



Dynamical properties of water molecules in the hydration shells of Na⁺ and K⁺: ab initio QM/MM molecular dynamics simulations

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Abstract

The librational and vibrational motions of water molecules in the first hydration shells of Na⁺ and K⁺ have been studied by combined ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics simulations, in which the ion and its first hydration sphere were treated at the Hartree–Fock level using LANL2DZ basis sets. The frequency shifts, together with the detailed analysis of water exchange processes and the mean residence times of the water molecules surrounding the ions, in comparison to those observed from a QM/MM simulation of pure water, provide a clear evidence for the background of the experimentally observed transition from structure-making to structure-breaking behavior from Na⁺ to K⁺.

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1. Introduction

Detailed knowledge of the dynamics of ligands, in particular water, in the coordination shell of ions is of particular interest for chemists and biologists in order to understand the reactivity of these ions in chemical and biological systems [1,2]. Although experimental methods such as nuclear magnetic resonance (NMR) [3,4] have been successfully employed to access the dynamics processes of the ion–water complexes, the time-scale of these methods is a limiting factor for the measurability of such data, especially for very fast reactions. Time-dependent simulation methods, in particular molecular dynamics (MD), have become an alternative way for the dynamical investigations at molecular level [5–7]. However, it has been shown in several cases that the exact dynamics of hydrated ions are highly sensitive to the accuracy of the simulation technique [8,9]. Simulations based on classical pair potentials, even with three-

body corrections, although providing fairly accurate data for the structure, often failed to correctly predict the dynamical data of such systems [9]. As the main reason the neglect of higher non-additive contributions has been identified, leading to incorrect description of the interactions and, consequently, the motions of each particle in the system. To reliably correct the effects of many-body interactions, a so-called combined ab initio quantum mechanical/molecular mechanical (QM/MM) molecular dynamics approach, which treats a sphere including at least the full first solvation shell of the ions quantum mechanically, has proven to be a suitable way to overcome this problem and to provide more reliable results for librational/vibrational motions as well as exchange rates and mean residence times of ligands in the hydration sphere of various ions [9–13].

In the present work, we have extended the previous QM/MM simulations of Na⁺ and K⁺ in water [14] in order to investigate the dynamical properties of these two hydrated ions. The characteristics of Na⁺ and K⁺ in aqueous solution are of substantial interest since their contrasting behavior is very crucial for ion pumping across the cell membrane [15]. Much detailed

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information is already available for the hydration structure of Na^+ and K^+ , but less is known about the detailed microscopic dynamics of these weakly hydrated ions. In our previous work [14], the effects of non-additive terms were found to play a significant role in the coordination numbers of both Na^+ and K^+ , and these effects were also found to affect the preferential orientation of water molecules in the hydration shell of the ions, reflecting the experimentally observed 'structure-making' and 'structure-breaking' behaviors of Na^+ and K^+ , respectively. It has been shown [14] that it is the relative ease of dehydration of these ions, which determines the ability to enter the ion channel, rather than the ion distance to the binding sites inside these channels [16]. Therefore, it appears of particular interest to investigate the dynamical properties of these two hydrated ions in detail, on the basis of accurate QM/MM simulations.

2. Methods

The QM/MM technique for the treatment of ions in solution has been discussed in detail previously [17,18]. By the QM/MM approach, the system is partitioned into a QM region and a region described by classical molecular mechanics (MM). The chemically most relevant region, in this case the ion and its first hydration sphere, is treated by Born–Oppenheimer *ab initio* quantum mechanics, while the rest of the system is described by simple pair potentials. In this work, the QM/MM molecular dynamics simulations of Na^+ and K^+ in water were carried out with the same conditions as reported in the previous paper [14]. Briefly, for the description of all particles within the QM region, the LANL2DZ basis sets [19,20] were chosen, compromising between the quality of the simulation results and the requirement of CPU time. The diameters of the first hydration shell of Na^+ and K^+ , namely 3.2 and 3.8 Å, were set as the size of the QM region, beyond which a smoothing function [21] is applied for an interval of 0.2 Å (i.e., up to 3.4 and 4.0 Å for Na^+ and K^+ , respectively), which leads smoothly into the MM region. A flexible model, which describes intermolecular [22] and intramolecular [23] interactions, was employed for water, ensuring compatibility and a smooth transition, when water molecules move from the QM region with full flexibility to the MM region. The pair potential functions for Na^+ – H_2O and K^+ – H_2O interactions were obtained from the previous work [14]. Both simulations were performed in a canonical ensemble at 298 K with a time step of 0.2 fs. The cubic box, with a box length of 18.19 Å, employed in the simulations contained one ion and 199 water molecules, assuming the experimental density of pure water. Long-range interactions were treated using the reaction-field procedure [24]. The QM/

MM simulations were performed for 60 000 time steps, collecting configuration data every 10th step.

