Water-Exchange Mechanism for Zinc(II), Cadmium(II), and Mercury(II) Ions in Water as Studied by Umbrella-Sampling Molecular-Dynamics Simulations

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Dedicated to Professor *André E. Merbach* in celebration of his 65th birthday

Umbrella-sampling molecular-dynamics simulations were performed to investigate the water-exchange reactions of zinc(II), cadmium(II), and mercury(II) ions in aqueous solution. The dissociation of a coordinating water molecule to the M–O distance at 3.34, 3.16, and 3.26 Å for Zn^{II}, Cd^{II}, and Hg^{II}, respectively, leads the system to a transition state. For Zn^{II}, the first hydration shell is occupied by five spectator water molecules in the transition state, indicating that the water-exchange reaction proceeds *via* a dissociative mode of activation. In contrast, the number of spectator water molecules of 5.85 and 5.95 for Cd^{II} and Hg^{II}, respectively, suggests an associative exchange for these larger metal ions. The average M–O distance of the spectator molecules is shortened by 0.06 Å for the dissociative exchange of Zn^{II}, while it is elongated by 0.04 and 0.03 Å for Cd^{II} and Hg^{II}, respectively. The water-exchange rate constants of 4.1×10^8, 6.8×10^8, and 1.8×10^9 s^{-1} are estimated for Zn^{II}, Cd^{II}, and Hg^{II}, respectively, at 298 K in terms of the transition-state theory based on the assumption of a transmission coefficient of unity.

1. Introduction. – Understanding the mechanisms of the solvent-exchange reactions of metal ions is fundamental to understanding the reactivity of metal ions in chemical and biological systems [1]. The simplest and most-common reaction is water exchange in aqueous solutions, where a coordinating water molecule in the first hydration shell is replaced with an entering water molecule in the second hydration shell. The water-exchange rate constant (k_{ex}) is experimentally defined as the inverse of the residence time of a specific water molecule in the first hydration shell. The water-exchange reaction is traditionally interpreted in terms of the classification of *Langford* and *Gray* [2], which describes two limiting mechanisms, *i.e.,* associative (A) and dissociative (D), and three intermediate categories, the associative interchange (I_a), interchange (I), and dissociative interchange (I_d) mechanisms. In the latter three, the importance of the contributions from bond breaking or bond-formation is conceptually used as a classification criterion. *Merbach* and co-workers introduced an experimental criterion for the classification in terms of the activation volume ($\Delta^{\ddagger}V^{\circ}$) [1][3]. The experimental and theoretical aspects of water-exchange reactions have been extensively reviewed [4][5].

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Molecular dynamics (MD) simulation techniques have been playing an important role in providing insight into water-exchange processes around some hydrated metal ions [6–9]. A significant problem when describing water-exchange processes is that the simulation period is generally limited to the order of nanoseconds, while water-exchange events on metal ions often occur on much longer time scales, especially for the transition metal ions. As a result, the probability of finding a system in the transition state is so low that the direct MD simulations cannot reliably calculate the relative *Gibbs* energies. One powerful approach to adequately sample high-energy, *i.e.*, a transition, states is the umbrella-sampling technique [10][11], which has been widely used to calculate the reaction profiles for chemical processes in solution [12–15]. In this technique, a suitable reaction coordinate is chosen, and a series of independent simulations are performed by spanning the relevant phase space of the reaction coordinate. A biasing potential is imposed to restrain the system to the desired point on the reaction coordinate, and the potential parameters are forced to change for a series of simulations along an assumed reaction coordinate. This results in the modification of the *Gibbs* energy distribution of the system according to the applied biasing potential, and the profile of the potential of mean force (PMF) for the chosen reaction coordinate is derived from the difference in the distribution for the system without the biasing potential. The most common and successful method to obtain the unbiased PMF profile is the weighted-histogram-analysis method (WHAM) [15–17], which is adopted in this study.

