J|A|C|S

A R T I C L E S

Hydration Structure and Free Energy of Biomolecularly Specific Aqueous Dications, Including Zn^{2+} and First Transition Row Metals

D. Asthagiri,[†] Lawrence R. Pratt,*,[†] Michael E. Paulaitis,[‡] and Susan B. Rempe[§]

Contribution from the Theoretical Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, Department of Chemical Engineering, The Johns Hopkins University, Baltimore, Maryland 21218, and Sandia National Laboratories, Albuquerque, New Mexico 87185

Received September 2, 2003; E-mail: lrp@lanl.gov

Abstract: The hydration of some of the alkaline earth divalent metal cations and first row transition metal cations is considered within the quasi-chemical theory of solutions. Quantum chemical calculations provide information on the chemically important interactions between the ion and its first-shell water molecules. A dielectric continuum model supplies the outer-shell contribution. The theory then provides the framework to mesh these quantities together. The agreement between the calculated and experimental quantities is good. For the transition metal cations, it is seen that the ligand field contributions play an important role in the physics of hydration. Removing these bonding contributions from the computed hydration free energy results in a linear decrease in the hydration free energy along the period. It is precisely such effects that molecular mechanics force fields have not captured. The implications and extensions of this study to metal atoms in proteins are suggested.

I. Introduction

Many biological processes depend on the presence of metal ions as cofactors or as active participants (for example, refs 1−3). Biologically significant metals include[4] the alkali metals Li, Na, and K; the alkaline earth metals Mg and Ca; and transition metals, notably Fe, Mn, and Cu. In addition, molecules designed to contain metal ions as key components are becoming increasingly prevalent as diagnostic or therapeutic agents to treat a wide variety of diseases and metabolic disorders.[5] Zinc, for example, is critically important in the gene-regulatory zinc-finger proteins[6,7] and is the principal target of the molecular theory of this report.

Here we apply quasi-chemical theory to the hydration of divalent ions of biophysical significance. At the same time, we collect recent results, not previously published, of quasi-chemical treatments of other common ions. An important issue for clarification as quasi-chemical theory and *ab initio* molecular dynamics calculations get worked out, is that the hydration of these common ions in aqueous solution is typically idiosyncratically different than that assumed in classical simulation models.

As those idiosyncratic details are better established, it is expected that classical simulation models will be revised to describe better the chemical details of ion hydration.

Part of the challenge of statistical mechanical treatments of these ion-hydration problems is that ion−water interactions are strong on a thermal energy scale; this is exacerbated for divalent ions compared to monovalent ions. Those interactions are as strong as chemical bonds, are responsible for chemical changes such as hydrolysis,[8,9] and otherwise exhibit chemical intricacies. The environment of a protein, with a richer suite of ligating possibilities, offers more complexity yet. Nevertheless, an appropriate characterization of metal−protein interactions can begin with a molecular description of ion hydration in an aqueous milieu.

A satisfactory molecular-scale description in aqueous electrolyte solutions, thus, should include appropriate treatment of both chemical and thermal energy scales. Recognizing the strong ion−water interactions, intuitive approaches have treated ion hydration by optimizing successive shells of water molecules, assuming convergence to a bulk-like water structure around the ion, and to the corresponding hydration thermodynamics. Aside from the drastic approximations implied for the temperature and pressure variations of ion-hydration thermodynamics, this approach does not solely yield the absolute hydration free energy, but also includes an approximate potential of the phase.[10] Those cluster treatments do include chemical interactions appropriately,

[†] Los Alamos National Laboratory.
[‡] The Johns Hopkins University.
[§] Sandia National Laboratories.
(1) Karlin, K. D. *Science* **1993**, *261*, 701.
(2) O'Halloran, T. V. *Science* **1993**, *261*, 715.
(3) Finney, L. A.; O'Halloran, T. V. *Science* **2003**, *300*, 931.
(4) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. *Molecular Biology of the Cell*; Garland Science: New York, 2002.
(5) Thompson, K. H.; Orvig, C. *Science* **2003**, *300*, 936.
(6) Berg, J. M.; Shi, Y. *Science* **1996**, *271*, 1081.
(7) Berg, J. M.; Godwin, H. A. *Annu. Rev. Biophys. Biomol. Struct.* **1997**, *26*, 357.