To reliably describe the influence of ions on the dynamics properties of the surrounding water molecules, a QM/MM molecular dynamics simulation of pure water has been additionally carried out using the same simulation protocol, simply by replacing the ion with a water molecule. With regards to this point, the bulk properties reported in this work refer to the properties of pure water treated at similar QM/MM level of accuracy. The system of 200 water molecules was initially equilibrated by performing a classical pair potential simulation for 100 000 time steps. Then, a combined QM/MM simulation, with a QM diameter of 3.8 Å, started with the re-equilibration for 25 000 time steps, followed by another 60 000 time steps to collect configurations every 10th step. To ensure a continuous change of forces at the transition between QM and MM region, the smoothing function [21] was again applied within an interval of 0.2 Å (i.e., between the O–O distance of 3.8–4.0 Å).

3. Results and discussion

3.1. Intramolecular geometry of water

The comparison with a QM/MM simulation of pure water allows a quite accurate investigation of the relative influence of ions on the intramolecular geometry of solvent molecules. Fig. 1 shows the distributions of O–H distances and H–O–H angles of water molecules inside the first hydration shells of Na^+ and K^+ , compared to the corresponding geometry of water molecules in the bulk. Apparently, the structure of bulk water is significantly modified by the introduction of Na^+ , resulting in a shift of the O–H bond length toward longer distances and in a simultaneous decrease of the H–O–H angle. In contrast to Na^+ , K^+ shows an opposite influence on the intramolecular geometry of its nearest water molecules: The O–H bond is slightly shortened, and larger H–O–H angles are found more often than in the bulk.

3.2. Librational motions

The power spectra obtained by the Fourier transformations of VACFs are discussed in terms of shifts of peak maxima as a result of the ionic influence. Based on the normal-coordinate analyses [25], the power spectra of the librational motions of water molecules are depicted in Fig. 2. Due to rather constant systematic errors of Hartree–Fock frequencies, a scaling factor of 0.89 [26] was employed to scale all frequencies obtained by the QM/MM simulations. For pure water, the order of $R_z < R_x < R_y$ is observed. In comparison to pure water, the rotational frequencies of water molecules in the hydration shell of Na^+ are all blue-shifted. The shift to

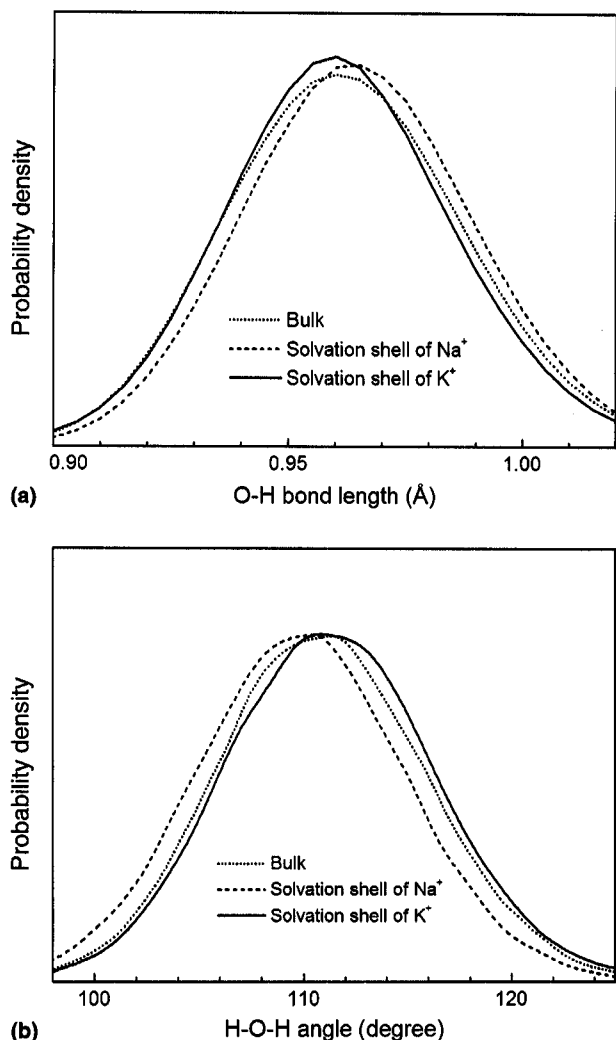


Fig. 1. Distributions of: (a) bond length and (b) angle of water molecules in the first hydration shell of water itself and of ions, as obtained by the QM/MM simulations.

