Absolute Hydration Free Energy of the Proton from First-Principles Electronic Structure Calculations

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The absolute hydration free energy of the proton, $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$, is one of the fundamental quantities for the thermodynamics of aqueous systems. Its exact value remains unknown despite extensive experimental and computational efforts. We report a first-principles determination of $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$ by using the latest developments in electronic structure theory including solvation effects. High level ab initio calculations have been performed with a supermolecule-continuum approach based on a recently developed self-consistent reaction field model known as surface and volume polarization for electrostatic interaction (SVPE) or fully polarizable continuum model (FPCM). In the supermolecule-continuum approach, part of the solvent surrounding the solute is treated quantum mechanically and the remaining bulk solvent is approximated by a dielectric continuum medium. With this approach, the calculated results can systematically be improved by increasing the number of quantum mechanically treated solvent molecules. $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$ is accurately predicted to be −262.4 kcal/mol based on high-level, first-principles solvation-included electronic structure calculations. The absolute hydration free energies of other ions can be obtained by using appropriate available thermodynamic data in combination with this value. The high accuracy of the predicted absolute hydration free energy of proton is confirmed by applying the same protocol to predict $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{Li}^+)$.

Introduction

The aqueous solvation of ions plays a vital role in chemical and biological systems containing ions and water.[1−19] It is fundamentally important for the investigation of numerous chemical and biological problems based on a thermodynamic analysis to know the absolute hydration (Gibbs) free energies of ions. Unfortunately, the absolute free energy of solvation of a single ion is difficult to determine by experiment because any stable, macroscopic solution contains equal amounts of positive and negative charge.[1,2] Without using additional approximations or models, an experiment can only be performed to determine the sum of hydration free energies of a pair of oppositely charged ions, such as $\mathrm{H}^+ + \mathrm{HO}^-$, $\mathrm{Li}^+ + \mathrm{HO}^-$, $\mathrm{Na}^+ + \mathrm{HO}^-$, $\mathrm{H}^+ + \mathrm{F}^-$, etc. It has not been possible to isolate one type of ion and measure its absolute hydration free energy. Hence, direct experimental data for different pairs of ions can provide information only for the relative magnitudes of the ionic hydration free energies. The proton hydration free energy, $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$, is used as the standard.[20] Given $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$, the absolute hydration free energies of other ions can be accurately determined by using available experimental data. Thus, the hydration free energy of proton is a fundamental quantity that has been investigated extensively by both experimental and computational approaches.[20−24] The reported "experimental" hydration free energy of the proton has a wide range from −252.6 to −264.1 kcal/mol.[22] Previous theoretical studies[21,22] based on *ab initio* electronic structure theory have used simple solvation models with empirical parameters or other approximations as well as relatively modest levels of electronic structure theory. Different standard "experimental" values of the proton hydration free energy have led to quite different "experimental" hydration free energies of other ions.[23] Thus, the uncertainty concerning the exact value of the absolute hydration free energy of the proton leaves in doubt reported "experimental" hydration free energies of other ions and reported absolute pK_a's that characterize the thermodynamic equilibration between protonated and deprotonated forms of a molecule in aqueous solution if the absolute pK_a's are predicted on the basis of the absolute hydration free energy of the proton. Herein, we present an *ab initio* electronic structure study in order to predict the absolute hydration free energy of the proton to chemical accuracy.

Computational Approach. The conceptually simplest theoretical determination of $\Delta G_{\mathrm{hyd}}{}^{298}(\mathrm{H}^+)$ based on ab initio electronic structure theory is to converge the free energy of reaction (1) by simply increasing n until the energy does not change on addition of successive waters[21]

$$\mathrm{H}^+(\mathrm{gas}) + (\mathrm{H_2O})_n(\mathrm{gas}) \rightarrow \mathrm{H_3O}^+(\mathrm{H_2O})_{n-1}(\mathrm{gas}) \qquad (1)$$

For large enough n, the cluster will approach the liquid. The corresponding protonated water cluster is expressed as $\mathrm{H_3O^+(H_2O)}_{n-1}$, instead of $\mathrm{H^+(H_2O)}_n$, because in water, the proton forms the hydronium ion, $\mathrm{H_3O^+}$, which hydrogen-bonds to other waters in its first solvation shell. The free energy of reaction (1) converged to $n \rightarrow \infty$ is the desired absolute hydration free energy of proton. However, the free energy of reaction (1) is slowly convergent because the bulk solvent (water) effects are dominated by long-range electrostatic interactions. High-level *ab initio* electronic structure calculations including even modest numbers of solvent molecules are impractical computationally.[25] We therefore have to consider alternative approaches that can practically account for the bulk solvent effects.

A computationally simpler approach is to consider a hydronium ion and a water molecule (as solutes) existing in an

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isotropic homogeneous continuous dielectric continuum medium that can be polarized by the solute leading to a reaction field that in turn polarizes the solute itself.[26a] This approach requires that an implicit solute−solvent interaction potential, the solvent polarization potential, be included in the solute Hamiltonian. Electronic structure calculations are then performed with this new Hamiltonian to evaluate the free energy of reaction (2)