(8) Martin, R. L.; Hay, P. J.; Pratt, L. R. *J. Phys. Chem. A* **1998**, *102*, 3565.
(9) Asthagiri, D.; Pratt, L. R. *Chem. Phys. Lett.* **2003**, *371*, 613.
(10) Asthagiri, D.; Pratt, L. R.; Ashbaugh, H. S. *J. Chem. Phys.* **2003**, *119*, 2702.
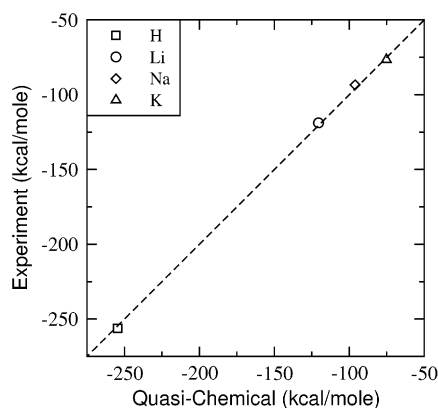
Figure 1. 1. Hydration free energy of monovalent cations calculated within the quasi-chemical framework. The most probable coordination numbers are as in Table 1. For the dielectric calculations, a cavity of radius 1.9, 2.3, and 2.7 Å was centered on Li^+, Na^+, and K^+, respectively. For H^+, a cavity of radius 1.172 Å was used. Small changes in these values do not change the computed result substantially. This is an example of the variationally constrained character of the theory. The experimental results are from ref 34.

that is, quantum mechanically, and are usually coupled with a dielectric continuum model for the remaining medium (for example, ref 11). In ref 11, it was argued that the inclusion of a second solvation shell is necessary for divalent and trivalent cations. Closer scrutiny of that work[8] emphasized that a lack of a statistical mechanical foundation limited those approaches, but that effort has now led to important progress.

Indeed, the recently developed molecular quasi-chemical theory of solutions has achieved a level of sophistication that makes it well-suited for such calculations.[8–10,12–24] This approach was designed[8,13,20] to subsume the intuitive cluster approaches indicated above, but was founded on well-established principles of statistical mechanics. Approximations necessary for practical calculations are then readily identified for scrutiny and improvement.

In the report below, we present the bare essentials of the theoretical methods we use (see, for example, refs 14, 20, 23). We then apply it to the hydration of Mg^{2+}, Ca^{2+}, the divalent transition metal ions from Mn to Cu, and to Zn^{2+}. For completeness, we also present (Figure 1) comparable results from studies on the monovalent ions H^+, Li^+, Na^+, and K^+

(11) Li, J.; Fisher, C. L.; Chen, J. L.; Bashford, D.; Noodleman, L. *Inorg. Chem.* **1996**, *35*, 4694.
(12) Hummer, G.; Pratt, L. R.; García, A. E. *J. Am. Chem. Soc.* **1997**, *119*, 8523.
(13) Pratt, L. R.; LaViolette, R. A. *Mol. Phys.* **1998**, *94*, 909.
(14) Pratt, L. R.; Rempe, S. B. In *Simulation and Theory of Electrostatic Interactions in Solution. Computational Chemistry, Biophysics, and Aqueous Solutions*; Vol. 492 of *AIP Conference Proceedings*; Pratt, L. R., Hummer, G., Eds.; American Institute of Physics: Melville, NY, 1999; pp 172–201.
(15) Hummer, G.; Garde, S.; García, A. E.; Pratt, L. R. *Chem. Phys.* **2000**, *258*, 349.
(16) Rempe, S. B.; Pratt, L. R.; Hummer, G.; Kress, J. D.; Martin, R. L.; Redondo, T. *J. Am. Chem. Soc.* **2000**, *122*, 966.
(17) Rempe, S. B.; Pratt, L. R. *Fluid Phase Equilib.* **2001**, *183–184*, 121.
(18) Pratt, L. R.; LaViolette, R. A.; Gomez, M. A.; Gentile, M. E. *J. Phys. Chem. B* **2001**, *105*, 11662.
(19) Grabowski, P.; Riccardi, D.; Gomez, M. A.; Asthagiri, D.; Pratt, L. R. *J. Phys. Chem. A* **2002**, *106*, 9145.
(20) Paulaitis, M. E.; Pratt, L. R. *Adv. Protein Chem.* **2002**, *62*, 283.
(21) Asthagiri, D.; Pratt, L. R.; Kress, J. D.; Gomez, M. A. HO⁻(aq) Hydration and Mobility (http://www.arxiv.org/abs/physics/0211057). Technical report, Los Alamos Natl. Lab. LA-UR-02-7006, 2002.
(22) Pratt, L. R.; Ashbaugh, H. S. *Phys. Rev. E* **2003**, *68*, 021505.
(23) Asthagiri, D.; Pratt, L. R.; Kress, J. D. *Phys. Rev. E* **2003**, *68*, 041505.
(24) Asthagiri, D.; Pratt, L. R.; Kress, J. D.; Gomez, M. A. *Chem. Phys. Lett.* **2003**, *380*, 530.