higher frequencies can be understood due to the strong interactions between ion and water. For water molecules in the hydration shell of K⁺, the frequencies are rather similar to those in the bulk. In terms of the peak maxima, a slight red-shift can be recognized for the frequency of the R_z mode, while the values of the R_x and R_y modes are slightly blue-shifted. The small changes in the frequency shifts reflect the weak influence of K⁺ on the rotation of its neighboring water molecules. This indicates a rather free orientational arrangement of the water molecules in the immediate surroundings of K⁺, even in some configurations belonging to the destabilizing region [14]. The results correspond to the experimental data concerning ion–water effects, in which the activation energies of approximately 4.6, 6.3 and 3.5 kcal mol⁻¹ were determined for rotational motion of a water molecule in liquid water and in the hydration spheres of Na⁺ and K⁺, respectively [27].

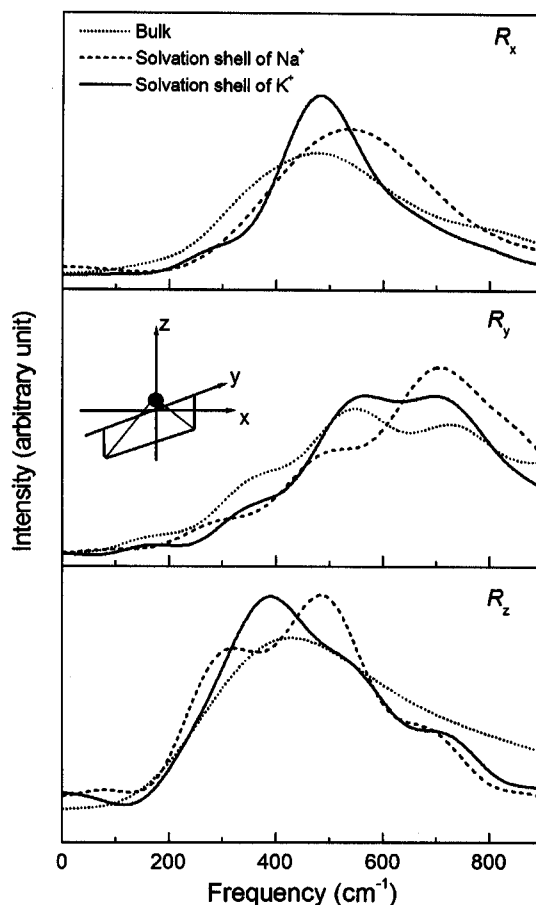


Fig. 2. Power spectra of the librational motions of water molecules in the first hydration shell of water itself and of ions, as obtained by the QM/MM simulations.

3.3. Vibrational motions

The three quantities Q_1 , Q_2 and Q_3 [25], calculated from the VACFs of hydrogens for describing symmetric stretching and bending and asymmetric stretching motions, respectively, are shown in Fig. 3. The frequencies of bulk water, evaluated by the classical MD method using BJH model for water, are also plotted for comparison. Obviously, the classical simulation overestimates the Q_2 mode by about 68 cm⁻¹ and underestimates the Q_1 and Q_3 modes by about 49 and 13 cm⁻¹, respectively, compared to the corresponding values obtained from the QM/MM simulation of pure water. In fact, the vibrational motions derived from the classical simulation are usually dominated by an analytical intramolecular potential, which has been fitted separately from the intermolecular potential to reproduce the experimental intramolecular motions. In contrast to this procedure, there is no separation between inter- and intramolecular interactions in the QM/MM method, instead, the vibrational motions are governed by the Newtonian equation of motion characterized by ab

