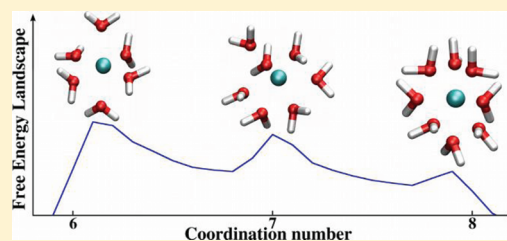


Free Energy Landscapes of Ion Coordination in Aqueous Solution

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ABSTRACT: We show how the fruitful concept of free energy landscape, as invoked in the description of complex biological systems, can be rather easily extended to build up a simple and accurate picture about solvent coordination around ions. This may represent a revealing key element for the qualitative and quantitative physical-chemical interpretation of a large number of phenomena occurring in solution, such as water exchange mechanisms, ion mobility, solvation dynamics, ion channel selectivity, and so on. In particular, using a computational approach rooted into molecular dynamics simulations and enhanced sampling techniques, we show how the free energy landscapes of ion coordination in solution can be very easily and accurately obtained in a number of illustrative examples.



INTRODUCTION

Aqueous solvation of simple ions plays a primary role in many physical, chemical, and biological processes, such as making and breaking of water structure,¹ catalytic activity,² and ion transport in solution and through membranes.³ Hence, by determining the detailed structural and thermodynamic characteristics of ion microsolvation, we may expect, in principle, to be able to interpret a number of physical-chemical phenomena at the atomistic level. To make just some examples, the solvent reorganization energy between ion redox couples (e.g., $\text{Cu}^+/\text{Cu}^{2+}$),⁴ the electrostriction effect in ionic solutions,⁵ or the water exchange mechanisms⁶ are all types of complex phenomena that could be better understood in terms of structural changes of ion coordination in solution.⁷ While different well-established and recently proposed experimental techniques, such as X-ray absorption and neutron diffraction spectroscopy,^{8,9} NMR¹⁰ and dielectric¹¹ relaxation measurements, thermodynamic measurements,^{6,12} and vibrational spectroscopy,^{13,14} do provide valuable information about ionic coordination and solvent exchange, quite often theoretical models are invoked for supporting such indirect experimental data. In this regard, most theoretical studies rely on high-level quantum mechanical (QM) calculations of simple molecular clusters,^{15,16} such as ions with a variable number of solvent molecules, and molecular dynamics (MD) simulations employing both force-field based^{17,18} and *ab initio*¹⁹ potentials. In particular, the use of molecular simulation methodologies seems well-suited to model ion solvation due to the proper inclusion, at the same time, of both finite-temperature and long-range solvent effects, which are usually missing in molecular cluster modeling. As an example, it has been shown how the combination of experimental EXAFS data and MD simulations can provide useful insights into the structural features of simple ions in water, possibly unraveling unexpected coordination configurations.^{20,21} Such a large amount of information gathered from extensive experimental and theoretical work is generally codified into a simple and static “molecular model” describing the

ion coordination in water in terms of a few structural parameters, such as, e.g., the average ion–water distance and the solvent coordination number.²² However, a static picture is often insufficient to satisfactorily explain relevant phenomena, such as the Na^+/K^+ membrane channel selectivity,³ the debated “Gadolinium break”²³ or the nonlinear solvent response induced by redox reactions.⁴ The reason is that, in most cases, ion coordination in solution is better regarded as a complex and dynamical phenomenon, involving different possible ion–water configurations weighted by their corresponding occurrence probability: in other words, what is required is some sort of free energy profile. In this regard, the most notable theoretical development has been recently achieved by the “quasi-chemical theory” by Pratt and co-workers, which is a molecular statistical mechanical theory fruitfully used to describe ion microsolvation.^{24–26} A major computational problem, however, concerns the effective sampling of the molecular configurations used to compute free energy contributions to ionic solvation.