and the divalent ion Be^{2+}.[9] The Supporting Information collects information on hydration numbers and solution structure that affects the present thermodynamic calculations. For Li^+, Na^+, K^+, and Be^{2+}, we have the density distribution of water around the ion from *ab initio* molecular dynamics simulations. For Li^+ and Be^{2+}, the solvation shell is sharply defined physically, and, therefore, the coordination number, which is a fundamental quantity in the quasi-chemical theory, is unambiguously established. For Na^+ and K^+, the density distributions are progressively less sharply defined physically. Yet, as will be seen, a satisfactory coordination number can be defined, and it leads to a reasonable estimate of the hydration free energy. The agreement with experimentally offered hydration free energies for both mono- and divalent cations is fair. More primitively, the trends in relative hydration free energies are correctly described.

For the transition metals, a principal focus of this work, the hydration free energies do not show a simple, monotonic trend across the period. This is also seen experimentally (for example, refs 25, 26). This lack of monotonicity is a consequence of the subtle interplay of electron distribution in orbitals and changes in the physical size of the cation. It is the latter quantity that is readily modeled in classical simulations. The former, for transition metals, involves the consequences of the splitting of d-orbitals in the field due to the surrounding ligands. The particular distribution of the electrons in these split d-orbitals has an energetic stabilizing effect, the ligand field stabilization energy (LFSE). Subtracting the LFSE readily gives the expected monotonic decrease in the hydration free energy across the period. These ligand field effects affect the differential binding of transition metal cations and Zn^{2+} to zinc-finger proteins. Our ability to describe these effects theoretically, in bulk solution, gives us a basis for pursuing studies on metal−protein systems.

II. Methods: Quasi-Chemical Approximation (QCA)

In the quasi-chemical theory,[13,14,20] the region around the solute of interest is partitioned into inner- and outer-shell domains. In the present study, the inner shell, where chemical effects are important, is treated quantum mechanically. The outer-shell contributions have been assessed using a dielectric continuum model. In principle, a variational check of this partition is available.[17,23] It has been argued that when the variational check of the partitioning is satisfied, the inevitable approximations are well-balanced.

The inner-shell reactions are

$$M^{q+} + nH_2O \rightleftharpoons M[H_2O]_n^{q+}$$
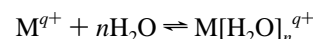
The free energy change for these reactions was calculated using the Gaussian suite of programs.[27] The clusters were geometry optimized in the gas phase using the B3LYP hybrid density functional[28] and the 6-31+G(d,p) basis set. Frequency calculations confirmed a true minimum, and the zero point energies were computed at the same level of theory. Single point energies were calculated with the 6-311+G(2d,p) basis set. For the open-shell transition metals, the unrestricted formalism was used. (Using the unrestricted formalism for the closed-shell systems

(25) Orgel, L. E. *An Introduction to Transition-Metal Chemistry: Ligand-field Theory*; Methuen & Co.: London, 1960.
(26) Shriver, D. F.; Atkins, P. W.; Langford, C. H. *Inorganic Chemistry*; W. H. Freeman and Co.: New York, 1990.

leads to insignificant changes in the energy.) The transition metal ions and their water complexes were modeled in the high-spin state. Thus, we have $Sc^{2+}(d^1)$, $Ti^{2+}(d^2)$, $V^{2+}(d^3)$, $Cr^{2+}(d^4)$, Mn^{2+}-(d^5), $Fe^{2+}(d^6)$, $Co^{2+}(d^7)$, $Ni^{2+}(d^8)$, and $Cu^{2+}(d^9)$ in the high-spin states. [Note that water is typically a weak-field ligand (for example, refs 25, 29) and a high-spin complex is expected. The small magnitudes of the field splitting[25,29] validate this choice for the metals studied in this work.]

