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The role of non-additive contributions on the hydration shell structure of Mg^{2+} studied by Born–Oppenheimer ab initio quantum mechanical/molecular mechanical molecular dynamics simulation

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Abstract

An ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics simulation has been performed to investigate the effects of non-additive contributions on the hydration shell structure of Mg^{2+} . The active-site region, the sphere including the second hydration shell of Mg^{2+} , was treated by Born–Oppenheimer ab initio quantum mechanics, while the rest is described by classical pair potentials. A hydration complex with six inner shell waters and 12 second shell waters was observed. It was also found that the effects of non-additive terms play an important role in the preferential orientation of water molecules inside the hydration sphere of Mg^{2+} . © 2001 Published by Elsevier Science B.V.

1. Introduction

Due to the diverse functions of metal ions in chemical and biological systems, understanding of the detailed structure of aqueous metal ions is of considerable interest for chemists and biologists. Among the alkaline-earth metal cations, Mg^{2+} is crucial for the structural integrity and biological activity of nucleic acids [1–3]. Mg^{2+} can stabilize RNA in several distinct ways, including diffuse binding and site binding, mostly distinguished by its hydration properties, and hence, has been

shown to be important for the specific structure and function of many RNAs [4,5].

Structural information on hydrated Mg^{2+} in aqueous solutions has been reported both from experiments and computer simulations. In experiments, a hexaaquo Mg^{2+} has been established by proton NMR [6], X-ray diffraction [7] and by Raman spectroscopy [8]. Computer simulations, by means of Monte Carlo and molecular dynamics simulations, have been carried out to investigate structural and other properties [9–12]. The results from computer simulations can in principle provide a more detailed interpretation and prediction of experimental observations at molecular level, in particular where the experimental results are prone to large errors [13,14]. In the earlier simulations,

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the structural details, such as the average number of water molecules surrounding Mg^{2+} , were found to be in fair agreement with experiments. However, it should be noted that those simulations relied on classical force fields. At this simulation level, the potential functions describing interactions are mostly based on pair-wise additive approximations in which the contributions of the higher n -body interactions are always assumed to be small and thus negligible. It has been reported [15,16] that three-body effects for the solutions of double-charged ions, such as Ca^{2+} and Mg^{2+} , are crucial to obtain a reliable first hydration shell structure. The many-body terms are also known to contribute significantly to intermolecular forces between water molecules, and hence, to influence the fluid structure [17,18]. In an early MC simulation [11], the non-additive terms, such as three-body terms for the Mg^{2+} -water interactions together with three-body and four-body terms for water-water interactions, have been included empirically in the interaction potentials. Nevertheless, one should realize that the construction of potential functions including many-body terms is a very subtle task due to the complicated orientation dependence of molecular systems. In addition, the constructed many-body potentials such as three-body potential might need, in some aspects, an additional adjustment to obtain a good fit of an analytical function [19]. As a consequence, the quality and accuracy of corrected analytical many-body potentials might be insufficient.

To reliably correct the effects of many-body contributions, the more sophisticated simulation technique 'Born-Oppenheimer ab initio quantum mechanical/molecular mechanical (QM/MM) dynamics' has been proposed and successfully applied to investigate the structural and dynamical properties of various ions in solutions [20–25]. By this technique, the solvation sphere of the ion in which the many-body contributions always play a crucial role, is treated by ab initio quantum mechanics, while the rest of the system is described by classical pair or pair plus three-body potentials. The results from this high-level QM/MM method have provided more insight into the role of many-body effects on both structural and dynamical properties of those solvated ions. These effects are

important, not only for the solvation structure of strongly interacting divalent cations, but also for the weaker solvation complexes of monovalent cations such as Li^+ , Na^+ and K^+ [22,23].

Since the effects of non-additivity in ion-water systems are related to the strength of binding between the ion and water, these effects in the hydration sphere of ions with a high charge-to-radius ratio, like Mg^{2+} , are expected to be large and by no means negligible. The energetic errors due to many-body effects for $\text{Mg}(\text{H}_2\text{O})_n^{2+}$ complexes, where $n = 2, 3, 4$ and 6 , have been investigated [26], yielding errors in the pair-wise additive approximations of 4.9%, 12.6%, 24.6% and 36.5%, respectively. These errors are obviously high and, of course, neglect of these contributions could artificially favor some geometrical arrangements, especially at short distances in the hydration shell of Mg^{2+} . In this work, therefore, the Born-Oppenheimer ab initio QM/MM molecular dynamics simulation technique was applied in order to achieve a refined structural analysis of the hydrated Mg^{2+} complex.