$$\mathrm{H^+(gas) + H_2O(aq) \rightarrow H_3O^+(aq)} \qquad (2)$$

where the "aq" in parentheses now represents the dielectric continuum of the aqueous solvent surrounding the solute under consideration. This electronic structure approach including solvation is known as the self-consistent reaction field (SCRF) theory.[27] The reliability of the SCRF calculation results is dependent on the accuracy of the determined solvent polarization potential in addition to the accuracy of the quantum chemical approximation level (discussed below) for predicting the gas-phase results. Within the continuum model of solvation, the exact solvent electrostatic polarization potential corresponding to a given solute electronic wave function is determined by the solution of the requisite Poisson's equation under certain boundary condition.[26a,27] The full solvent electrostatic polarization consists of both surface and volume polarization.[26a] The latter is due to the part of the solute electron charge which quantum mechanically penetrates outside the cavity accommodating the solute. A surface and volume polarization for electrostatic interaction (SVPE) procedure[26] has recently been developed to fully evaluate both the surface and volume polarization, and this procedure is also known as the fully polarizable continuum model (FPCM).[28−30] This SVPE procedure is currently the only implementation capable of directly determining the volume polarization for a general irregularly shaped solute cavity in addition to the more commonly treated surface polarization, although the analytic energy derivatives required for geometry optimization have not been implemented yet. In other SCRF implementations, volume polarization effects are ignored or approximately modeled by modifying the surface polarization charge distribution through a simulation and/or charge renormalization,[22,27,31−33] or the solute charge distribution is simply represented by a set of point charges at the solute nuclei.[21,23] Since the solute cavity surface is defined as a solute electron charge isodensity contour determined self-consistently during the SVPE iteration process, the SVPE results, converged to the exact solution of Poisson's equation with a given numerical tolerance,[26a] depend only on the contour value at a given dielectric constant and on the quantum chemical approach that has been used. The single parameter value has been determined to be 0.001 au based on an extensive calibration study[26b] seeking the best overall agreement with experimental conformational free energy differences (62 experimental observations) of various polar solutes existing in various solvents. On the basis of the fitting process employed in the calibration, the root-mean-squares (rms) deviation of the 62 experimental values from the results calculated by the SVPE method using the 0.001 au contour is 0.096 kcal/mol.[26b] The SVPE procedure using the 0.001 au contour has been shown to be reliable for evaluating the bulk solvent effects.[26b,28,29]

Although high level electronic structure calculations with the SVPE method can give accurate results within the continuum model of solvation, the continuum model itself completely ignores the solvent structure and, therefore, does not account for important effects due to specific solute−solvent interactions.[29] As a result, whereas the continuum model can satisfactorily describe the dominant long-range electrostatic interactions and associated inductive interactions between solute and solvent, there are also other nonelectrostatic interactions (such as cavitation, dispersion, and Pauli repulsion) that are short-range, usually caused by the specific solute−solvent interactions, such as hydrogen bonding, within the first solvation shell.[27d] The SVPE results can be consistently improved by coupling with a supermolecule model that includes solute and some solvent molecules interacting with the solute so that the short-range nonelectrostatic interactions between the solute and the first (and even the second) solvation shell solvent waters are fully included in the SVPE electronic structure calculation.[29] The overall nonelectrostatic interaction between the explicit solvent water molecules in the hydrated ion, $\mathrm{M^+(H_2O)}_n$, and the bulk solvent should be similar to that between the corresponding water cluster, $\mathrm{(H_2O)}_n$, and the bulk solvent, because they are all due to water−water interactions. The difference is expected to disappear for the large *n* limit. The physical meaning of such an SVPE-based hybrid supermolecule-continuum approach, i.e., performing an SVPE calculation on the supermolecular solute, is that the part of the solvent surrounding the solute is treated quantum mechanically and the remaining bulk solvent is still approximated as the dielectric continuum medium and accounted for by SVPE.[29] Obviously, the more solvent molecules treated quantum mechanically, the better the calculated results; as noted above, the improvement on increasing the number of solvent molecules in the supermolecular solute will systematically approach the limit for large *n*. Thus, the hydration free energy of proton is the free energy of reaction (3), $\Delta\mathbf{G}_{\mathrm{hyd}}[\mathrm{H^+},n]$, converged to $n \rightarrow \infty$

$$\mathrm{H^+(gas) + (H_2O)}_n\mathrm{(aq) \rightarrow H_3O^+(H_2O)}_{n-1}\mathrm{(aq)} \qquad (3)$$

Actually, reaction (2) is a special case of reaction (3) with $n = 1$. With increasing *n*, the electronic structure calculations with the hybrid supermolecule-continuum approach for reaction (3) are expected to converge much faster than the corresponding calculations for reaction (1).

To calculate the free energy for reaction (3), we need to know the Gibbs free energies of $\mathrm{H^+(gas)}$, $\mathrm{(H_2O)}_n\mathrm{(aq)}$, and $\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(aq)}$. The free energy change of the gas-phase proton, $\mathbf{G}[\mathrm{H^+(gas)}]$ from 0 K to 298 K, has been determined by well-established approaches to be −6.3 kcal/mol[21] when the pressure is 1 atm. For each of the two aqueous clusters $\mathrm{(H_2O)}_n\mathrm{(aq)}$ and $\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(aq)}$, its free energy, $\mathbf{G}[\mathrm{(H_2O)}_n\mathrm{(aq)}]$ or $\mathbf{G}[\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(aq)}]$, can be expressed as a sum of the free energy of the corresponding gas-phase cluster, $\mathrm{(H_2O)}_n\mathrm{(gas)}$ or $\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(gas)}$, and the bulk solvent shift

$$\mathbf{G}[\mathrm{(H_2O)}_n\mathrm{(aq)}] = \mathbf{G}[\mathrm{(H_2O)}_n\mathrm{(gas)}] + \Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{(H_2O)}_n] \qquad (4)$$

$$\mathbf{G}[\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(aq)}] = \mathbf{G}[\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(gas)}] + \Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H_3O^+(H_2O)}_{n-1}] \qquad (5)$$

Thus, we can evaluate the hydration free energy of the proton as

$$\Delta\mathbf{G}_{\mathrm{hyd}}[\mathrm{H^+},n] = \Delta\mathbf{G}_{\mathrm{gas}}[\mathrm{H^+},n] + \Delta\Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H^+},n] \qquad (6)$$

where $\Delta\mathbf{G}_{\mathrm{gas}}[\mathrm{H^+},n] = \mathbf{G}[\mathrm{H_3O^+(H_2O)}_{n-1}\mathrm{(gas)}] - \mathbf{G}[\mathrm{(H_2O)}_n\mathrm{(gas)}] - \mathbf{G}[\mathrm{H^+(gas)}]$ is the contribution of the explicitly considered water molecules to the proton hydration free energy, and $\Delta\Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H^+},n] = \Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H_3O^+(H_2O)}_{n-1}] - \Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{(H_2O)}_n]$ is due to the bulk solvent effects. To determine $\Delta\mathbf{G}_{\mathrm{hyd}}[\mathrm{H^+},n]$ with high accuracy, both $\Delta\mathbf{G}_{\mathrm{gas}}[\mathrm{H^+},n]$ and $\Delta\Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H^+},n]$ must be calculated at a sufficiently high level of theory as described below.