Here, in analogy with the well-known concept of free energy landscape for protein folding,²⁷ we want to define a free energy landscape governing ion coordination in solution that is well-suited to describe aqueous solvation, as seen in the framework of “quasi-chemical theory”.²⁴ For convenience, we assume that such a free energy landscape depends only on one collective variable corresponding to the solvent coordination number around an ion, which is treated as a continuous measure for this purpose. Remarkably, we show how such a free energy landscape can be accurately and effectively evaluated by a MD simulation of an ion–solvent system using an enhanced configurational sampling approach, e.g., the metadynamics method.²⁸ As illustrative examples, we have considered aqueous solutions of Na^+ , Zn^{2+} , Hg^{2+} , Cd^{2+} , Ca^{2+} , and Gd^{3+} . While the detailed features of the reported free energy profiles may depend on the accuracy of the adopted

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analytical intermolecular potentials, we would like to point out that more refined evaluations are actually feasible by performing a sufficient number of short first-principle MD simulations. Therefore, in the following discussion we would like to focus primarily on the qualitative aspects of the obtained free energy landscapes.

METHODS

Accurate free energy changes, ΔA , corresponding to different molecular conformations or arrangements could be determined, in principle, from molecular simulations. Due to the high complexity of molecular systems in the condensed phase, i.e., large number of degrees of freedom, in most cases the main problem is related to the identification of only one or a few collective variables that may properly represent, within a simplified and effective picture, a given physical or chemical transformation. In an attempt to investigate in deeper detail the aqueous solvation structure around simple ions, we have assumed that the solvent coordination number, hereafter denoted as s , can be used to describe an ion–water system, as proposed elsewhere.^{29,30} Accordingly, we have defined the free energy landscape of ion coordination in solution, as $\Delta A = A(s)$. Further, we have expressed the coordination number, s , as a continuous measure by adopting a smooth switching function^{29,30} that, for each water molecule, gently goes from 1 to 0 around a given ion–oxygen cutoff distance, r_0 . Such a variable is evaluated as follows:

$$s = \sum_i^N [1 - 1/(1 + \exp(-a(r_i - r_0)))] \quad (1)$$

where the sum is extended over the whole number (N) of solvent molecules, r_i is the ion–oxygen distance of the i th molecule, and a is a parameter that controls the smoothness of the function. To ensure an extended sampling of the configurational space described by s , as well as an accurate evaluation of the free energy landscapes, the metadynamics technique²⁸ has been used to overcome possible free energy barriers. Briefly, the metadynamics method consists of growing up “on the fly”, i.e., during a molecular simulation, an adaptative potential that works against the most visited configurations of the chosen collective variable, so as to provide the system with enough energy to escape free energy wells and sample a more extended region of the phase space with respect to standard nonperturbed simulations. Accordingly, the free energy is recovered as the opposite of the added potential. In the following, we report results obtained from metadynamics simulations carried out in combination with some of the best available force-field based ion–water potentials to model the ionic coordination of a set of mono-, di-, and trivalent cations in aqueous solution.

MD simulations of ions in aqueous solution were carried out at room temperature according to an NVT ensemble under periodic boundary conditions using a time step of 2 fs. In each simulation, ion position was constrained at the center of a cubic box of 25 Å edge and solvated with 511 water molecules. Coulomb interactions were computed according to Ewald summation. The ion–water dispersion–repulsion intermolecular potentials, along with the water model, were chosen among some standard and purposely developed force fields as indicated in the following: Na^+ (SPC³¹ water) and Ca^{2+} (SPC water), GROMOS96 force field;³² Zn^{2+} (SPC/E³³ water), ref 18; Hg^{2+} (SPC/E water), ref 21; Cd^{2+} (SPC/E water), ref 20; Gd^{3+} (SPC/E water), ref 17. After some test simulations, the parameter a in eq 1 was set to 4.0 Å^{−1} in all cases, whereas the ion–oxygen cutoff distance, r_0 , was chosen on the basis of the first radial distribution function minimum (see Figure 3) and, for convenience, was set to 3.2 Å with the exception of the two largest ions (Ca^{2+} , Gd^{3+}), for which a value of 3.4 Å was selected. Note that the main features of the