Water-exchange rate constants have been determined for a majority of transition metal cations by nuclear magnetic resonance (NMR) [5]. There are, however, several cations for which water-exchange rate constants are inaccessible by direct measurement, among which are zinc(II), cadmium(II), and mercury(II) ions. The d^{10} Zn^{II}, Cd^{II}, and Hg^{II} ions are diamagnetic, and NMR cannot be applied with success to study their very fast water-exchange rates. Some rate constants for the water exchange on the Zn^{II}, Cd^{II}, and Hg^{II} ions deduced from the ligand substitution studies are available (*vide infra*). In this study, umbrella-sampling MD simulations have been first applied to the water-exchange reaction of a series of Zn^{II}, Cd^{II}, and Hg^{II} ions, and their water-exchange mechanisms have been microscopically clarified.

2. Calculation Methods. – The umbrella-sampling MD simulations were performed in the *NVT* ensemble with a time step of 0.2 fs by means of a general predictor-corrector algorithm [18]. The density of the simulation box was set to the experimental value (0.997 g cm^{-3}) of pure water at 298 K. Periodic boundary conditions were applied and the reaction-field method was used to treat the long-range electrostatic potentials and forces. The MD simulations were performed for a system composed of one divalent metal ion and 499 water molecules with a two-body potential between the M^{II} ion and H_2O, including the three-body corrections reported in previous publications [19–22]. The CF 2 model was used for the intermolecular potential between the H_2O molecules [23] by combining the intramolecular potential developed by *Bopp et al.* [24].

The umbrella-sampling MD simulations were started from an equilibrated configuration of the standard MD simulation. A randomly chosen coordinated water molecule was moved between the first and second hydration shells under the influence of the umbrella potential (V_{umb}):

$$V_{\text{umb}}(R_{\text{O}}) = \frac{f}{2}(R_{\text{Ob}} - R_{\text{O}})^2 \quad (1)$$

where R_{O} is the instantaneous M–O distance between the M^{II} ion and the biasing water molecule, and f and R_{Ob} denote the force constant and the restrained M–O distance, respectively. A total of 15 independent simulations were carried out with different biasing parameters f and R_{Ob}. Configurations were collected for 200 ps for the data analyses after the equilibration period of 2 ps. The *Gibbs* energy distributions were determined for each simulation and were pieced together with the WHAM technique to calculate the unbiased probability distribution $<\rho(R_{\text{O}})>$. The PMF profile (W) as a function of R_{O} was then obtained by means of *Eqn. 2:*

$$W(R_{\text{O}}) = -k_{\text{B}}T \ln\langle\rho(R_{\text{O}})\rangle + C \quad (2)$$

where k_{B} is the *Boltzmann* constant, T is the temperature, and C is an arbitrary constant. A series of test simulations were carried out by changing the biasing water molecule, and it was confirmed that the PMF profile is independent of the choice. The $<\rho(R_{\text{O}})>$ values of the 15 simulations are depicted in *Fig. 1* together with the radial distribution function (RDF) obtained by the standard MD simulation for the Zn^{II} ion. Sufficient overlap of the $<\rho(R_{\text{O}})>$ values that cover the full R_{O} range is demonstrated in *Fig. 1*, ensuring that the chosen parameters, f and R_{Ob}, in the applied biasing potential permit reliable calculation of the PMF profile for the dissociation process of the coordinating water molecule.