Computational Details. The geometries of all clusters $(H_2O)_n$ and $H_3O^+(H_2O)_{n-1}$ were first optimized in the gas phase by using gradient corrected density functional theory (DFT) with Becke's three-parameter hybrid exchange functional and the Lee−Yang−Parr correlation functional (B3LYP)[34] and with the 6-31++G** basis set.[35] The DFT geometry optimizations were followed by analytic second-derivative calculations to ensure that the optimized geometries are minima on the potential energy hypersurface (all real frequencies) and to evaluate the thermal and vibrational corrections to the Gibbs free energies (at 298 K and 1 atm).[36] We considered $n = 1$, 4 and 10: $n = 1$ for the simplest case without explicitly considering any solvent water surrounding the hydronium ion; $n = 4$ for quantum mechanically treating the complete first solvation shell; and $n = 10$ for quantum mechanically treating the complete first and second solvation shells. The geometries of H_2O and H_3O^+ were also optimized at the MP2/6-31++G**, MP2/aug-cc-pVDZ and CCSD(T)/aug-cc-pVDZ levels. To estimate the bulk solvent effects on the cluster geometries, for the most interesting case of $n = 4$ (see below), we also performed geometry optimizations by using the quantum Onsager model implemented in the *Gaussian98* program.[37] The cavity radii used for the $(H_2O)_4$ and $H_3O^+(H_2O)_3$ clusters were determined to be 3.70 and 3.83 Å, respectively, by following the standard procedure of volume calculation recommended in the *Gaussian98* program.

The geometries optimized at the B3LYP/6-31++G** level were then used in single-point energy calculations at the second-order Møller−Plesset (MP2) and coupled-cluster with single and double substitutions with a noniterative triples correction (CCSD(T))[38] levels with different basis sets including the correlation-consistent basis sets denoted by aug-cc-pVXZ (X = D, T, and Q).[39−41] To extrapolate to the frozen core complete basis set (CBS) limit, we used a 3-parameter, mixed exponential/Gaussian function of the form

$$E(x) = E_{\mathrm{CBS}} + B \cdot \exp[-(x-1)] + C \cdot \exp[-(x-1)^2] \quad (7)$$

where $x = 2$, 3, and 4 for aug-cc-pVDZ, aug-cc-pVTZ, and aug-cc-pVQZ, respectively.[41] For the most interesting case of $n = 4$ (see below), the core-valence effects were calculated at the MP2/cc-pCVTZ level,[42] and the scalar relativistic correction was calculated as the sum of the expectation values of the mass-velocity and 1-electron Darwin terms in the Breit-Pauli Hamiltonian based on single and double excitation configuration interaction wave functions using the cc-pVTZ basis set.[43] These calculations were done with the MOLPRO-2000 program.[44] Finally, the bulk solvent shifts, $\Delta\Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H}^+,n]$, were evaluated with the SVPE method implemented in a local version of the GAMESS program[45] at the MP2/6-31++G** level. The dielectric constant of water used for the SVPE calculations is 78.5. Once the solute cavity is defined and the dielectric constant is known, the accuracy of the SVPE numerical computation depends only on the number of surface nodes (N) representing the cavity surface and number of layers (M) describing the volume polarization charge distribution within a certain, sufficiently large three-dimensional space outside the solute cavity. If one could use an infinite number of nodes and an infinite number of layers, then the numerical results obtained from the SVPE computation would be exactly the same as those determined by the exact solution of the Poisson's equation for describing the solvent polarization potential. We have shown that the accuracy of the SVPE numerical computations employed in this study with $N = 974$ and $M = 40$ (for a step size of 0.3 Å) is sufficient for the accuracy required in this work. For the SVPE calculations with the MP2 method, the MP2 perturbation procedure was performed for the electron correlation correction after the converged HF wave function of the solute in the reaction field is obtained.

Unless indicated otherwise, the geometry optimizations were performed by using *Gaussian98*,[37] and the MP2 and CCSD(T) energy calculations were performed by using *NWChem*.[46] All the calculations were carried out on a 16-processor SGI Origin 2000 and a 512-processor IBM SP massively parallel supercomputer.

Results and Discussion

The optimized geometries for the various species are depicted in Figure 1, and the calculated free energies of solvation are summarized in Table 1. The optimized geometries of H_2O and H_3O^+ do not show a strong dependence on the computational method. The geometries for $(H_2O)_4$ and $(H_3O)^+(H_2O)_3$ do not show a dependence on whether they are optimized in the gas phase or in the presence of a solvent model.

It has been demonstrated that the bulk solvent shifts of the free energies calculated with the SVPE method are rather insensitive to the electron correlation level and basis set used.[26,29] To further verify this point, we compared the SVPE results calculated at the MP2/6-31++G** level with the corresponding results calculated at the Hartree−Fock (HF) level (in which the electron correlation is completely ignored) using the same basis set. The differences between the HF/6-31++G** and MP2/6-31++G** results are on the order of 0.2 to 0.3 kcal/mol. A further test with the SVPE calculations indicates that the change of the SVPE result is negligible (<0.1 kcal/mol) when the 6-31++G** basis set is replaced by the larger aug-cc-pVTZ basis set. Hence, to obtain the value of $\Delta\mathbf{G}_{\mathrm{hyd}}[\mathrm{H}^+,n]$ in eq (6), we will always use the $\Delta\Delta\mathbf{G}_{\mathrm{sol}}[\mathrm{H}^+,n]$ value calculated at the MP2/6-31++G** level no matter which level of gas-phase calculation was performed to determine the $\Delta\mathbf{G}_{\mathrm{gas}}[\mathrm{H}^+,n]$ value.

The convergence of the calculated hydration free energy with respect to n can be examined by comparing the results calculated at the same level of theory for different n values. There is a significant change (∼13 kcal/mol) in the calculated hydration free energy from $n = 1$ to $n = 4$, whereas the further change from $n = 4$ to $n = 10$ is negligible. The change from $n = 4$ to $n = 10$ is always within 0.1 kcal/mol no matter whether the MP2/6-31++G** or MP2/aug-cc-pVTZ results are used; the convergence with respect to n does not depend on the level of theory. These results reveal that the solvent molecules in the first solvation shell must be treated quantum mechanically, and that it does not matter whether the second solvation shell is also considered quantum mechanically or regarded as part of the dielectric medium. The proton hydration free energy calculations are well converged at $n = 4$ and, thus, we performed our higher level energy calculations for $n = 4$.