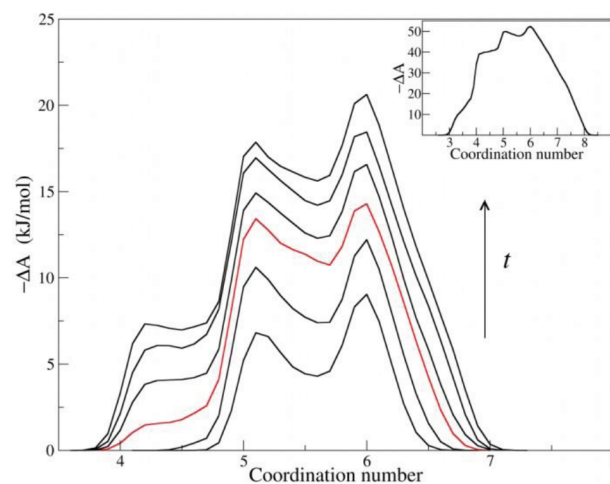


Figure 1. Free energy profile of Na^+ coordination in water as a function of time, evaluated at 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 ns time intervals, issuing from a metadynamics MD simulation. Red curve, free energy profile at 1.5 ns. In the inset, free energy profile after 20 ns.

computed free energy profiles were not very much affected by different reasonable choices of such parameters. To ensure a fast and stable convergence of the free energy landscapes, we have discretized the coordination number variable, $s \equiv s_p$, in bins of 0.1 Å width and added an integer number of Gaussian functions, $n(s_i)$, (with $\sigma = 0.1$ Å and height of 0.25 kJ/mol) on each bin center every 100 ps according to the corresponding residence time of the coordination measure, $t_r(s_i)$, divided by a given time threshold, t_s ($t_s = 1$ ps), that is, $n(s_i) = t_r(s_i)/t_s$.

RESULTS AND DISCUSSION

As an illustrative example of the proposed methodology, in Figure 1 we report the free energy profile of Na^+ in aqueous solution as computed from a metadynamics simulation at different time intervals, starting from 0.5 ns up to 3.0 ns in steps of 0.5 ns. Already after about 1.5 ns (red curve in Figure 1), the three most favorable water coordination numbers, namely $s = 6, 5$, and 4, do appear to be populated according to the corresponding relative free energies, $\Delta A(6 \rightarrow 5) = 1.2$ kJ/mol and $\Delta A(6 \rightarrow 4) = 12.8$ kJ/mol. Note that such free energy changes do not vary significantly when computed at later times, with an estimated small statistical error of about 1–2 kJ/mol.

In addition, such an error can be drastically reduced by averaging ΔA over several time intervals, thus leading to quite accurate free energy change evaluations. Moreover, by carrying on the simulation, the free energy landscape slowly grows, becoming higher and wider and so also accessing unfavorable coordination number configurations, such as 3 and 7 (see the inset in Figure 1 for ΔA at 20 ns). The same computational method has been applied to evaluate the free energy landscapes for water coordination around Zn^{2+} , Hg^{2+} , Cd^{2+} , Ca^{2+} , and Gd^{3+} . For convenience, in all cases we have reported ΔA as a function of the coordination number, as issuing from 5 ns metadynamics simulations. Results are shown in Figure 2. Before going into details, it is worth noting that the overall picture, in a very direct and unraveling way, provides a glimpse of ionic diversity, where each ion is characterized by its own “molecular fingerprint”, i.e., the free energy landscape, from which a number of quantitative and qualitative information can be readily extracted. Indeed, ions