For estimating the outer-shell contribution, the ChelpG method[30] was used to obtain partial atomic charges. With the radii set developed by Stefanovich et al.,[31] surface tessera were then generated,[32] and the hydration free energies of the clusters were calculated using a dielectric continuum model.[33] With this information and the binding free energies for the chemical reactions, a primitive quasi-chemical approximation to the excess chemical potential of the metal ion M(aq) in water is

$$\beta\mu_M^{ex} \approx -\ln[\tilde{K}_n \rho_{H_2O}{}^n] \tag{1}$$

where $\tilde{K}_n = K_n^{(0)} \exp[-\beta(\mu_{M(H_2O)_n^+}^{ex} - n\mu_{H_2O}^{ex})]$. $K_n^{(0)}$ is the equilibrium constant for the reaction in an ideal gas state, n is the most probable hydration number, and $\beta = 1/k_BT$. The density factor ρ_{H_2O} appearing in eq 1 reflects the actual density of liquid water, and its effect is included by a replacement contribution of $-nk_BT \ln(\rho_{H_2O}/\rho_0) = -nk_BT \ln(1354)$, where $\rho_{H_2O} = 1$ gm/cm^3, and $\rho_0 = 1$ atm/RT. (A discussion on standard states and this replacement contribution can be found in ref 19.)

The more general theory involves a logarithm of a sum over inner-shell compositions, n in eq 1. Yet limiting that sum to the most probable n makes a negligible difference in these situations (for example, ref 24). There are two reasons for that. The first is succeeding terms in such a sum reflect chemical energy differences. A slight advantage in energy on a chemical scale for one term means that it dominates all others on a thermal energy scale. The second reason is only a finite, and small, number of terms are contained in the full sum, so there is not a chance to accumulate a significant entropic contribution in that way. For example, if two terms in the general sum were precisely the same, the present neglect would entail an error in the free energy of $k_BT \ln 2$, which is a negligible magnitude here. A more significant entropic contribution is the temperature dependence of the densities (ρ_{H_2O}) that are displayed in eq 1. The same point applies to pressure−volume effects. It should be emphasized, however, that eq 1 does assume primitive approximations for outer-shell contributions, and a broader investigation of those approximations remains for future work.

(27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.2; Gaussian, Inc.: Pittsburgh, PA, 1998.
(28) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(29) Figgis, B. N.; Hitchman, M. A. *Ligand Field Theory and Its Applications*; Wiley-VCH: New York, 2000.
(30) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.
(31) Stefanovich, E. V.; Truong, T. N. *Chem. Phys. Lett.* **1995**, *244*, 65.
(32) Sanner, M. F.; Spehner, J.-C.; Olson, A. J. *Biopolymers* **1996**, *38*, 305.
(33) Yoon, B. J.; Lenhoff, A. M. *J. Comput. Chem.* **1990**, *11*, 1080.

Table 1. Free Energy $\Delta G°$ for Forming the Defined Cluster from One Cation and n Water Molecules in the Ideal Gas State[a]

cluster	$\Delta G°$	$\mu^\star$	μ	μ_{expt}
H_2O		−7.7		
$H[H_2O]_2^+$	−183.9	−77.5	−254.6	−254.3
$Li[H_2O]_4^+$	−70.1	−64.0	−120.5	−116.9
$Na[H_2O]_4^+$	−47.7	−62.0	−96.1	−91.5
$K[H_2O]_4^+$	−30.1	−58.7	−75.2	−74.6
$Be[H_2O]_4^{2+}$	−350.4	−230.2	−567.0	−576.5
$Mg[H_2O]_6^{2+}$	−254.2	−199.5	−433.3	−441.2
$Ca[H_2O]_6^{2+}$	−183.8	−191.3	−354.7	−364.0
$Sc[H_2O]_6^{2+}$	−215.2	−195.2	−390.0	
$Ti[H_2O]_6^{2+}$	−233.1	−196.8	−409.5	
$V[H_2O]_6^{2+}$	−253.4	−198.0	−431.0	
$Cr[H_2O]_6^{2+}$	−251.7	−198.0	−429.3	−446.4
$Mn[H_2O]_6^{2+}$	−240.5	−196.7	−416.8	−424.9
$Fe[H_2O]_6^{2+}$	−261.2	−198.5	−439.3	−443.6
$Co[H_2O]_6^{2+}$	−272.5	−199.3	−451.4	−461.3
$Ni[H_2O]_6^{2+}$	−292.6	−200.6	−472.6	−479.4
$Cu[H_2O]_6^{2+}$	−292.9	−201.1	−473.6	−483.7
$Zn[H_2O]_6^{2+}$	−279.2	−199.3	−458.1	−471.1