2. Methods

In the QM/MM technique, the system is partitioned into two parts, named QM and MM regions. The QM region includes all particles within the second hydration shell of Mg^{2+} and is treated by means of Hartree-Fock level quantum mechanics, while the MM region, the rest of the system, is described by classical pair potentials. During the simulation, the exchange of water molecules between the QM and MM region can occur frequently. In this case, forces are switched according to the defined region upon entering or leaving of the molecule. Since the complicated many-body interactions are mostly significant at short range, it is assumed that the quantum mechanical forces beyond the QM region would smoothly converge to pair potential forces and the QM region used in our simulation has been considered large enough to make the difference in forces at the boundary between QM and MM region to be rather marginal. The accurate description of intermolecular interactions within the QM

region principally depends on the use of basis sets. The use of small basis sets such as STO-3G can result in an overestimation of the hydration number [21], while the use of large basis sets is still impractical for current computational feasibility. A suitable basis set can be considered as a compromise between the quality and the requirement of CPU time. The DZV basis set for water and Los Alamos ECP plus DZ basis set for Mg^{2+} (LANL2DZ basis set in GAUSSIAN 94 [27,28]) were selected since ab initio geometry optimizations using these basis sets [26] reproduce structural properties rather well with respect to calculations using larger basis sets such as D95V+(d,p) basis set. Although the use of LANL2DZ basis set will produce a rather large H–O–H angle of about 112° , compared to the experimental value of 104.5° , this wider angle of water has been checked and it was found that it does not affect the coordination number as well as the geometry arrangement of the hydration complex [21–23]. Further, it has been shown that the basis set superposition error is very small for this type of basis set (following the CP method [29], the BSSE results as $-9.5 \text{ kcal mol}^{-1}$ for the $\text{Mg}(\text{H}_2\text{O})_6^{2+}$ complex, i.e., $\sim 2.6\%$ of the total binding energy in the equilibrium geometry), which is another advantage for the simulation, as it would not be feasible to perform BSSE corrections throughout the simulation process. Finally, the inclusion of electron correlation in the quantum mechanical calculations would be very time-consuming and it can be expected that its effect is small, if not negligible [26].

A flexible water model, which includes intermolecular [30] and intramolecular interactions [31], was employed for water. The pair potential function for Mg^{2+} – H_2O interactions was newly constructed using DZV+P basis set [27] for H_2O and the Los Alamos ECP plus DZ basis set [28] for

Mg^{2+} . The 1300 Hartree–Fock interaction energy points obtained from GAUSSIAN 94 [32] calculations were fitted to the analytical form

$$\Delta E_{\text{Mg}^{2+}-\text{H}_2\text{O}} = \sum_{i=1}^3 \left(\frac{A_{ic}}{r_{ic}^6} + \frac{B_{ic}}{r_{ic}^7} + C_{ic} \exp(-D_{ic}r_{ic}) + \frac{q_i q_c}{r_{ic}} \right), \quad (1)$$

where A , B , C and D are the fitting parameters (see Table 1), r_{ic} denotes the distances between Mg^{2+} and the i th atom of water and q are the atomic net charges. The charges on Mg^{2+} , and O and H of water were set to 2.0, -0.6598 and 0.3299 , respectively.

A molecular dynamics simulation based on classical pair potentials was performed first. After that, the Born–Oppenheimer ab initio QM/MM dynamics simulation was carried out, starting from the equilibrium configuration resulting from the pair potential simulation. Both simulations were carried out in a canonical ensemble at 298 K with a time step size of 0.2 fs. The cubic box, with a box length of 18.19 \AA , employed in the simulations contained one Mg^{2+} and 199 water molecules, assuming the experimental density of pure water. Long-range interactions were treated using the reaction-field procedure [33]. The classical pair potential molecular dynamics simulation started from a random configuration and was equilibrated for 50 000 time steps. The simulation was continued for 100 000 time steps to collect configurations every 10th step.

Since the QM region is the most expensive computational part, selection of the QM size is a crucial point. According to the Mg–O radial distribution function (RDF) in the pair potential simulation (see Fig. 1), the second minimum of the Mg–O peak is located at a Mg–O distance of around 5.2 \AA . The number of water molecules involved within this region is about 25–30. In

Table 1
Optimized parameters of the analytical pair potential for the interaction of water with Mg^{2+} (interaction energies in kcal mol^{-1} and distances in \AA)

Pair	A ($\text{kcal mol}^{-1} \text{ \AA}^6$)	B ($\text{kcal mol}^{-1} \text{ \AA}^7$)	C (kcal mol^{-1})	D (\AA^{-1})
Mg–O	–12 668.1324	12 088.9853	74147.214596	3.361504052
Mg–H	–5736.48320	5292.23849	18 898.224478	3.037641038