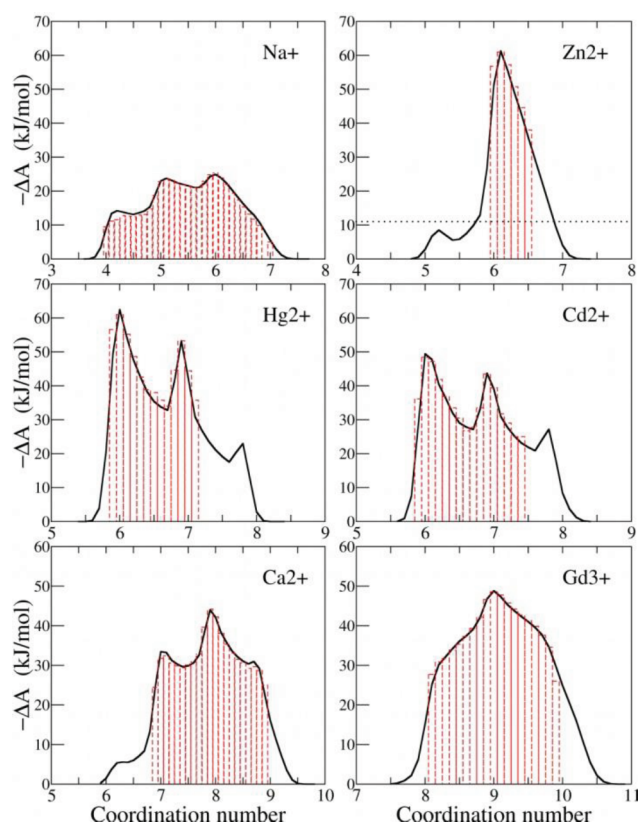


Figure 2. Free energy landscapes of ion coordination in water issuing from metadynamics MD simulations, after about 5 ns. Red bars, free energy profiles as obtained from standard very extended MD simulations, according to the expression $\Delta A = -kT \ln P(s)$, where $P(s)$ is the probability distribution of s , k is the Boltzmann constant, and T is the absolute temperature. The Zn^{2+} ΔA profile above the dashed line has been used as a “smoothing potential” to study water exchange in test simulations.

that usually show similar structural features in terms of radial distribution functions (see, e.g., Figure 3), now appear well distinguished by their own free energy profile, as in the case of Zn^{2+} and Hg^{2+} or Ca^{2+} and Gd^{3+} . For comparison, the same free energy landscapes have been evaluated from standard (nonmetadynamics) simulations expanded in time scale by one or 2 orders of magnitude (about 50 to 200 ns), as depicted by red bars in Figure 2. Remarkably, the ΔA profiles are in very good agreement in all cases, even if the solvent coordination space accessible to standard simulations is often quite limited. The divalent zinc ion shows an energetically and structurally very stable esa-coordinated water cluster in aqueous solution, as expected.

Interestingly, at higher ΔA values, a sort of disordered (not structured) 7-fold coordination comes into play. Therefore, examination of the Zn^{2+} free energy profile already suggests a possible interpretation about the water exchange mechanism: although the epta-coordinated ion–water cluster does not correspond to a stable local minimum (in agreement with QM calculations of $\text{Zn}^{2+}-(\text{H}_2\text{O})^7$ clusters^{34,35}), the water exchange may proceed through a so-called intermediate-associative mechanism, i.e., $s = 6 \rightarrow 7 \rightarrow 6$. This hypothesis has been confirmed in test simulations where the associative mechanism occurred in about 50% of the total solvent exchanges, when introducing a fixed potential, as determined from the metadynamics simulation,

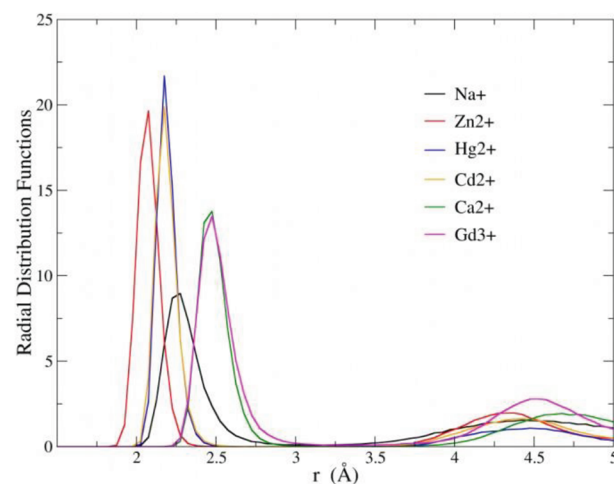


Figure 3. Radial distribution functions of the ion-oxygen atom pair issuing from standard MD simulations.