[a] $\mu^\star$ is the excess chemical potential of the cluster obtained via the dielectric model. μ is the quasi-chemical approximation of the hydration free energy of the corresponding metal ion. μ_{expt} is the experimental value from ref 34, which has been adjusted to correspond to a transfer from 1 M (ideal gas) to 1 M (ideally diluted) solution.

We will denote this primitive quasi-chemical approximation by QCA.

A further aspect of the theory is its variational character (for example, refs 17, 23). One consequence of this character is the computed excess chemical potential of the metal ion is insensitive to modest changes in the radii parameters used in the dielectric continuum calculations. The general efficacy of this simple QCA for ion-hydration free energies has been the subject of validation calculations utilizing classical simulations with conventional force fields; for example, see ref 10.

III. Absolute Hydration Free Energies

Table 1 lists the free energy of forming the defined cluster in the ideal gas state and the excess chemical potential of those clusters.

This information, the excess chemical potential of water, and the proper account of standard states readily gives the excess chemical potential of the cations. Consideration of the chemical contribution to the hydration is cation-specific. For the transition metals, the contribution is about 60%; for the alkali metals, this ranges from about 40% (for K^+) to 60% (for Li^+); and for the alkaline earth metals, it ranges from about 50% (for Ca^{2+}) to about 60% (for Be^{2+}). Not surprisingly, for H^+, local chemistry accounts for about 70% of the hydration free energy. Although details of the solvent structure around the cation do influence the net hydration free energy, the local chemical effects dominate the hydration phenomena.

Figures 1−3 compare the calculated hydration free energies to the values offered in ref 34. Several points need emphasis, lest the good agreement mask the challenges in the physics of cation hydration: (a) the experimentally suggested hydration free energies likely have significant uncertainties, and (b) they also very likely include some aspects of the potential of the phase, a quantity distinct from the absolute hydration of the ion of first interest. Issues relating to the potential of the phase have been discussed recently.[10] Because the dielectric models

(34) Marcus, Y. *Ion Solvation*; Wiley: London, 1985.
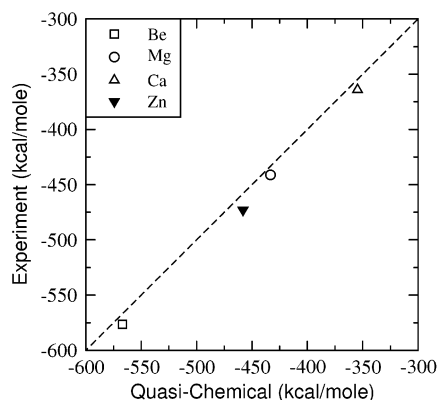
Figure 2. Hydration free energy of alkaline earth metal cations calculated within the quasi-chemical framework. Zn is included to depict better its relation to the biologically important closed-shell cations Mg^{2+} and Ca^{2+}. A cavity of radius 2.2 Å defined the inner shell. Small changes in these values do not change the computed result substantially. The rest is as in Figure 1.
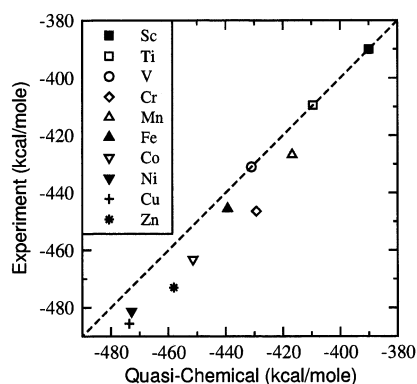
Figure 3. Hydration free energy of first row transition metal cations calculated within the quasi-chemical framework. A cavity of radius 2.2 Å defined the inner shell. Experimental estimates are not available for Sc^{2+}, Ti^{2+}, and V^{2+}, and for graphing purposes, the theoretical value is assumed for experiments as well. The rest is as in Figure 1.

are parameterized[31] against similar experimental values, they also include this potential of the phase. Recent studies[10,35] suggest that this potential is negative and about -10 kcal/(mol e) in value. Further, as shown in ref 10, a more sophisticated model for outer-shell contributions can give results that are in good agreement with the unambiguously determined solvation free energies of neutral pairs. However, the dielectric model is still worthy in describing the relative free energy of cation hydration correctly. Thus, the more distinguishing and nontrivial aspect of Figures 1−3 is the correct description of experimental trends for both the monovalent and the divalent cations. This is especially important in understanding, for example, competition experiments of two different metals binding to a given protein (for example, ref 7).