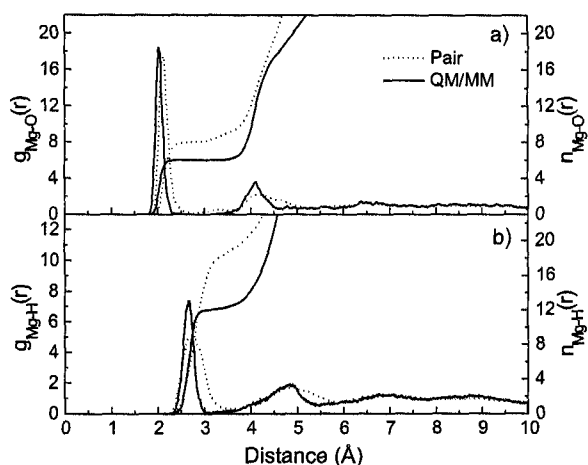


Fig. 1. (a) Mg–O and (b) Mg–H RDFs and their corresponding integration numbers.

order to investigate the structural properties up to the second hydration shell, a diameter of 10.4 Å should be selected as the size of the QM region. However, performing of *ab initio* quantum mechanical force calculations for each step with this QM size would be too time-consuming. From our experiences, correction of non-additive terms for the strongly interacting ion–water systems generally results in lower coordination numbers [21,22]. Therefore, we started the QM/MM simulation with a smaller QM region with a diameter of 8.0 Å. This QM region includes the first hydration shell and some parts of the second hydration shell of Mg^{2+} . After a re-equilibration for 10 000 time steps, the hydration shell structure of the Mg^{2+} is rearranged and a new second Mg–O peak seems to be recognizable at a shorter Mg–O distance, between 3.8–4.5 Å. At this stage, as expected, the amount of water molecule residing within the hydration complex had decreased. The system was re-equilibrated again for 15 000 time steps during which an increased diameter of 9.0 Å was applied as the size of the QM region. With this QM size, most water molecules involved in both the first and second hydration spheres of Mg^{2+} are included. After that, the QM/MM simulation was continued for another 30 000 time steps to collect configurations every 5th step. To ensure a continuous change of forces at the transition between QM and MM region, a smoothing function [34] was applied

within an interval of 0.2 Å (i.e., between the Mg–O distances of 4.0–4.2 and 4.5–4.7 Å for the first and second re-equilibration steps, respectively).

3. Results and discussion

The Mg–O and Mg–H RDFs and their corresponding integration numbers, obtained from both classical pair potential and combined QM/MM simulations, are presented in Fig. 1. In the pair potential simulation, a sharp first Mg–O peak exhibits the maximum at 2.13 Å and the first hydration shell is rather well separated from the second one, leading to the average coordination number of 8. A broad second Mg–O peak is observed between 3.7–5.2 Å with the maximum at 4.23 Å, consisting of about 19 water molecules located within this second shell. A small overlap between the first and second shell, both in Mg–O and Mg–H RDFs, indicates that interchanging of water molecules between the first and second shell should easily occur. In the QM/MM simulation, a slightly sharper and more pronounced first Mg–O peak is observed at a shortened Mg–O distance of 2.03 Å. The narrower Mg–O peak is normally related to a more rigid hydrated Mg^{2+} complex. The first hydration shell is completely separated from the second one, giving a clear coordination number of 6. A well-pronounced second Mg–O peak is found between 3.7–4.6 Å with the maximum at 4.12 Å, yielding about 12 water molecules located within this shell. A comparison of the structural parameters from this work and the data from the earlier simulations is summarized in Table 2. Most simulations predicted a coordination number of 6, though, a discrepancy in the first hydration shell radii is observed. The pair potential simulation in this work even overestimated the coordination number. The observed differences are clearly due to non-additive effects in the hydrated Mg^{2+} complex. It looks surprising at the first glance that earlier simulations based on pairwise additivity led to a coordination number of 6 for the first shell. However, such simulations have either used an over-simplified ion–water potential consisting of a Coulomb plus Lennard–Jones term only, which may lead to error compensations, or they have

Table 2

Comparison of hydration parameters for Mg^{2+} ; $r_{\text{max}1}$, $r_{\text{max}2}$, $r_{\text{min}1}$ and $r_{\text{min}2}$ denote the first maximum, the second maximum, the first minimum and the second minimum of the RDFs in Å, and $n_{\text{min}1}$ and $n_{\text{min}2}$ are the average number of water molecules obtained by integration up to $r_{\text{min}1}$ and $r_{\text{min}2}$, respectively