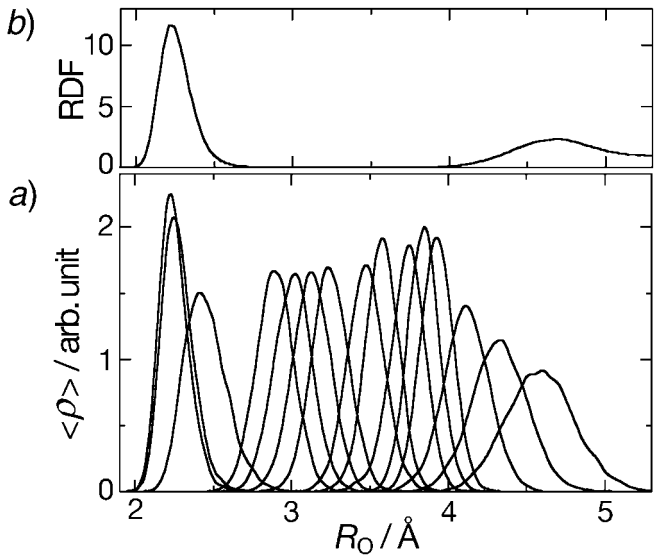

Fig. 1. a) Gibbs *energy distribution* $<\rho(R_{\text{O}})>$ *as a function of Zn–O distance for the biasing water molecule.* b) *Radial-distribution function of the Zn–O pair for the standard MD simulation without the biasing potential.*

3. Results and Discussion. – 3.1. *Potential of Mean Force and Rate Constants.* In *Fig. 2*, the PMF (*W*) profiles for the Zn^{II}, Cd^{II}, and Hg^{II} ions as a function of the M–O distance of a dissociating water molecule are compared. The vertical *Gibbs* energy is relative to that at the first minimum. The standard MD simulations without the umbrella-bias potential demonstrate that all of these M^{II} ions take the six-coordinate octahedral hydration structure in the ground state [19–22]. The M–O distance at the first minimum of PMF (R_O in the ground state in the *Table:* 2.23 Å for Zn^{II}, 2.35 Å for Cd^{II}, and 2.45 Å for Hg^{II}) is in good agreement with the average M–O distance for the first hydration shell observed by the standard MD simulations. At the second minimum of PMF, the dissociating water molecule is moved into the second hydration shell, and the six-coordinate octahedral first shell is recovered, indicating that the water-exchange reaction proceeds along the dissociation of a coordinating water molecule.

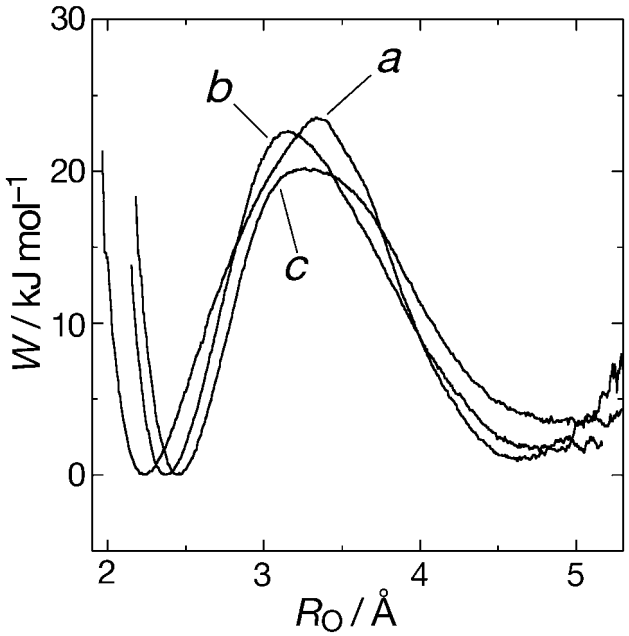

Fig. 2. *Potential of mean force* (PMF; *W*) *for the water-exchange processes of* a) *Zn^{II},* b) *Cd^{II}, and* c) *Hg^{II}*

The PMF profile (*Fig. 2*) shows the maximum at $R_O = 3.34$ Å for Zn^{II}, 3.16 Å for Cd^{II}, and 3.26 Å for Hg^{II} corresponding to the transition state of the water-exchange process. The *Gibbs* energies ($\Delta^{\ddagger}G^{\circ}$) determined from the PMF profiles are 23.6 (Zn), 22.6 (Cd), and 20.2 (Hg) kJ mol^{-1}. The value obtained for the Zn^{II} ion is consistent with the theoretical dissociative activation in the gas phase estimated by *Rotzinger* (27.3 kJ mol^{-1} [25]) and *Tsutsui et al.* (26.3 kJ mol^{-1} [26]), and is slightly greater than that estimated by *Hartmann et al.* (18–19 kJ mol^{-1} [27]). According to transition-state theory, in which the rate constant k_{ex} is expressed by *Eqn. 3*, the k_{ex} value is estimated to be 4.1×10^8 (Zn), 6.8×10^8 (Cd), and 1.8×10^9 (Hg) s^{-1} at 298 K, under the assumption that the transmission coefficient (κ) is unity.