to disfavor the very stable esa-coordinated configuration (see Figure 2 and corresponding caption). Such a result is at variance with previous studies based on QM calculations of $\text{Zn}^{2+}-(\text{H}_2\text{O})_n$ clusters,^{34,35} which excluded the possibility of an associative pathway by suggesting instead a dissociative route involving a penta-coordinated configuration. In this regard, we suggest that a tailored study based on ab initio MD simulations, performed with a similar smoothing potential (see caption of Figure 2), could possibly shed light on the relative importance of the two competitive mechanisms. On the other hand, the Hg^{2+} and Cd^{2+} free energy landscapes show similar structural features, with a relatively small difference between the esa- and epta-coordinated clusters, $\Delta A(6 \rightarrow 7) = 8.9$ kJ/mol for Hg^{2+} and $\Delta A(6 \rightarrow 7) = 5.5$ kJ/mol for Cd^{2+} , and a less favorable octa-coordinated configuration. At the same time, the computed free energy profiles also provide an explanation about the difficulty of sampling both the 6- and 7-fold ion–water coordination by standard MD simulations, as reported in previous studies:^{20,21} the observed free energy barrier on going from $s = 6$ to 7 is up to 23 kJ/mol for Cd^{2+} and 30 kJ/mol for Hg^{2+} , thus predicting a negligible number of water rearrangements in the typical time scales of room-temperature simulations (pico- to nanoseconds). Coming to other ions, both Ca^{2+} and Gd^{3+} show a quite large and flexible first solvation sphere, although some substantial differences do emerge between the two ions. Calcium has at least three distinguishable ion–water coordinations, specifically $s = 7, 8$, and 9, that are accessible within 13 kJ/mol and characterized by well-defined local minima, whereas Gd^{3+} has an overall disordered first solvation shell with just one free energy minimum corresponding to the nona-coordinated ion configuration. Therefore, the free energy landscapes do show not only a different most probable water configuration, but also a more structured solvent arrangement of Ca^{2+} with respect to Gd^{3+} , which eventually may affect the chemistry of such ions. Note that the only appreciable difference issuing from the radial distribution functions of both ions is the integral of the first peak that provides a coordination number of about 8 for Ca^{2+} and 9 for Gd^{3+} .

In conclusion, the concept of free energy landscape usually encountered in biology has been extended to describe an elementary key process governing a large number of physical and chemical phenomena: the aqueous solvation of simple ions.

By performing MD simulations in combination with the metadynamics methodology, we have shown how it is possible to readily obtain effective thermodynamic pictures, namely the free energy profiles of ion coordination in solution, which are remarkably rich of information and well suited to characterize ionic diversity in an easy to accomplish and systematic way. While the discussion has been limited to some crucial qualitative features of the free energy profiles, we believe that the route is paved for a more accurate and comprehensive investigation of ion solvation and solvent exchange processes, possibly connected to the interpretation of an extended range of electrical, catalytic, and transport phenomena of interest in several biological and technological applications.