The CCSD(T) method can predict total molecular dissociation energies involving covalent bonds based on the valence electrons to within tenth(s) of a kcal/mol[47,48] when a sufficiently large basis set is used and extrapolated to the complete basis set (CBS) limit and if other effects such as those of core-valence corrections, relativity, and zero-point energies are properly accounted for. The MP2 method has been shown to give very good energies for hydrogen bonded systems.[49] The electronic energy changes caused by core-valence correlation and relativistic effects are calculated to be −0.21 and 0.14 kcal/mol, respectively, when $n = 4$; the overall shift is only −0.07 kcal/mol. We can extrapolate the MP2 energies to the CBS limit by using the augmented correlation-consistent basis sets: aug-cc-pVDZ, aug-cc-pVTZ, and aug-cc-pVQZ. The MP2 results in Table 1 indicate that the results are reasonably well-converged

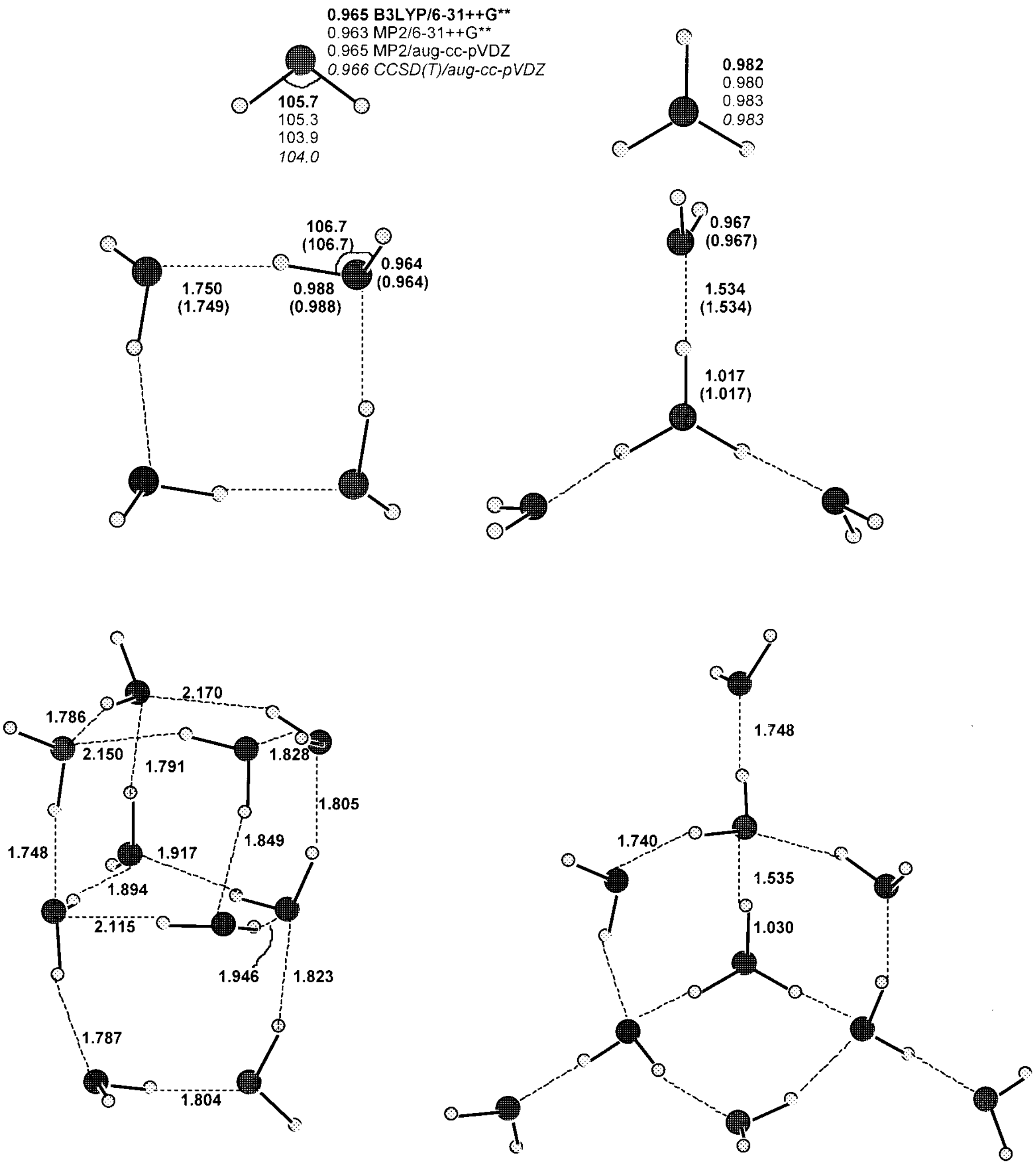

Figure 1. Optimized geometries of the hydrated proton cluster models and the corresponding water clusters: H_2O, H_3O^+, $(H_2O)_4$, $H_3O^+(H_2O)_3$, $(H_2O)_{10}$, and $H_3O^+(H_2O)_9$ in their most stable structures. Note that the H_3O^+ unit is nonplanar and has a C_{3v} point-symmetry so that $H_3O^+(H_2O)_3$ and $H_3O^+(H_2O)_9$ both have a C_3 symmetry. The geometric parameters in parentheses for $(H_2O)_4$ and $H_3O^+(H_2O)_3$ were optimized including bulk solvent effects.

at the aug-cc-pVTZ level. The differences between the MP2 results calculated at the aug-cc-pVTZ and aug-cc-pVQZ levels are within 0.3 kcal/mol; the differences between the MP2/aug-cc-pVQZ and MP2/CBS results are within 0.1 kcal/mol. The CCSD(T) binding energy is 1.1 kcal/mol greater than the MP2 value with the aug-cc-pVTZ basis set. The best estimate of our gas-phase result is the CCSD(T)/aug-cc-pVTZ value plus the CBS correction defined as the change from the MP2/aug-cc-pVTZ value to the MP2/CBS value. This leads to a gas-phase electronic contribution to the proton affinity of −171.44 kcal/mol, when $n = 1$, compared to −171.43 kcal/mol extrapolated by directly using the CCSD(T) energies calculated with the aug-cc-pVDZ, aug-cc-pVTZ, aug-cc-pVQZ, and aug-cc-pV5Z basis sets.[47] The best estimate of the gas-phase free energy is −211.0 kcal/mol for $n = 4$, without consideration of the core-valence correlation and relativistic effects. It becomes −211.1 kcal/mol when the core-valence correlation and relativistic effects are included. Further inclusion of the bulk solvent effects leads to our best estimate of the absolute hydration free energy of proton as −262.4 kcal/mol, calculated with $n = 4$.