Table 1. *Water-Exchange Rate Constants and Structural Parameters around the Metal Ion during the Activation Process Obtained by Umbrella-Sampling MD Simulation for Zn^{II}, Cd^{II}, and Hg^{II}*

Parameter	Metal Ion		
	Zn^{II}	Cd^{II}	Hg^{II}
k_{ex} [s^{-1}][a])	4.1×10^8	6.1×10^8	1.8×10^9
$\Delta^{\ddagger}G^{\circ}$ [kJ mol^{-1}][a])	23.6	22.6	20.2
R_O [Å] in the ground state	2.23	2.35	2.45
R_O [Å] in the transition state	3.34	3.16	3.26
ΔR_O [Å]	+1.11	+0.81	+0.81
N_S in the transition state	5.05	5.85	5.95
R_S [Å] in the transition state	2.17	2.39	2.48
$R_S - R_O$ [Å][b])	−0.06	+0.04	+0.03

[a]) At 298 K. [b]) The difference between R_S in the transition state and R_O in the ground state.

$$k_{ex} = \kappa \frac{k_B T}{h} \exp\left(-\frac{\Delta^{\ddagger} G^{\circ}}{RT}\right) \quad (3)$$

where h is the *Planck* constant, and R is the gas constant.

The water-exchange rate constant of the Zn^{II} ion is difficult to directly determine by experiments [28] and is usually derived from the second-order complexation rate constants, which are divided by the *Debye–Hückel* theory based equilibrium constant for outer-sphere association (the *Eigen–Wilkins* mechanism) [29]. Rate constants of *ca.* 3×10^7 [30], $(0.3-6) \times 10^8$ [31], and 5×10^7 s^{-1}[28] have been previously proposed, and the value of 4.1×10^8 s^{-1} obtained in this study is regarded to be consistent with the experimental estimates when considering the uncertainty of κ. The experimental obscurity is rather conspicuous for the Cd^{II} and Hg^{II} ions, and the k_{ex} value is reported to be almost 3×10^8 and 2×10^9 s^{-1}, respectively, on the basis of the complexation rate measured by the ultrasonic absorption technique [30]. The present umbrella-sampling MD simulations reproduce well the experimental order of the k_{ex} values for these divalent metal ions.

3.2. *Structural Properties of the Transition State.* The RDF and its running integration have been calculated on the basis of configurations with the R_O value within a certain range, and they are compared with those for the standard MD simulation in *Fig. 3* for the Zn–O pair at $R_O = 3.34 \pm 0.02$ Å, which almost corresponds to the transition state. A sharp spike with a peak area of 1 observed at around 3.34 Å denotes the biasing water molecule. *Fig. 3* shows that, in the transition state, a contracted first hydration shell is formed with five coordinating water molecules as spectators. The peak maximum of the spectator molecules is centered at 2.17 Å, and is 0.06 Å shorter than that (2.23 Å) in the ground state. The second-shell peak maximum (4.59 Å) is synchronously shortened by *ca.* 0.1 Å with a slightly reduced integration number.

In *Fig. 4*, the average number of spectator molecules (N_S) and the average M–O peak maximum (R_S) for the first hydration shell are plotted as a function of R_O for the Zn^{II}, Cd^{II}, and Hg^{II} ions. The N_S values are obtained from the first-shell plateau of the running integration of RDF, calculated by excluding the biasing water molecule. In the