(A) Ligand Field Effects. The transition metal ions studied in this paper are all predicted to be hexa-hydrated, and the structure of these clusters shows nearly octahedral symmetry. (Note that we avoided imposing symmetry in our geometry optimizations, and clusters involving Cr^{2+} and Cu^{2+}, most notably, show Jahn−Teller distortion effects, as expected, ref 25.) From the theory of ligand fields, it is known that in the octahedral field the metal d-orbitals split into a lower t_{2g} (set of three orbitals) and an upper e_g (set of two orbitals).[25,29] The

(35) Sokhan, V. P.; Tildesley, D. J. *Mol. Phys.* **1997**, *92*, 625.

Table 2. Hydration Free Energy μ of the Cations[a]

metal ion	μ	S	LFSE	Δ	μ'
Ca	−354.7	0			−354.7
Sc	−390.0	$1/2$	$-3/5$		
Ti	−409.5	1	$-4/5$		
V	−431.0	$3/2$	$-6/5$	36.0	−387.8
Cr	−429.3	2	$-3/5$	39.7	−405.5
Mn	−416.8	$5/2$	0	22.3	−416.8
Fe	−439.3	2	$-2/5$	29.7	−427.4
Co	−451.4	$3/2$	$-4/5$	26.6	−430.1
Ni	−472.6	1	$-6/5$	24.3	−443.4
Cu	−473.6	$1/2$	$-3/5$	36.0	−452.0
Zn	−458.1	0			−458.1

[a] S is the net spin on the cations. LFSE is the ligand field stabilization energy in terms of Δ. Spectroscopic estimates of Δ are from ref 25. μ' is the hydration free energy with the LFSE removed. All energies are in kcal/mol. Note that experimental values for Δ for Sc^{2+} and Ti^{2+} are unavailable in ref 25 (or ref 29).

splitting between these levels can be characterized by Δ, the ligand field splitting parameter. Because we know how the electrons distribute among the levels, we can compute the ligand field stabilization energy (LFSE). Briefly, the nominal energy of the d-orbital prior to introduction in the ligand field is given a value of zero. The lower three t_{2g} orbitals each get a weight of $-2/5$, and the upper gets a weight of $3/5$. (See also ref 25.) Some examples help clarify this concept. For Mn^{2+}, with five-half-filled orbitals, the ligand field stabilization (as a fraction of Δ) is $-2/5 \times 3 + 3/5 \times 2 = 0$; for Fe^{2+}, the LFSE is $-2/5 \times 4 + 3/5 \times 2 = -2/5$; and for Zn^{2+}, the LFSE is $-2/5 \times 6 + 3/5 \times 4 = 0$ (Table 2).

These Δ values can, in principle, be calculated from quantum chemical calculations. For high-spin systems, this, however, is a separate area of research, and realistic calculations are challenging, especially for protein systems that are of primary interest (R. L. Martin, personal communications). We have therefore taken spectroscopic values of the splitting parameter. We must emphasize that ligand field stabilization is not solely responsible for stabilizing influences. Jahn−Teller effects, most clearly revealed for Cr^{2+} and Cu^{2+}, also contribute to the stability. (For example, for the hexa-hydrated Cr^{2+} and Cu^{2+}, four of the bonds to water are shorter and two are longer as is expected for these ions in an octahedral environment.)[25] However, LFSE is expected to be the principal stabilizing component.

Table 2 lists the hydration free energies of the cations, the ligand field stabilization contributions, and the hydration free energy with the LFSE removed. (Observe that there is no ligand field stabilization for $Mn^{2+}(d^5)$ and $Zn^{2+}(d^{10})$.) Table 1, Table 2, and Figure 4 emphasize the fact that much of the discrimination between the transition metal ions comes from the local chemical effects.

