quite impossible, however, due to the large number of very similar atoms and atomic distances in the solution.

Computational techniques like Monte Carlo simulations or molecular dynamics are the only way at present to give access to detailed structural data of such systems.

The case of macrocyclic compounds is of peculiar interest for the solution chemist, as these compounds display very remarkable metal binding abilities and deserve interest also in connection with biological systems. The special complexation abilities have been ascribed to the so - called "macrocyclic effect"¹, which should consist of enthalpic contributions, mainly due to electronic binding phenomena and the specific molecular structure, as well as entropic effects related to solvation and desolvation phenomena.

The effects related to binding and structural changes of the ligand have been investigated recently by means of ab initio molecular orbital calculations^{2,3} which have supplied satisfactory data on metal specificity of the macrocyclic ligands and on the energy contributions to the complex stabilization.

The present study intends to reveal data on the solvation structure of a macrocyclic ligand. Such data will not only be useful in order to understand the reaction pathways

^bPermanent address: Department of Chemistry, University of Innsbruck, A-6020 Innsbruck, Austria

which have to be followed during the complexation of the ligand by a metal ion, but also help to understand the solubilities and structural influence of a larger organic compound consisting of hydrophobic and hydrophilic functional groups.

The interaction potential between 1,4,7,10 - tetraazacyclododecane (cyclen) and water was obtained from an ab initio HF - MO calculation of the corresponding energy surface consisting of 250 points, from which an analytical expression consisting mainly of $1/r^n$ terms was obtained⁴. For the water - water interaction potential, the expression derived by Clementi and co-workers⁵ was used.

The basic box of the Monte - Carlo simulation - based on a modified Metropolis procedure⁶ - consisted of one cyclen molecule and 200 water molecules within a cube of sidelength 18.34 Å, corresponding to a density of 1.0 g/cc. The simulations were performed for room temperature (297 K).

Equilibrium was established after approximately 1.4×10^6 configurations. Another 1.1×10^6 configurations were evaluated after this for the presentation of data in this work.

The evaluation of the hydration structure was performed by dividing the basic box into slices of 0.4 Å diameter, located at various distances z , parallel to the molecular plane (xy plane). For each of these slices, water distribution plots have been constructed according to the probability contributions derived from the simulation. Only the oxygen atoms of water molecules have been plotted, and in order to rationalize the plotting procedure, water molecules located closer than 0.2 Å to a previously recorded molecule have been neglected.

The calculations have been performed mostly at the computer center of the University of Innsbruck, partly at the computer center of Chulalongkorn University. The plots have been made with a CALCOMP plotter.

The water distribution plots for z values from 0 to 6 Å are shown in Figures 1 a to 1 i. The water distribution in the molecular plane (Fig. 1 a), which is dominated by the hydrophobic functional groups of the ligand molecule, shows a rather random distribution of water, where the solvent structure is only influenced by the size of the cavity necessary to take up the cyclen molecule. Around the ligand, clearly two shells of water can be recognized and the distance between the shells corresponds to the average hydrogen bond distance between water molecules in liquid water. This picture clearly shows, that the ligand will influence the structure of the surrounding solvent at least up to a distance of about 8 Å from the molecular center. This also means, that the size of the basic box might have to be enlarged even, in order to recognize the upper limit of the structural influence.

At a distance of 1.5 Å above the molecular plane, the aforementioned hydrophobic structure is still the dominating element for the solvent distribution. However, some grouping in the first shell water structure can be recognized already (Fig. 1 b).