We now briefly discuss the standard states for free energy of solvation in order to properly compare our prediction with other results and to guide the future use of our predicted absolute proton hydration free energy of −262.4 kcal/mol. Different standard states have been used in the literature for the determination of experimental solvation free energies,[50−54] and most of the used standard states differ only in the pressure or concentration of hypothetical ideal gases leading to different entropy contributions to the hydration free energy. According to the most popular choice of the standard states, the solvation free energy is determined as the free energy change from the hypothetical $P = 1$ atm standard state of gas-phase solute at T

TABLE 1: Absolute Hydration Free Energy of the Proton (in kcal/mol) Calculated as the Converged Free Energy Change from $\mathrm{H}^+(\mathrm{gas}) + (\mathrm{H_2O})_n(\mathrm{aq})$ to $\mathrm{H_3O}^+(\mathrm{H_2O})_{n-1}(\mathrm{aq})$ at $T = 298$ K

	Gibbs free energy change		
calculation method[a]	$n = 1$	$n = 4$	$n = 10$
without bulk solvent shift (i.e., $\Delta\mathbf{G}_{\text{gas}}[\mathrm{H}^+,n]$)[b]			
MP2/6-31++G**	−158.5	−212.0	−234.8
MP2/aug-cc-pVDZ	−154.7	−208.0	
MP2/aug-cc-pVTZ	−155.9	−209.6	−232.3
MP2/aug-cc-pVQZ	−156.0	−209.8	
MP2/CBS	−156.0	−209.9	
CCSD(T)/aug-cc-pVTZ	−157.2	−210.7	
best estimate	−157.3[d]	−211.0[e] (−211.1)[f]	
bulk solvent shift (i.e., $\Delta\Delta\mathbf{G}_{\text{sol}}[\mathrm{H}^+,n]$)[c]			
	−90.6	−51.3	−28.6
including bulk solvent shift (i.e., $\Delta\mathbf{G}_{\text{hyd}}[\mathrm{H}^+,n]$)			
MP2/6-31++G**	−250.1	−263.3	−263.4
MP2/aug-cc-pVDZ	−246.2	−259.3	
MP2/aug-cc-pVTZ	−247.5	−260.8	−260.9
MP2/aug-cc-pVQZ	−247.6	−261.1	
MP2/CBS	−247.6	−261.2	
CCSD(T)/aug-cc-pVTZ	−249.7	−261.9	
best estimate	−249.8	−262.3 (−262.4)[f]	

[a] Method for the energy calculations in the gas phase. All energy calculations were performed by using the geometries optimized at the B3LYP/6-31++G** level. [b] Without bulk solvent effects, $\Delta\mathbf{G}_{\text{gas}}[\mathrm{H}^+,n]$ can actually be regarded as the free energy of reaction (1). [c] Calculated by performing the SVPE calculations at the MP2/6-31++G** level. [d] $\Delta\mathbf{E}_{\text{elec,gas}}[\mathrm{H}^+,1] = -171.44$; $\Delta\mathbf{H}_{\text{elec,gas}}[\mathrm{H}^+,1] = -164.67$; $-\mathbf{T}\Delta\mathbf{S}_{\text{elec,gas}}[\mathrm{H}^+,1] = 7.41$ kcal/mol. [e] $\Delta\mathbf{E}_{\text{elec,gas}}[\mathrm{H}^+,4] = -220.82$; $\Delta\mathbf{H}_{\text{elec,gas}}[\mathrm{H}^+,4] = -215.68$; $-\mathbf{T}\Delta\mathbf{S}_{\text{elec,gas}}[\mathrm{H}^+,4] = 4.69$ kcal/mol. [f] When the core-valence correlation and relativistic effects are included.

= 298.15 K to the 1 M solution at $T = 298.15$ K and $P = 1$ atm with the assumption that there are no interactions between the protons.[50,53] Our calculated results summarized in Table 1 all correspond to this free energy change. If a different definition of the standard states is used, our predicted absolute solvation free energy needs to be adjusted accordingly. For example, if the solvation free energy is defined as the free energy change from the gas-phase solute state of 1 M (a hypothetical ideal gas) at 298.15 K to the solution of 1 M at 298.15 K and 1 atm,[50,53] then our predicted absolute proton hydration free energy becomes −264.3 kcal/mol, which accounts for the gas-phase translational entropy change from $P = 1$ atm to 1 M ($P \approx 24.5$ atm at 298.15 K) leading to a gas-phase proton free energy change of 1.9 kcal/mol[53] at 298.15 K. Below, we limit our discussion to the gas-phase standard state of 1 atm and 298.15 K for both calculated and experimental results.

Our predicted absolute proton hydration free energy of −262.4 kcal/mol is in excellent agreement with an "experimental" extrapolation, −262.4 ± 0.2 kcal/mol, reported by Klots.[24] This extrapolation is based on the assumption that for sufficiently large clusters, the free energy change of reaction $\mathrm{M}^+(\mathrm{H_2O})_n + \mathrm{H_2O} \rightarrow \mathrm{M}^+(\mathrm{H_2O})_{n+1}$ is independent of the central ion and will depend only on the volume of the cluster. Thus, the experimental thermodynamic data collected for 10 pairs of ions can be used to obtain absolute proton hydration free energy values, giving a value in excellent agreement with our value. Among other available "experimental" values of the absolute proton hydration free energy, the latest one, −264.1 kcal/mol,[20] is closest to our prediction of −262.4 kcal/mol and to the value given by Klots.[24] The next closest "experimental" value is the tabulated value of −260.5 kcal/mol.[50] The experimental value of −264.1 kcal/mol[20] was obtained by extrapolating gas-phase cluster binding energies for a number of ions in water clusters, similar to the approach of Klots[23] but using different data and assumptions.