Solute	Ion/water ratio or molarity (M)	$r_{\text{max}1}$	$r_{\text{max}2}$	$r_{\text{min}1}$	$r_{\text{min}2}$	$n_{\text{min}1}$	$n_{\text{min}2}$	Method	Reference
Mg	1:199	2.13	4.23	2.81	5.18	8.0	26.6	MD (2-body)	This work
	1:199	2.03	4.12	2.47	4.68	6.0	18.3	MD (QM/MM)	This work
	1:525	2.2	–	3.1	–	6.2	–	MD (2-body)	[9]
	1:480	2.12	4.40	–	–	6.0	18	MC (2+3-body)	[11]
$\text{Mg}(\text{NO}_3)_2$	1.00	2.07	–	–	–	5.7	–	XD	[7]
	MgCl ₂	1.00	2.12	–	–	6	–	XD	[7]
		2.05	2.10	–	–	6	–	XD	[7]
		4.84	2.10	–	–	6	–	XD	[7]
$\text{Mg}(\text{H}_2\text{PO}_4)_2$	1.1	2.00	4.57	2.3–3.0	–	6.0	–	MD (2-body)	[10]
	18.5	2.1	–	–	–	6	–	XD	[7]
$\text{Mg}(\text{CH}_3\text{COO})_2$	1.68	2.10	–	–	–	6	–	XD	[7]
	3.73	2.10	–	–	–	6	–	XD	[7]
MgCl ₂	4.34	2.00	–	–	–	5.9	–	XD	[7]

included higher terms empirically into the pair potential, e.g., the Monte Carlo simulation, in which the interaction pair potential used included such empirical polarization and non-additivity effects, depicted the first hydration shell radius close to the experimental value. However, when looking at the full picture of the hydration, the limitations of such methods are recognised: for the second shell, a rather large distance of 4.4 Å from the ion is observed, compared to the experimental value of 4.1 Å [35].

Fig. 2a shows the probability distributions of the coordination numbers, calculated up to the Mg–O distances of 5.2 and 4.6 Å for the pair potential and QM/MM simulations, respectively. The distributions of coordination numbers within the first and second hydration shell are plotted separately in Fig. 2b. In the pair potential simulation, the first hydration shell of Mg^{2+} prefers a coordination number of 8 (and 9 in small amounts) and the second hydration shell prefers a coordination number of 19 (in addition to 18, 20, 17, 21 and 16 in decreasing amounts). In the QM/MM simulation, the first hydration shell prefers a sole coordination number of 6 and the second hydration shell favors a coordination number of 12 (followed by 11, 13, 10 and 14 in smaller amounts).

Fig. 3 shows the O–Mg–O angular distributions, calculated up to the first minimum of the Mg–O RDFs. An octahedral geometry is well

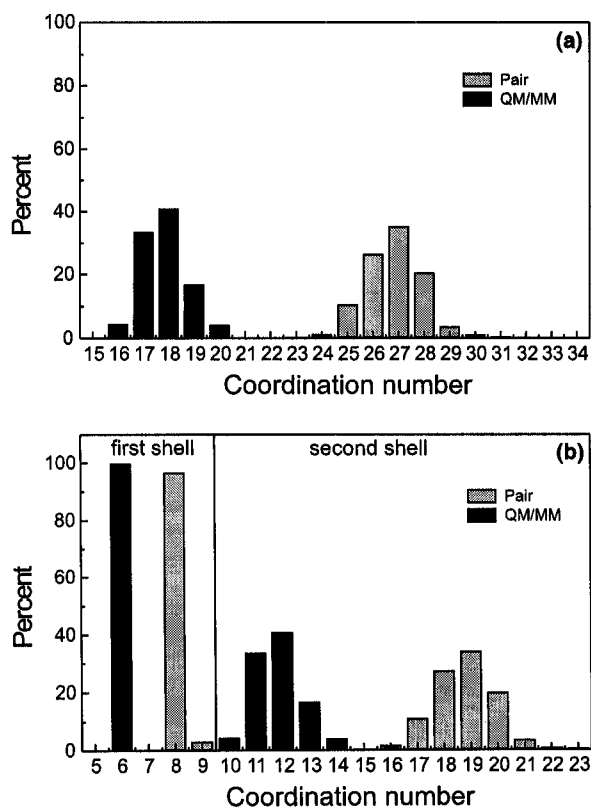


Fig. 2. Coordination number distributions: (a) calculated up to the second minimum of the Mg–O RDFs and (b) calculated within the first and the second hydration shell.