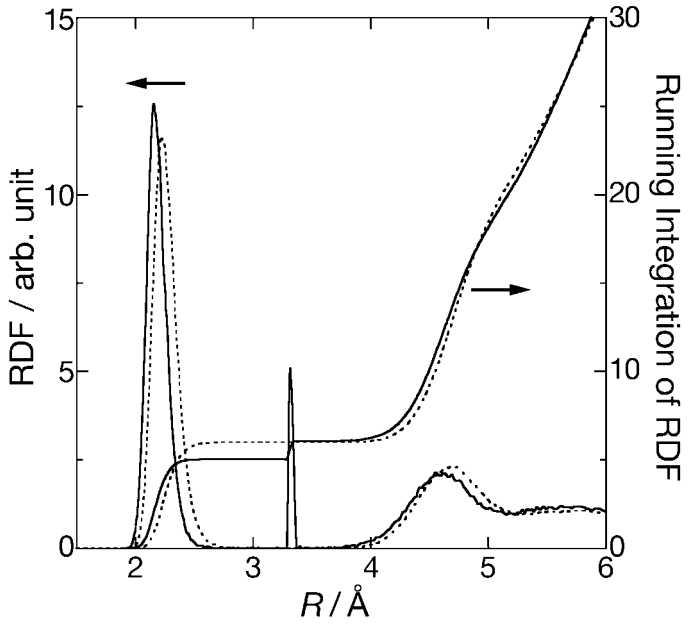

Fig. 3. *Radial-distribution function with running integration of the Zn–O pair for the configurations with the* R_O *value of 3.34 ± 0.02 Å.* The dotted lines correspond to the standard MD simulation.

case of the Zn^{II} ion, when R_O is smaller than 3.34 Å (the Zn–O distance at the transition state), N_S remains at a constant value of 5, while R_S gradually decreases from 2.23 to 2.17 Å, indicating relaxed repulsion between the spectator molecules and a decrease in the repulsive three-body effects. The increase in N_S from 5 to 6 at $R_O >$ 3.34 Å indicates the entrance of a water molecule from the second to first hydration shell, accompanied by the simultaneous elongation of R_S. The slightly smaller R_S value (2.22 Å) than the equilibrium distance (2.23 Å) at $R_O > 3.85$ Å is due to the potential applied to the biasing water molecule in the second hydration shell.

The variations in N_S and R_S for the Cd^{II} and Hg^{II} ions during the activation process are significantly different from those of the Zn^{II} ion. The increase in N_S occurs earlier, and this value reaches 5.85 and 5.95 in the transition state ($R_O = 3.16$ and 3.26 Å) for the Cd^{II} and Hg^{II} ions, respectively. The R_S value shows a much more-complex change, *i.e.*, it first decreases but then recovers and reaches a higher value in the transition state than in the ground state. The N_S values of nearly 6 clearly indicate that one other water molecule moves from the second hydration shell into the first shell in the transition state. The recovery and elongation of R_S is synchronous with the increase in N_S, indicating the interpenetration of an entering water molecule. The structural parameters during the activation process of the water-exchange reaction are summarized in the *Table* together with the estimated rate constants and the *Gibbs* energies of activation.

The structural properties of the transition state clearly demonstrate that the water-exchange reaction proceeds *via* the dissociative mode of activation for the Zn^{II} ion.