Our predicted absolute hydration free energy of proton, −262.4 kcal/mol, is close to the previously calculated values at a lower level, −263.20, −261.63 and −263.26 kcal/mol of Tawa et al.[21] with $n = 4$, 5, and 6, respectively, but is considerably different from the most recently reported results calculated by Mejias et al.[22] The values reported by Tawa et al. clearly exhibit a cancellation of errors in the gas phase and solvation calculations on the order of a few kcal/mol. Their gas phase $\Delta\mathbf{G}_{\text{gas}}[\mathrm{H}^+,4]$ value of −213.02 kcal/mol differs to ours by ~2.0 kcal/mol, most likely due to their use of a smaller basis set. The solute charge distribution was simply represented by a set of effective point charges centered at the solute nuclei in their dielectric continuum calculation of the bulk solvent effects. Such an approximation has to be balanced by the use of three sets of empirical parameters in their SCRF calculations,[21] which they varied from the standard values used before in order to reproduce correct values for the hydration free energy of water by their pure SCRF calculations. Our experience with various SCRF calculations[26d,29,55] suggests that while an SCRF-based hybrid supermolecule-continuum approach leads to calculated results in excellent agreement with experimental data,[29] the corresponding pure SCRF calculations necessarily cannot also satisfactorily reproduce experimental results for systems involving strong solute−solvent hydrogen bonding.[26d] The hydration free energy of water determined by the pure SVPE calculation ignoring contributions from all short-range solute−solvent interactions is ~ −8.9 kcal/mol, which differs the experimental value of −6.32 kcal/mol[52] by ~2.6 kcal/mol. The result can be improved by performing the corresponding hybrid supermolecule-continuum calculations.[55]

The hybrid supermolecule-continuum calculations calculations reported by Mejias et al.[22] were performed by use of a conductor-like screening model (COSMO) and density functional theory (DFT). Ignoring the inherent accuracy of their DFT energy calculations in the gas phase, their COSMO-DFT calculations considerably underestimate the bulk solvent effects. The largest number of water molecules considered in their work is 13. On the basis of three approaches, they calculated a range of values: $\Delta\mathbf{G}_{\text{hyd}}[\mathrm{H}^+,4] = -202.9$ to −208.0 kcal/mol, $\Delta\mathbf{G}_{\text{hyd}}[\mathrm{H}^+,10] = -233.3$ to −246.2 kcal/mol, and $\Delta\mathbf{G}_{\text{hyd}}[\mathrm{H}^+,13] = -245.0$ to −262.5 kcal/mol. Their values are not converged at $n = 4$ as found by us and Tawa et al.[21] most likely due to considerable underestimation of the bulk solvent effect. Even more surprising, their $\Delta\mathbf{G}_{\text{hyd}}[\mathrm{H}^+,n]$ calculations are apparently not converged even at $n = 13$.

To confirm the high accuracy of our theoretical prediction for the proton, the absolute hydration free energy of the Li^+ ion has been calculated with a similar theoretical protocol. A recent ab initio molecular dynamics simulation of Li^+ hydration[56] as well as quantum chemical calculations[57,58] reveal that the first solvation shell of Li^+ ion consists of four water molecules. We, therefore, consider the absolute hydration free energy of Li^+ as the free energy of reaction 8

$$\mathrm{Li}^+(\mathrm{gas}) + (\mathrm{H_2O})_4(\mathrm{aq}) \rightarrow \mathrm{Li}^+(\mathrm{H_2O})_4(\mathrm{aq}) \qquad (8)$$

The geometry of the $\mathrm{Li}^+(\mathrm{H_2O})_4$ cluster optimized at the B3LYP/6-31++G** level is shown in Figure 2. Our best calculated value for the absolute hydration free energy of the Li^+ ion is −125.1 kcal/mol (CCSD(T)/aug-cc-pVTZ plus the MP2 CBS correction plus the SVPE-MP2 bulk solvent shift and excluding the small relativistic and core/valence corrections). The calcu-

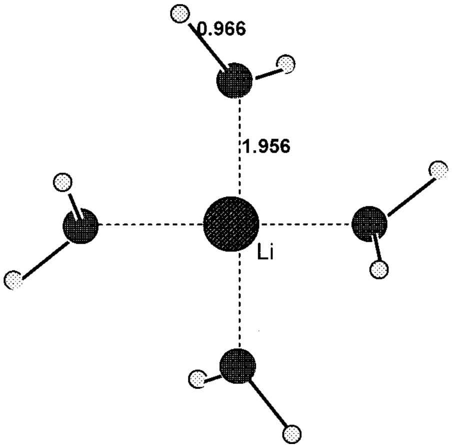

Figure 2. Geometry of $Li^+(H_2O)_4$ optimized at the B3LYP/6-31++G** level. The four oxygen atoms tetrahedrally coordinate to Li^+.

lated hydration free energy change for solvation of a proton to solvation of Li^+ is 137.5 kcal/mol from the latest collection of experimental data[20] and 137.0 kcal/mol from the earlier experimental data.[50] Our theoretical value of 137.3 kcal/mol is between the two experimental values. This adds further evidence that our free energy of hydration of the proton is good to within ±1 kcal/mol. Topol et al.[23] used a procedure similar to that of Tawa et.al.[21] to calculate the absolute hydration free energy of the Li^+ ion and obtained -122.6 kcal/mol. This value differs from our calculated value by ~2.5 kcal/mol. This difference is likely to be related to their use of density functional theory (with the B3LYP functional) for their energy calculations and the ionic radius of 1.32 Å for Li^+ in their solvation calculations. For example, for $n = 4$, their calculated bulk solvent shift is ~ -51.0 kcal/mol, which differs ours (-52.4 kcal/mol) by ~1.4 kcal/mol.

On the basis of our calculated absolute proton hydration free energy value of -262.4 kcal/mol, the absolute hydration free energies of other ions can be readily determined when their hydration free energies relative to that of the proton can be taken from available experimental on total hydration free energies of pairs of oppositely charged ions. For example, utilizing the experimental data in ref 20, we can obtain absolute hydration free energies (in kcal/mol) of the following interesting ions: Li^+ (-124.9), Na^+ (-99.7), K^+ (-82.5), Rb^+ (-77.1), HO^- (-104.5), F^- (-104.1), Cl^- (-74.3), Br^- (-67.9), and I^- (-59.0). For other ions whose relative hydration free energies cannot be drawn from available experimental data, their absolute hydration free energies may be predicted by using the same theoretical protocol as used here for proton.