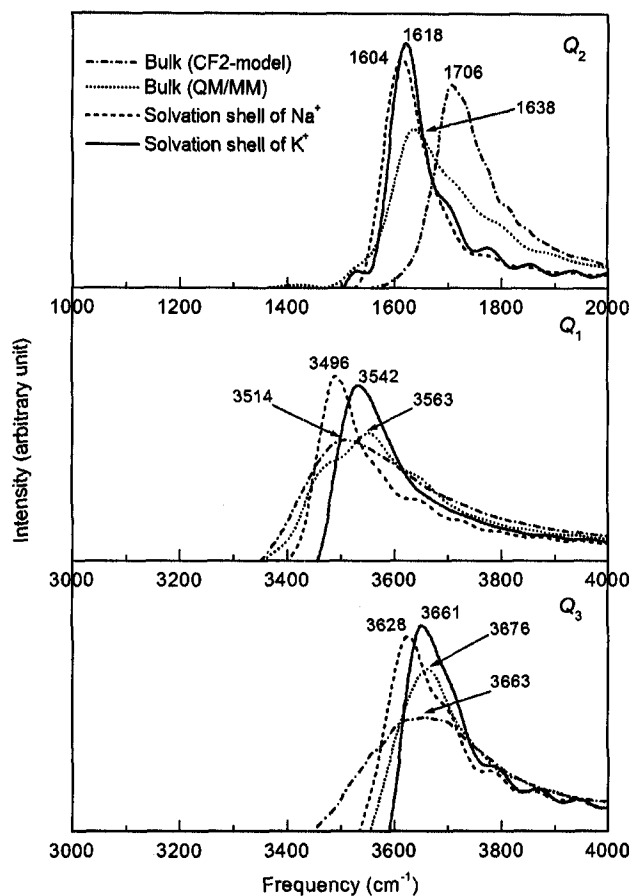


Fig. 3. Power spectra of the intramolecular vibrational motions of water molecules in the first hydration shell of water itself and of ions, as obtained by the QM/MM simulations.

initio forces. Therefore, it seemed of particular importance to carry out a compatible QM/MM simulation for pure water, in order to avoid any misinterpretation of

the frequency shifts due to the influence of different methodologies.

The vibrational frequencies of water obtained from various simulations and experiments are given in Table 1. In the QM/MM simulation of pure water, a peak maximum at $1638 \pm 3 \text{ cm}^{-1}$ is found for the symmetric bending, and peak maxima at 3563 ± 3 and $3676 \pm 2 \text{ cm}^{-1}$ are observed for symmetric and asymmetric stretching, respectively. In the hydration shell of Na^+ , the bending and stretching frequencies of water molecules are red-shifted. The red-shift for both bending and stretching modes can be ascribed due to the strong Na–O attraction and Na–H repulsion that elongate the O–H bond length and hence reduce the repulsion between the hydrogen atoms of water. For water molecules in the hydration shell of K^+ , only very slight red-shifts are observed for bending and stretching frequencies, indicating a rather negligible influence of K^+ on the structure of its surrounding water molecules. This can be seen as the weakness of the hydrated K^+ complex, which therefore produces an overall ‘structure-breaking’ effect in the solution.

3.4. Water exchange in the hydration sphere of ions

In all QM/MM simulations, water molecules in the hydration shell of water itself and in the hydration shell of the ions can exchange by any of the proposed ‘classical’ types, namely associative (A) and dissociative (D) as well as associative (I_a) and dissociative (I_d) interchange mechanisms [34]. During the simulation time of 12 ps, several water exchange processes are observed, involving a total of 32, 25 and 40 water molecules in pure water, and in hydrated Na^+ and K^+ , respectively.

Table 1

Comparison of the intramolecular vibrational frequencies of water obtained from various simulations and experiments

Phase	Frequency (cm^{-1})			Ref.
	Q_1	Q_3	Q_2	
Bulk	3514	3663	1706	This work, Pair potential
	3563	3676	1638	This work, QM/MM (LANL2DZ)
	3475	3580	1715	[25]
	3345 ^a	3445 ^a	1645 ^a	[28]
	3527	3527	1715	[29]
Hydration shell of Na^+	3489	3592	1695	This work, Pair potential
	3496	3628	1604	This work, QM/MM (LANL2DZ)
	3433	3538	–	[30]
	3437	3537	–	[31]
Hydration shell of K^+	3485	3576	1695	This work, Pair potential
	3542	3663	1618	This work, QM/MM (LANL2DZ)
Gas	3584 ^b	3741 ^b	1660 ^b	QM (LANL2DZ)
	3832 ^c	3943 ^c	1649 ^c	[32]
	3657 ^d	3756 ^d	1595 ^d	[33]

^a Experimental frequencies in liquid water.

^b Computed frequencies in gas-phase (scaled).

^c Simulation frequencies in gas-phase.

^d Experimental frequencies in gas-phase.