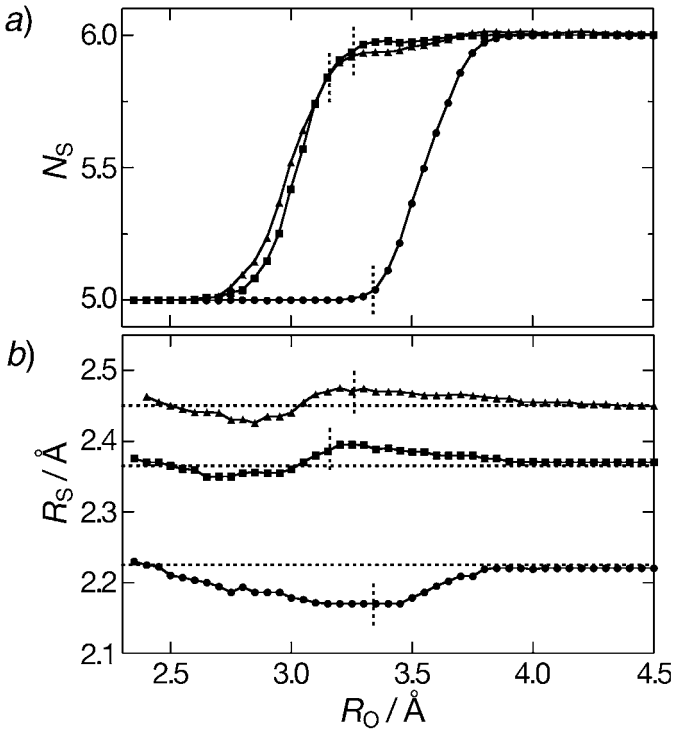

Fig. 4. *The values* a) N_S *and* b) R_S *for* Zn^{II} (–●–), Cd^{II} (–■–), *and* Hg^{II} (–▲–) *as a function of* R_O. The dotted vertical lines denotes the R_O distance at the transition state. The dotted horizontal line in *b*) represents the average M–O distance of the first hydration shell in the ground state.

Since an intermediate state is not apparently observed in the PMF profile (see *Fig. 2*), the present exchange reaction is considered to proceed *via* an I_d mechanism with very strong dissociative character in terms of the *Langford–Gray* criterion, because the N_S value is nearly 5 in the transition state. The experimentally observed independence of the complexation rate constants for a series of entering ligands suggests the dissociative mode of activation for the ligand substitution reactions [30][31]. Furthermore, according to the theoretical analyses of the transition state by means of *ab initio* molecular-orbital calculations [25–27], the five-coordinate species was found to be at a local minimum on the potential-energy surface in the gas phase. Moreover, the seven-coordinate species of Zn^{II} is indicated to be at the physically meaningless second-order saddle point [26]. The present umbrella-sampling MD simulations support the D mechanism for the Zn^{II} ion and suggest that a volumetric contraction is expected not only for the first hydration shell, which has a reduced coordination number, but also for the second hydration shell during the activation process. The reduction of the Zn–O distance consequently leads to a closer approach to the Zn^{II} center of the second-shell water molecules to maintain the effective H-bonding interactions between the first and second shells. In contrast to the Zn^{II} ion, the water-exchange reactions of the Cd^{II} and Hg^{II} ions are reasonably concluded to proceed *via* the associative mode of activation

consistent with the N_S value of nearly 6 in the transition state. A slightly smaller N_S value for the Cd^{II} ion (5.85) than the Hg^{II} ion (5.95) may suggest that the reaction of Cd^{II} is less associative than that of Hg^{II}. The mechanistic changeover from a dissociative to associative mechanism between Zn^{II} and Cd^{II} is clearly due to the ionic sizes of the metal ion series. The crowded first hydration shell of the smaller Zn^{II} ion requires the distant dissociation of the leaving water molecule, while the necessary elongation is much smaller for the Cd^{II} and Hg^{II} ions, having a very relaxed first hydration shell in the ground state. As a result, the R_O value in the transition state is rather smaller for Cd^{II} and Hg^{II} than Zn^{II} (see the *Table*).

4. Conclusions. – This study is the first application of umbrella-sampling MD simulations to the water-exchange dynamics of metal ions in aqueous solution. The analysis of the *Gibbs* energy profiles and structural parameters during the activation process of water exchange on the Zn^{II}, Cd^{II}, and Hg^{II} ions enabled us to conclude that the water-exchange mechanism of the Zn^{II} ion is of the D type, which is in agreement with experimental predictions, and that the larger Cd^{II} and Hg^{II} ions prefer the associative mode of activation due to the structurally relaxed first hydration shell in the ground state. Furthermore, the order of the rate constants for the series of Zn^{II}, Cd^{II}, and Hg^{II} ions obtained from the PMF profile, which strictly corresponds to the maximum limits because the transmission coefficient is assumed to be unity, is in accordance with the experimental results. These agreements demonstrate that the umbrella-sampling technique is a reliable tool to study ligand-exchange/substitution processes around metal ions, and, hence, opens the door to the microscopic evaluation of the reaction dynamics and energetics. Application of this method to other metal ions of interest is presently under study.

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