Conclusion

The absolute hydration free energy of the proton has been accurately calculated to be -262.4 kcal/mol by using a reliable protocol of first-principles solvation-included electronic structure calculations. The absolute hydration free energies of other ions can be obtained by using appropriate available thermodynamic data in combination with this value. The high accuracy of the predicted absolute hydration free energy of the proton is further confirmed by applying the same protocol to predict $\Delta G_{\mathrm{hyd}}^{298}(Li^+)$ and hence the difference in free energies of solvation for H^+ and Li^+.

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References and Notes

(1) Conway, B. E. *Ionic Hydration in Chemistry and Biophysics*; Elsevier: New York, 1981.

(2) Marcus, Y. *Ion Solvation*; Wiley: New York, 1985.

(3) Hille, B. *Ionic Channels of Excitable Membranes*; Sinauer: Sunderland, MA, ed. 2, 1992.

(4) Franks, N. P.; Lieb, W. R. *Nature* **1997**, *389*, 334.

(5) Gunshin, H.; Mackenzie, B.; Berger, U. V.; Gunshin, Y.; Romero, M. F.; Boron, W. F.; Nussberger, S.; Gollan, J. L.; Hediger, M. A. *Nature* **1997**, *388*, 482.

(6) Doyle, D. A.; Cabral, J. M.; Pfuetzner, R. A.; Kuo, A.; Gulbis, J. M.; Cohen, S. L.; Chait, B. T.; MacKinnon, R. *Science* **1998**, *280*, 69.

(7) MacKinnon, R.; Cohen, S. L.; Kuo, A.; Lee, A.; Chait, B. T. *Science* **1998**, *280*, 106.

(8) Nakamura, T.; Akutagawa, T.; Honda, K.; Underhill, A. E.; Coomber, A. T.; Friend, R. H. *Nature* **1998**, *394*, 159.

(9) Roux, B.; MacKinnon, R. *Science* **1999**, *285*, 100.

(10) Wu, K.; Iedema, M. J.; Cowin, J. P. *Science* **1999**, *286*, 2482.

(11) Anson, L. *Nature* **1999**, *402*, 739.

(12) MacFarlane, D. R.; Huang, J.; Forsyth, M. *Nature* **1999**, *402*, 792.

(13) Kolbe, M.; Besir, H.; Essen, L.-O.; Oesterhelt, D. *Science* **2000**, *288*, 1390.

(14) Weber, J. M.; Kelley, J. A.; Nielsen, S. B.; Ayotte, P.; Johnson, M. A. *Science* **2000**, *287*, 2461.

(15) Aqvist, J.; Luzhkov, V. *Nature* **2000**, *404*, 881.

(16) Williams, K. A. *Nature* **2000**, *403*, 112.

(17) Pasquarello, A.; Petri, I.; Salmon, P. S.; Parisel, O.; Car, R.; Tóth, É.; Powell, D. H.; Fischer, H. E.; Helm, L.; Merbach, A. *Science* **2001**, *291*, 856.

(18) Kielpinski, D.; Meyer, V.; Rowe, M. A.; Sackett, C. A.; Itano, W. M.; Monroe, C.; Wineland, D. J. *Science* **2001**, *291*, 1013.

(19) Kropman, M. F.; Bakker, H. J. *Science* **2001**, *291*, 2118.

(20) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V. *J. Phys. Chem. A* **1998**, *102*, 7787.

(21) Tawa, G. J.; Topol, I. A.; Burt, S. K.; Caldwell, R. A.; Rashin, A. A. *J. Chem. Phys.* **1998**, *109*, 4852.

(22) Mejias, J. A.; Lago, S. *J. Chem. Phys.* **2000**, *113*, 7306.

(23) Topol, I. A.; Tawa, G. J.; Burt, S. K.; Rashin, A. A. *J. Chem. Phys.* **1999**, *111*, 10 998.

(24) Klots, C. E. *J. Phys. Chem.* **1981**, *85*, 3585.

(25) Bandyopadhyay, P.; Gordon, M. S. *J. Chem. Phys.* **2000**, *113*, 1104.

(26) (a) Zhan, C.-G.; Bentley, J.; Chipman, D. M. *J. Chem. Phys.* **1998**, *108*, 177. (b) Zhan, C.-G.; Chipman, D. M. *J. Chem. Phys.* **1998**, *109*, 10 543. (c) Zhan, C.-G.; Chipman, D. M. *J. Chem. Phys.* **1999**, *110*, 1611. (d) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Phys. Chem. A* **2000**, *104*, 7672.

(27) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Cramer, C. J.; Truhlar, D. G. in *Solvent Effects and Chemical Reactions*, Tapia, O., Bertran, J., Eds.; Kluwer: Dordrecht, 1996; p 1. (c) Chipman, D. M. *J. Chem. Phys.* **1997**, *106*, 10 194. (d) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161. (e) Chipman, D. M. *J. Chem. Phys.* **2000**, *112*, 5558.

(28) Zhan, C.-G.; Norberto de Souza, O.; Rittenhouse, R.; Ornstein, R. L. *J. Am. Chem. Soc.* **1999**, *121*, 7279.

(29) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Am. Chem. Soc.* **2000**, *122*, 2621.

(30) (a) Zhan, C.-G.; Zheng, F. *J. Am. Chem. Soc.* **2001**, *123*, 2835. (b) Zhan, C.-G.; Niu, S.; Ornstein, R. L. *J. Chem. Soc., Perkin Trans. 2* **2001**, *1*, 23. (c) Zhan, C.-G.; Landry, D. W. *J. Phys. Chem. A* **2001**, *105*, 1296.

(31) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(32) Tomasi, J.; Mennucci, B.; Cances, E. *J. Mol. Struct. (THEOCHEM)* **1999**, *464*, 211.

(33) (a) Cancès, E.; Mennucci, B. *J. Chem. Phys.* **2001**, *114*, 4744. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Chem. Phys.* **2001**, *114*, 5691.

(34) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(35) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1987.