Figure 4 highlights the local chemical (or bonding) effect in the hydration of the transition metal ions. Removing the ligand field stabilization term from the computed hydration free energies reveals a clear monotonic decrease in the hydration free energy as we proceed along the period. This is expected because the atomic number and the electronegativity increase[25] and the atomic radius is expected to decrease (for the cations).[25] Specifically, for the radius, one expects $r \propto 1/(Z - S)$ (for example, ref 36), where r is the cationic radius, Z is the atomic number, and S is some shielding constant that accounts for the effective nuclear charge. (S would be the shielding due to the
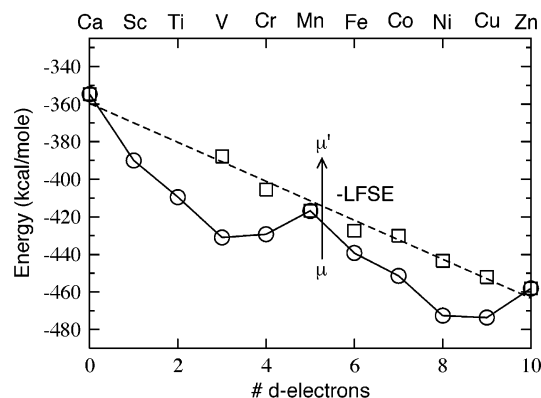
Figure 4. Hydration free energy of the transition metals with and without ligand field contributions. The open circles are the quasi-chemical estimate of the hydration free energies, μ. $\mu' = \mu - \text{LFSE} = \mu - \alpha\Delta$, where the factor α is the fourth column in Table 2. The dashed line is a straight line fit ($R^2 = 0.98$) to μ'.

orbitals up to and including 3P and would have the same value for Zn^{2+} to Zn^{2+}.) Without consideration of azimuthal quantum numbers, that is, angular momentum effects, this proportionality will not hold directly for the extent of the d-orbitals. Once account is taken of the effects specific to the d-orbitals (here the LFSE), it is reasonable to expect that a spherically symmetrical ion results and this proportionality holds. By the Born model, one then expects $\mu' \propto 1/r$, and hence $\mu' \propto (Z - S)$. The obtained linear trend (Figure 4) supports this expectation.

Thus, specific details of the electronic structure mask the periodic trends. (Note that this is not a new result,[25,26] but the salient aspect is that these results have a significant and nontrivial theoretical component.) It is precisely these local bonding effects that classical models are ill-suited to describe accurately. Although attempts have been made to describe transition metal atoms in proteins classically (see, for example, ref 37), rigorous validation and broader applicability of the parameters are unresolved matters. Finally, the consistency of all of the results (Figure 4) gives further confidence in the necessary approximations made in applying a rigorous theory to practical calculations.

IV. Concluding Discussions

The quasi-chemical approach provides a concise framework to model hydration phenomena, and the good agreement between calculations and experiments on divalent cations validates the robustness of the framework. Although approxima-

tions are necessary in applying the theory to practical cases, these approximations are well-defined and therefore open to scrutiny and improvement.

Many of the transition metals studied in this paper are biologically important. So far, however, a theoretical description of their hydration has been unsatisfactory. The quasi-chemical approach illuminates the dominance of local chemical effects in the hydration phenomena. These effects that pose an immense challenge to the development of realistic classical parameters for metal atom simulations are facilely handled within the quasi-chemical approach.

The ligand field effects that have a subtle effect on the hydration of transition metals are also at the heart of why Zn^{2+} binds the tetrahedral sites of zinc-finger proteins better than the transition metals considered in this paper.[6,7] For Zn^{2+}, there is no loss of ligand field stabilization as it binds to the finger environment, but the other, perhaps equally readily available, transition metal ions, such as Fe^{2+}, do lose this stabilizing contribution and hence are not as strongly bound as Zn^{2+}.[6] Interestingly, this tetrahedral coordination of Zn^{2+} appears to also suppress catalytic/hydrolytic activity seen in zinc enzymes having only three coordinating groups. (See ref 6, for example.)

More importantly, our results highlight the importance of understanding cation hydration in water in interpreting cation binding to proteins. Having established our ability to model realistically the bulk solution properties of these important metals, we are thus better prepared to treat those systems theoretically.

Supporting Information Available: Water coordination numbers and solution structural information (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(36) Pauling, L. *General Chemistry*; Dover: New York, 1988.
(37) Comba, P.; Remenyi, R. *Coord. Chem. Rev.* **2003**, *238−239*, 9.

JA0382967