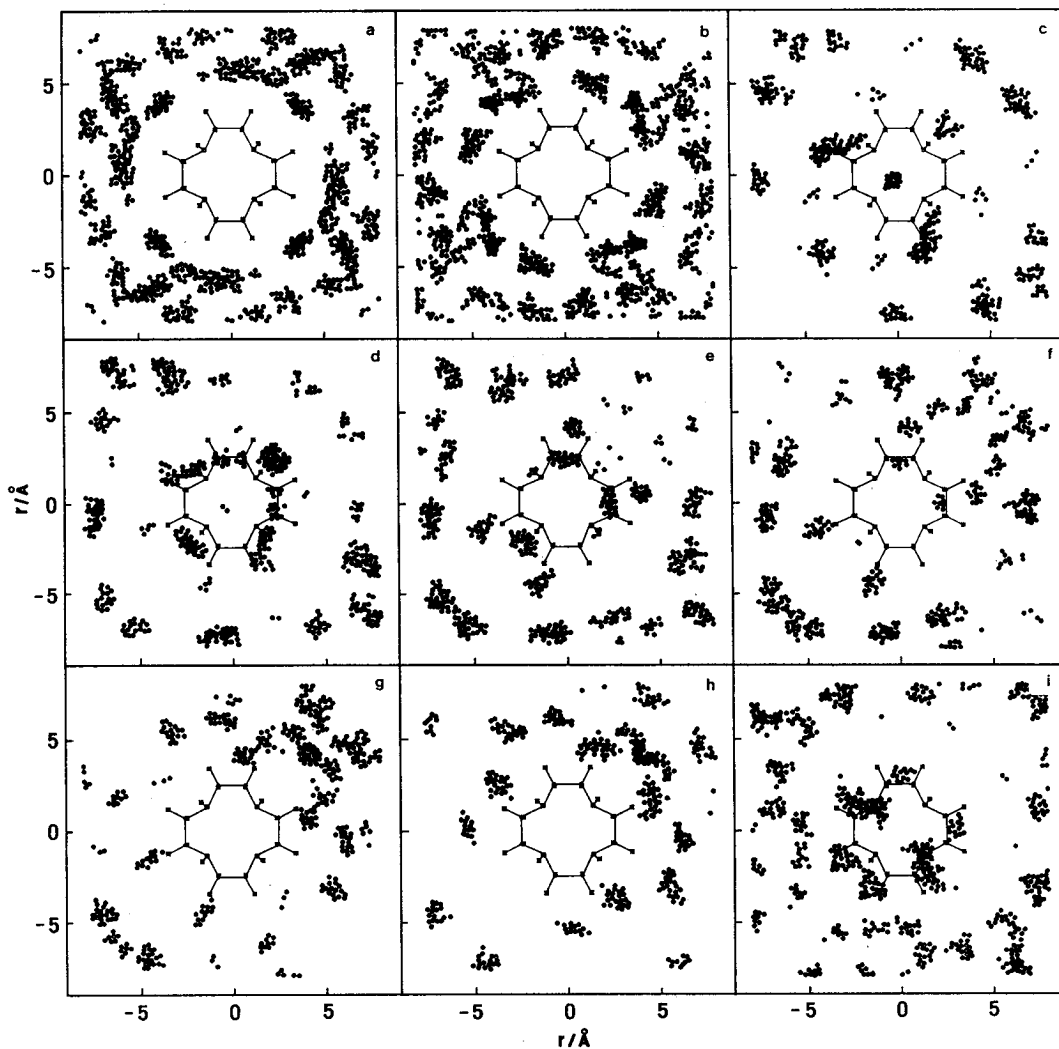


Figure 1. Water distribution in and above the molecular plane of 1, 4, 7, 10-tetraazacyclododecane (cyclen) within ± 0.2 Å of the selected value of the z-axis (molecular plane = xy-plane). a : $z = 0.0$ Å; b : $z = 1.5$ Å; c : $z = 2.5$ Å; d : $z = 3.0$ Å; e : $z = 3.5$ Å; f : $z = 4.0$ Å; g : $z = 4.5$ Å; h : $z = 5.0$ Å; i : $z = 6.0$ Å.

The situation completely changes after moving up to a distance of 2.5 Å above the molecular plane. A very distinct coordination center for water appears in the top of the ligand (cf. Fig 1 c). A comparison with the following figures 1 d and e shows, that the location of this water is rather exactly limited to a distance of about 2.5 Å to less than 3 Å. This corresponds very well to the radial distribution functions (RDF), reported elsewhere (7), which have indicated that one water molecule is centered above the plane with a maximum in the RDF at 2.6 Å, pointing towards the molecular center with one of its hydrogen atoms and with the O - H bond coinciding with the z axis.