Table 2

Mean residence times of water molecules in bulk and in the hydration shell of ions, calculated using the direct method [35] in ps as a function of t^*

Solute/ion	CN	t_{sim}	$t^* = 0$ ps		$t^* = 0.5$ ps		$t^* = 2.0$ ps	
			N_{ex}^0	$\tau_{\text{H}_2\text{O}}^0$	$N_{\text{ex}}^{0.5}$	$\tau_{\text{H}_2\text{O}}^{0.5}$	$N_{\text{ex}}^{2.0}$	$\tau_{\text{H}_2\text{O}}^{2.0}$
H ₂ O	4.6	12.0	292	0.2	31	1.8	11	5.0
Na ⁺	5.4	12.0	146	0.4	27	2.4	10	6.5
K ⁺	8.0	12.0	295	0.3	48	2.0	17	5.6

N_{ex} is the number of accounted exchange events, t_{sim} the simulation time in ps and CN the average coordination number of the first hydration shell of water and ions.

The observed exchanges indicate that the K⁺ complex is not only more labile than the Na⁺ complex, but also than the solvent structure itself. Numerous species of hydrated K⁺ appear, varying from 6- to 10-fold coordinated complexes, as reported in the previous work [14].

Since detailed information on water exchange between hydration shell of ions and bulk is fundamental for the reactivity of the ions, the rates of water exchange processes in the bulk and at the ions were evaluated by means of mean residence times (MRT) of the water molecules in the first coordination shell. The mean lifetimes of a single water molecule in the first coordination sphere of Na⁺ and K⁺ have been roughly estimated on the basis of NMR measurement to be in the range of $<10^{-9}$ s [4]. In this work, the MRT values were calculated using a 'direct' method [35], being the product of the average number of water molecules in the hydration sphere with the duration of the QM/MM simulation, divided by the number of exchange events. For such weakly hydrated ions, like Na⁺ and K⁺ in which the peak minima of their RDFs are often broad, setting of hydration shell limits might lead to some possible ambiguities on the calculated MRT data, and thus the accuracy limit of the method is estimated as $\pm 10\%$ [35]. Based on the direct accounting and setting various time parameter t^* , the MRT values for pure water and for water molecules in the hydration shells of Na⁺ and K⁺ are listed in Table 2. The time parameter t^* has been defined as a minimum duration of the ligand's displacement from its original coordination shell. The choice of t^* is quite arbitrary, being a value of 2 ps as suggested by Impey et al. [6] while the $t^* = 0.5$ ps was proposed in accordance to the 'direct' method [35]. For all t^* , the order of $\tau_{\text{H}_2\text{O}}(\text{Na}^+) > \tau_{\text{H}_2\text{O}}(\text{K}^+) \approx \tau_{\text{H}_2\text{O}}(\text{H}_2\text{O})$ is observed. For the number of exchange events, however, a clear order of $\text{K}^+ > \text{H}_2\text{O} > \text{Na}^+$ is observed, in particular for $t^* = 0.5$ ps, which is the best choice for these hydrated ions [35] as it corresponds to the mean lifetime of hydrogen bonds. In comparison to pure water, it is obvious that water molecules in the hydration shell of Na⁺ are quite strongly attached to the ion, while those in the hydration sphere of K⁺ are very labile. These data, therefore, also confirm the 'structure-breaking' ability of the K⁺ ion. Compared to the experimental estimations, the real exchange rates for water

ligands in the first hydration shells of Na⁺ and K⁺ should be about two orders of magnitude higher, i.e., in the range of 10^{11} s⁻¹. In the case of K⁺, a less significant difference from the rate of pure water is seen, but the mobility of water molecules in the hydration shell of K⁺ is higher than in the pure solvent, recognizable from the larger amount of events (N_{ex}).

4. Conclusion

The QM/MM results concerning the dynamical properties of hydrated Na⁺ and K⁺ have provided data for the ultrafast dynamics of water ligands and thus more insight into the specific behavior of these two ions in water. Na⁺ obviously acts as a 'structure-making' ion which forms a rather strong hydrated complex, while K⁺ can be seen as a perturbation to its surrounding solvent environment, reflecting the experimentally observed 'structure-breaking' ability of this ion. The precise behavior of these two ions is of substantial interest especially for a correct interpretation on the functionality of specific ion channels in cell membranes [15,16]. Since the ions must lose their hydration water molecules to enter the channels, the selectivity of the channels is necessarily related to the hydration properties of the ions, and hence the difference in the dehydration ability between these two ions is an important, probably the decisive factor for the ability of the K⁺ channels to uptake K⁺ and not Na⁺ ions.

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