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REFERENCES

- (1) Marcus, Y. Effect of Ions on the Structure of Water: Structure Making and Breaking. *Chem. Rev.* **2009**, *109* (3), 1346–1370.
- (2) Richens, D. T. *The Chemistry of Aqua Ions: Synthesis, Structure, and Reactivity: A Tour through the Periodic Table of the Elements*; J. Wiley: New York, 1997.
- (3) Gouaux, E.; MacKinnon, R. Principles of Selective Ion Transport in Channels and Pumps. *Science* **2005**, *310* (5753), 1461–1465.
- (4) Blumberger, J. $\text{Cu}_{\text{aq}}^+/\text{Cu}_{\text{aq}}^{2+}$ Redox Reaction Exhibits Strong Nonlinear Solvent Response Due to Change in Coordination Number. *J. Am. Chem. Soc.* **2008**, *130* (47), 16065–16068.
- (5) Marcus, Y. Electrostriction, Ion Solvation, and Solvent Release on Ion Pairing. *J. Phys. Chem. B* **2005**, *109* (39), 18541–18549.
- (6) Helm, L.; Merbach, A. E. Inorganic and Bioinorganic Solvent Exchange Mechanisms. *Chem. Rev.* **2005**, *105* (6), 1923–1959.
- (7) Ohtaki, H.; Radnai, T. Structure and Dynamics of Hydrated Ions. *Chem. Rev.* **1993**, *93* (3), 1157–1204.
- (8) Lindqvist-Reis, P.; Munoz-Paez, A.; Diaz-Moreno, S.; Pattanaik, S.; Persson, I.; Sandstrom, M. The Structure of the Hydrated Gallium(III), Indium(III), and Chromium(III) Ions in Aqueous Solution. A Large Angle X-ray Scattering and EXAFS Study. *Inorg. Chem.* **1998**, *37* (26), 6675–6683.
- (9) Soper, A. K.; Neilson, G. W.; Enderby, J. E.; Howe, R. A. Neutron-Diffraction Study of Hydration Effects in Aqueous-Solutions. *J. Phys. C: Solid State Phys.* **1977**, *10* (11), 1793–1801.
- (10) Chizhik, V. I. NMR Relaxation and Microstructure of Aqueous Electrolyte Solutions. *Mol. Phys.* **1997**, *90* (4), 653–659.
- (11) Kaatz, U. The Dielectric Properties of Water in Its Different States of Interaction. *J. Solution Chem.* **1997**, *26* (11), 1049–1112.
- (12) Marcus, Y. The Standard Partial Molar Volumes of Ions in Solution. Part 4. Ionic Volumes in Water at 0–100 °C. *J. Phys. Chem. B* **2009**, *113* (30), 10285–10291.
- (13) Rudolph, W.; Brooker, M. H.; Pye, C. C. Hydration of Lithium Ion in Aqueous Solution. *J. Phys. Chem.* **1995**, *99* (11), 3793–3797.
- (14) Kropman, M. F.; Bakker, H. J. Dynamics of Water Molecules in Aqueous Solvation Shells. *Science* **2001**, *291* (5511), 2118–2120.
- (15) Erras-Hanauer, H.; Clark, T.; van Eldik, R. Molecular Orbital and DFT Studies on Water Exchange Mechanisms of Metal Ions. *Coord. Chem. Rev.* **2003**, *238*, 233–253.
- (16) Rotzinger, F. P. Treatment of Substitution and Rearrangement Mechanisms of Transition Metal Complexes with Quantum Chemical Methods. *Chem. Rev.* **2005**, *105* (6), 2003–2037.
- (17) Floris, F. M.; Tani, A. A Study of Aqueous Solutions of Lanthanide Ions by Molecular Dynamics Simulation with Ab Initio Effective Pair Potentials. *J. Chem. Phys.* **2001**, *115* (10), 4750–4765.
- (18) Chillemi, G.; D'Angelo, P.; Pavel, N. V.; Sanna, N.; Barone, V. Development and Validation of an Integrated Computational Approach for the Study of Ionic Species in Solution by Means of Effective Two-Body Potentials. The Case of Zn^{2+} , Ni^{2+} , and Co^{2+} in Aqueous Solutions. *J. Am. Chem. Soc.* **2002**, *124* (9), 1968–1976.