(36) The vibrational contributions to the entropies and the thermal energy corrections were calculated in the harmonic approximation. Anharmonic corrections may be important but the effects will approximately cancel as

there are comparable numbers of low-frequency modes: 10 frequencies for $(H_2O)_4$ and 12 frequencies for $H_3O^+(H_2O)_3$ below 1 kcal/mol = 350 cm^{-1} where $kT \approx 0.6$ kcal/mol = 210 cm^{-1}.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; 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.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, A. C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.6, Gaussian, Inc., Pittsburgh, PA, 1998.

(38) (a) Purvis, G. D., III; Bartlett, R. J. *J. Chem. Phys*. **1982**, *76*, 1910. (b) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett*. **1989**, *157*, 479. (c) Watts, J. D.; Gauss, J.; Bartlett, R. J. *J. Chem. Phys*. **1993**, *98*, 8718.

(39) Dunning, T. H., Jr. *J. Chem. Phys*. **1989**, *90*, 1007.

(40) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys*. **1992**, *96*, 6796.

(41) Peterson, K. A.; Wood, D. E.; Dunning, T. H., Jr. *J. Chem. Phys*. **1994**, *100*, 7410.

(42) Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys*. **1995**, *103*, 4572.

(43) Davidson, E. R.; Ishikawa, Y.; Malli, G. L. *Chem. Phys. Lett.* **1981**, *84*, 226.

(44) Werner, H. J.; Knowles, P. J.; Almlof, J.; Amos, R. D.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert, F.; Elbert, S. T.; Hampel, C.; Lindh, R.; Lloyd, A. W.; Meyer, W.; Nicklass, A.; Peterson, K. A.; Pitzer, R. M.; Stone, A. J.; Taylor, P. R.; Mura, M. E.; Pulay, P.; Schütz, M.; Stoll, H.; Thorsteinsson, T. *MOLPRO*, Universität Stüttgart, Stüttgart, Germany, University of Sussex, Falmer, Brighton, England, 1997.

(45) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(46) Anchell, J.; Apra, E.; Bernholdt, D.; Borowski, P.; Bylaska, E.; Clark, T.; Clerc, D.; Dachsel, H.; de Jong, W. A.; Deegan, M.; Dupuis, M.; Dyall, K.; Elwood, D.; Fann, G.; Fruchtl, H.; Glendenning, E.; Gutowski, M.; Harrison, R.; Hess, A.; Jaffe, J.; Johnson, B.; Ju, J.; Kendall, R.; Kobayashi, R.; Kutteh, R.; Lin, Z.; Littlefield, R.; Long, X.; Meng, B.; Nichols, J.; Nieplocha, J.; Rendall, A.; Rosing, M.; Sandrone, G.; Stave, M.; Straatsma, T.; Taylor, H.; Thomas, G.; van Lenthe, J.; Windus, T.; Wolinski, K.; Wong, A.; Zhang, Z. *NWChem*, Version 4.0.1, Pacific Northwest National Laboratory, Richland, Washington, 2001.

(47) Peterson, K. A.; Xantheas, S. S.; Dixon, D. A.; Dunning, T. H., Jr. *J. Phys. Chem. A* **1998**, *102*, 2449.

(48) (a) Feller, D.; Peterson, K. A. *J. Chem. Phys.* **1999**, *110*, 8384. (b) Ruscic, B.; Feller, D.; Dixon, D. A.; Peterson, K. A.; Harding, L. B.; Asher, R. L.; Wagner, A. F. *J. Phys. Chem. A* **2001**, *105*, 1.

(49) (a) Feller, D. *J. Chem. Phys.* **1992**, *96*, 6104. (b) Feyereisen, M. W.; Feller, D.; Dixon, D. A. *J. Phys. Chem*. **1996**, *100*, 2993. (c) Xantheas, S. *J. Chem. Phys.* **1996**, *104*, 8221.

(50) Friedman, H. L.; Krishnan, V. V. *Water*: *A Comprehensive Treatise*; Plenum: New York, 1973.

(51) Conway, B. E. *J. Solution Chem.* **1978**, *7*, 721.

(52) Ben-Naim, A.; Marcus, Y. *J. Chem. Phys.* **1984**, *81*, 2016.

(53) Hummer, G.; Pratt, L. R.; Garcia, A. E. *J. Phys. Chem.* **1996**, *100*, 1206.

(54) Martin, R. L.; Hay, P. J.; Pratt, L. R. *J. Phys. Chem. A* **1998**, *102*, 3565.

(55) We can also calculate the hydration free energy of the water molecule as the free energy of reaction $H_2O(gas) \rightarrow (1/n)(H_2O)_n(aq)$. At the MP2/aug-cc-pVTZ//B3LYP/6-31++G** electronic level and MP2/6-31++G** level for the SVPE calculations, we find $\Delta\mathbf{G}_{hyd}[H_2O, 4] = -6.2$ kcal/mol, $\Delta\mathbf{G}_{hyd}[H_2O, 8] = -5.3$ kcal/mol, and $\Delta\mathbf{G}_{hyd}[H_2O, 10] = -5.3$ kcal/mol. The converged result of −5.3 kcal/mol differs from the experimental value by 1.0 kcal/mol. The primary source of the difference is likely due to more complicated nonelectrostatic solute−solvent interactions that do not cancel for the "reactant" H_2O(gas) and "product" $(H_2O)_n$(aq) because only the "product" involves the cluster approximation and nonelectrostatic solute−solvent interactions. It is not surprising that the solvation calculations for the pure water reaction $H_2O(gas) \rightarrow (1/n)(H_2O)_n(aq)$ is not as accurate as the solvation calculations for the proton as given in reaction (3) and for the Li^+ ion as given in reaction (8) due to the fact that the structure of the first solvation shell is not reproduced for the pure water reaction but is for the processes involving the ions.

(56) Lyubartsev, A. P.; Laasonen, K.; Laasonen, A. *J. Chem. Phys*. **2001**, *114*, 3120.

(57) Feller, D.; Glendening, E. D.; Kendall, R. A.; Peterson, K. A. *J. Chem. Phys*. **1994**, *100*, 4981.

(58) Feller, D.; Glendening, E. D.; Wood, D. E.; Feyereisen, M. W. *J. Chem. Phys*. **1995**, *103*, 3526.