Figure 1 d then reveals further details of a distinct hydration structure, which can be ascribed to interaction with both the central water at 2.6 Å and the hydrophilic groups (NH) of cyclene. 4 - 5 water molecules are contained in this shell, which is again in good agreement with the integration numbers of the corresponding RDF's (7).

Figures 1 e and f show, that this first shell of (hydrophilic) hydration exerts still a considerable influence to more far located solvent molecules, forming a second hydration sphere which is still well ordered and not randomly distributed. Hydrogen bonding towards the first shell is assumed to be determined, therefore, by the structural influence of the ligand via its first shell hydration water. At the same time it is seen, that above the ligand cavity no water molecules are located, even up to a distance of 6 Å above the molecular plane (Fig. 1 e to i).

A further fact, which can be recognized from Figures 1 g to i is, that the space surrounding the ligand at a level of 4 - 5 Å above the molecular plane is a rather water - poor region compared to the molecular plane itself. Even 6 Å far from the molecular center we still find considerable structural elements related to the central water and the other first shell molecules above the molecular plane, whereas the side region seems to return to the structure characteristic for the pure solvent at room temperature. From the most far located positions displayed in Figure 1 i we can conclude, that the ligands influence should cease at distances of about 10 Å far from the molecular center, where these water molecules are located.

Taking into consideration the summarized data of this work, the hydration area around cyclen can be separated clearly into a hydrophobic region surrounding the molecule in its plane and extending 1.5 Å above (and below) this plane. Above this area, a hydrophilic region is found with a distinct solvation structure located within a hemisphere of about 7 - 9 Å radius.

The specific structure of this hydrophilic region is of peculiar interest for the ability of such ligands to bind cations. Due to the existence of only one water molecule above the ring and the large cavity free of water molecules, an approach will be strongly facilitated for a metal cation of suitable size. In the last reaction step, only one water molecule has to be removed in order to let the cation enter its binding side, i.e. the macrocyclic cavity. The other water molecules located around the molecular cavity above

the plane as indicated in Fig. 1 d to f, will further facilitate this reaction, as they form a funnel-shaped network, which will help to replace the metal ion's hydration water by offering alternative coordination sites. Besides all energetic effects provided by the specific molecular structure of a macrocyclic ligand, the binding of metal ions to such ligands can be understood, therefore also by the specific hydration structure of the ligand and a "cooperative" mechanism provided by this structure for the approach of the ion.

The large number of water molecules involved in the formation of both hydrophilic and hydrophobic structures around the ligand can be taken as an indication for the reasons of the limited solubility of such compounds in water. From the 200 water molecules involved in this simulation, only very few can be considered to represent bulk water molecules. Most of them are directly or indirectly ordered through the presence of the ligand, although the ligand/solvent relation here already corresponds to a quite dilute solution (0.28 M). Based on the results of this investigation, a similar simulation on a macrocyclic complex containing the central metal ion in its binding position will be performed, in order to reveal structural differences between ligand and complex hydration.

The results of this work also suggest, that for analogous investigations on larger macrocyclic compounds, the size of the basic box and thereby, the number of water molecules involved in the Monte Carlo procedure should be increased in order to include all effects up to the transition into the bulk structure.

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บทคัดย่อ

ได้ศึกษาโครงสร้างของน้ำที่อยู่ล้อมรอบโมเลกุลของ 1,4,7,10 - tetraazocyclododecane โดยใช้เทคนิคของ Monte - Carlo simulation พบว่าสามารถแสดงออกถึงข้อแตกต่างระหว่างบริเวณที่เป็น hydrophobic และบริเวณที่เป็น hydrophilic อย่างชัดเจน รวมทั้งทราบถึง hydration structure ของโมเลกุลด้วย