- (19) Raugei, S.; Klein, M. L. An Ab Initio Study of Water Molecules in the Bromide Ion Solvation Shell. *J. Chem. Phys.* **2002**, *116* (1), 196–202.
- (20) Chillemi, G.; Barone, V.; D'Angelo, P.; Mancini, G.; Persson, I.; Sanna, N. Computational Evidence for a Variable First Shell Coordination of the Cadmium(II) Ion in Aqueous Solution. *J. Phys. Chem. B* **2005**, *109* (18), 9186–9193.
- (21) Chillemi, G.; Mancini, G.; Sanna, N.; Barone, V.; Della Longa, S.; Benfatto, M.; Pavel, N. V.; D'Angelo, P. Evidence for Sevenfold Coordination in the First Solvation Shell of Hg(II) Aqua Ion. *J. Am. Chem. Soc.* **2007**, *129* (17), 5430–5436.
- (22) Marcus, Y. Ionic Radii in Aqueous Solutions. *Chem. Rev.* **1988**, *88* (8), 1475–1498.
- (23) Persson, I.; D'Angelo, P.; De Panfilis, S.; Sandstrom, M.; Eriksson, L. Hydration of Lanthanoid(III) Ions in Aqueous Solution and Crystalline Hydrates Studied by EXAFS Spectroscopy and Crystallography: The Myth of the “Gadolinium Break”. *Chem.—Eur. J.* **2008**, *14* (10), 3056–3066.
- (24) Rempe, S. B.; Pratt, L. R.; Hummer, G.; Kress, J. D.; Martin, R. L.; Redondo, A. The Hydration Number of Li^+ in Liquid Water. *J. Am. Chem. Soc.* **2000**, *122* (5), 966–967.
- (25) Rempe, S. B.; Asthagiri, D.; Pratt, L. R. Inner Shell Definition and Absolute Hydration Free Energy of K_{aq}^+ on the Basis of Quasi-Chemical Theory and Ab Initio Molecular Dynamics. *Phys. Chem. Chem. Phys.* **2004**, *6* (8), 1966–1969.
- (26) Pratt, L. R.; Asthagiri, D.; Dixit, P. D.; Merchant, S.; Paulaitis, M. E.; Rempe, S. B.; Varma, S. Ion Selectivity from Local Configurations of Ligands in Solutions and Ion Channels. *Chem. Phys. Lett.* **2010**, *485* (1–3), 1–7.
- (27) Bryngelson, J. D.; Onuchic, J. N.; Socci, N. D.; Wolynes, P. G. Funnels, Pathways, and the Energy Landscape of Protein Folding: A Synthesis. *Proteins: Structure, Function, and Bioinformatics* **1995**, *21* (3), 167–195.
- (28) Laio, A.; Parrinello, M. Escaping Free-Energy Minima. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99* (20), 12562–12566.
- (29) Blumberger, J.; Sprik, M. Free Energy of Oxidation of Metal Aqua Ions by an Enforced Change of Coordination. *J. Phys. Chem. B* **2004**, *108* (21), 6529–6535.
- (30) Chempath, S.; Pratt, L. R.; Paulaitis, M. E. Quasichemical Theory with a Soft Cutoff. *J. Chem. Phys.* **2009**, *130* (5), 054113.
- (31) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. In *Intermolecular Forces*; Pullman, B., Ed.; Reidel: Dordrecht, The Netherlands, 1981; pp 331–342.
- (32) van Gunsteren, W. F.; Billeter, S. R.; Eising, A. A.; Hunenberger, P. H.; Kruger, P.; Mark, A. E.; Scott, W. R. P.; Tironi, I. G. *Biomolecular Simulation: The GROMOS96 Manual and User Guide*; Hochschulverlag AG an der ETH Zürich: Zürich, 1996.
- (33) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. The Missing Term in Effective Pair Potentials. *J. Phys. Chem.* **1987**, *91* (24), 6269–6271.
- (34) Hartmann, M.; Clark, T.; van Eldik, R. Hydration and Water Exchange of Zinc(II) Ions. Application of Density Functional Theory. *J. Am. Chem. Soc.* **1997**, *119* (33), 7843–7850.
- (35) Rotzinger, F. P. Mechanism of Water Exchange for the Di- and Trivalent Metal Hexaqua Ions of the First Transition Series. *J. Am. Chem. Soc.* **1997**, *119* (22), 5230–5238.