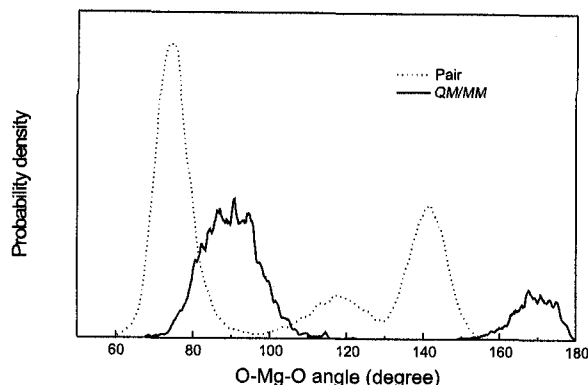


Fig. 3. O–Mg–O angular distributions, calculated up to the first minimum of the Mg–O RDFs.

recognized in the QM/MM simulation, by the two pronounced peaks between 80° and 100° and between 160° and 180°. In the classical pair potential simulation, the narrower O–Mg–O angles around 65°–85° and around 130°–150° are related to the larger number of water molecules in the first hydration shell. Fig. 4 provides more detailed information on the orientation of water molecules around Mg^{2+} . The orientation of water molecules is described in terms of the distribution of angle θ , as defined by the dipole vector of the water molecule and the $Mg \cdots O$ vector. As can be seen from Fig. 4a, the first hydration shell waters in the QM/MM simulation are more rigidly dipole-oriented

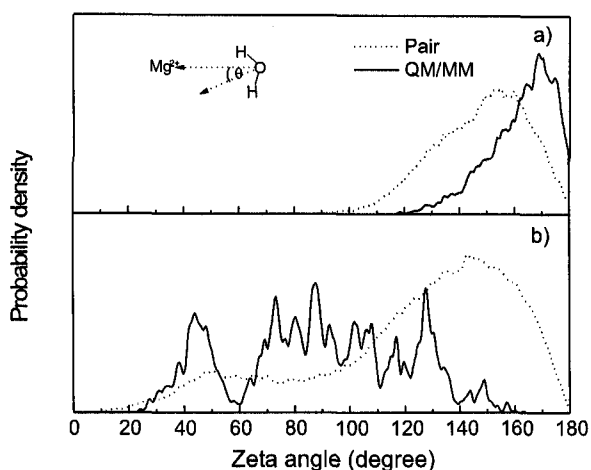


Fig. 4. Distributions of θ : (a) in the first hydration shell of Mg^{2+} and (b) in the second hydration shell of Mg^{2+} .

than those in the pair potential simulation. A different trend is observed in the second hydration shell. As can be seen in Fig. 4b, water molecules in the pair potential simulation show a pronounced preference for a dipole-oriented arrangement towards the central ion. In the QM/MM simulation, the orientation of water molecules in the second shell seems to be rather determined by ligand–ligand interactions, and by optimal hydrogen bonding between second shell and bulk.

With respect to the role of Mg^{2+} in RNA stability [1,2], the stabilization of RNA by the ion is characterized by two different modes of binding, diffuse binding and site binding. In diffuse binding, fully hydrated Mg^{2+} interacts with the RNA via non-specific long-range electrostatic interactions, which are responsible for the ‘delocalized’ counterion atmosphere surrounding all nucleic acids. In site binding, dehydrated Mg^{2+} interacts with anionic ligands specifically arranged by the RNA fold to act as coordinating ligands for the ion. These ligands are able to dehydrate the ion, forming an ‘inner-sphere’ complex. In this context, the results from the QM/MM simulation concerning the stability and structure of the hydrated Mg^{2+} complex provide more detailed information on the relationship between diffuse and site binding since these differences strongly depend on the Mg^{2+} hydration properties, in particular on the ability to remove parts of the hydration shell and the flexibility of ligand orientation.

4. Conclusion

The observed differences in coordination numbers as well as the geometrical arrangements of the hydrated Mg^{2+} ion are obviously due to the effects of non-additive contributions, which apparently play a significant role not only in the first hydration shell, but also for the shape and size of the second hydration shell of Mg^{2+} . These effects are also reflected in differences in the packing of the water molecules surrounding this ion. The results from the QM/MM simulation indicate that six water molecules are strongly bound to Mg^{2+} and the $Mg(H_2O)_6^{2+}$ complex can be considered as a well-defined octahedral structure embedded in a

H-bonded second shell. The QM corrections up to the second hydration shell of Mg^{2+} proved substantial to gain more insight into the structure of this second shell, and hence, for understanding the properties of hydrated Mg^{2+} in electrolyte solutions, in particular related to the role of Mg^{2+} in RNA stability.

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