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Calculation of Solvation Free Energies of Charged Solutes Using Mixed Cluster/Continuum Models

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We derive a consistent approach for predicting the solvation free energies of charged solutes in the presence of implicit and explicit solvents. We find that some published methodologies make systematic errors in the computed free energies because of the incorrect accounting of the standard state corrections for water molecules or water clusters present in the thermodynamic cycle. This problem can be avoided by using the same standard state for each species involved in the reaction under consideration. We analyze two different thermodynamic cycles for calculating the solvation free energies of ionic solutes: (1) the cluster cycle with an *n* water cluster as a reagent and (2) the monomer cycle with *n* distinct water molecules as reagents. The use of the cluster cycle gives solvation free energies that are in excellent agreement with the experimental values obtained from studies of ion–water clusters. The mean absolute errors are 0.8 kcal/mol for H^+ and 2.0 kcal/mol for Cu^{2+}. Conversely, calculations using the monomer cycle lead to mean absolute errors that are >10 kcal/mol for H^+ and >30 kcal/mol for Cu^{2+}. The presence of hydrogen-bonded clusters of similar size on the left- and right-hand sides of the reaction cycle results in the cancelation of the systematic errors in the calculated free energies. Using the cluster cycle with 1 solvation shell leads to errors of 5 kcal/mol for H^+ (6 waters) and 27 kcal/mol for Cu^{2+} (6 waters), whereas using 2 solvation shells leads to accuracies of 2 kcal/mol for Cu^{2+} (18 waters) and 1 kcal/mol for H^+ (10 waters).

1. Introduction

The ability to predict accurately the hydration free energies of ionic species, including the calculations of their pK_a, stability constants, and redox potentials through the use of appropriate thermodynamic cycles, is of crucial importance in many areas of chemistry and biochemistry.[1–3] Accurately calculating the hydration free energies for ions, however, is a challenging task because continuum dielectric solvent models are often inadequate when one is dealing with ionic solutes that have concentrated charge densities with strong local solute–solvent interactions.[4–6] To overcome this deficiency of continuum solvent models, it has become a common practice to add explicit solvent molecules to the model ionic systems.[7–27] For example, Kelly et al. showed that adding one explicit solvent molecule significantly improves the accuracy of the calculated aqueous solvation free energies[7,8] and the acid dissociation constants[9] when using the SM6 continuum solvation model. Pliego and Riveros reported that a cluster-continuum solvent model with two to three explicit water molecules gives calculated pK_a's of 17 organic molecules that are in better agreement with the measurements than those calculated by using pure continuum solvent methods.[10,11] Solvation calculations for bare metal ions should include at least a complete first coordination sphere of solvent (water) molecules.[12–21]

Herein, we derive a thermodynamically consistent approach for the accurate prediction of the solvation free energies of charged solutes in the presence of implicit and explicit solvent molecules from first principles without additional parameters beyond those used for neutral solutes. We find that some published methodologies make systematic errors in the computed free energies because of the incorrect accounting of the standard state corrections for water molecules[7,8] or water clusters[22–26] present in the thermodynamic cycle. We show that this problem can be avoided by using the same standard state for each species involved in the reaction under consideration.[28–30]

SCHEME 1: Thermodynamic Cycle 1 (Monomer Cycle) for the Calculation of $\Delta G^*_{solv}(A^{m\pm})$

$$\begin{tikzcd}
A^{m\pm}\,(g) \arrow[d, "\Delta G^*_{solv}(A^{m\pm})"] & + & nH_2O\,(g) \arrow[r, "\Delta G^o_{g,bind}(I) - n\Delta G^{o-*}"] \arrow[d, "n\Delta G^*_{solv}(H_2O)"] & {[A(H_2O)_n]^{m\pm}\,(g)} \arrow[d, "\Delta G^*_{solv}([A(H_2O)_n]^{m\pm})"] \\
A^{m\pm}\,(aq) & + & nH_2O\,(aq) \arrow[r, "nRT\ln[H_2O]"'] & {[A(H_2O)_n]^{m\pm}\,(aq)}
\end{tikzcd}$$

SCHEME 2: Thermodynamic Cycle 2 (Cluster Cycle) for the Calculation of $\Delta G^*_{solv}(A^{m\pm})$

$$\begin{tikzcd}
A^{m\pm}\,(g) \arrow[d, "\Delta G^*_{solv}(A^{m\pm})"] & + & (H_2O)_n\,(g) \arrow[r, "\Delta G^o_{g,bind}(II) - \Delta G^{o-*}"] \arrow[d, "\Delta G^*_{solv}((H_2O)_n)"] & {[A(H_2O)_n]^{m\pm}\,(g)} \arrow[d, "\Delta G^*_{solv}([A(H_2O)_n]^{m\pm})"] \\
A^{m\pm}\,(aq) & + & (H_2O)_n\,(aq) \arrow[r, "RT\ln([H_2O]/n)"'] & {[A(H_2O)_n]^{m\pm}\,(aq)}
\end{tikzcd}$$

Cluster/continuum calculations of solvation free energies of ions with different thermodynamic cycles (see Schemes 1 and 2) have been reported by several research groups.[10–14,22–26]

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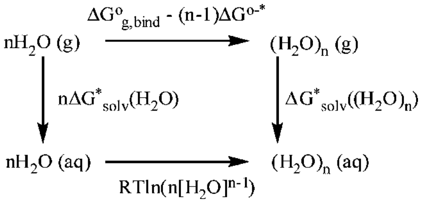
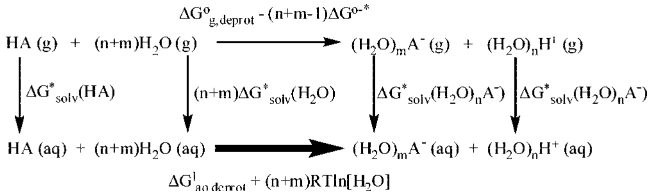
SCHEME 3: Thermodynamic Cycle for the Formation of Water Clusters



SCHEME 4: Thermodynamic cycle for the calculation of p*K*a.



However, the existing discrepancy among the calculated solvation free energies using different thermodynamic cycles has not been discussed in the literature. In this article, we compare the performance of two thermodynamic cycles in terms of their ability to predict solvation free energies for H^+ and Cu^{2+} ions. On the basis of the present and reported cluster/continuum calculations, we provide a rationale for selecting the most-appropriate thermodynamic cycle for the mixed cluster/continuum calculations of ion solvation free energies.

2. Thermodynamics of Solvation

A brief overview of solvation thermodynamics follows the work of Ben-Naim[31,32] and Marcus,[32] to which the reader should refer for a more thorough discussion. The chemical potential of a solute S in the gas phase and dilute solution (at a given temperature T and pressure P) can be expressed as

$$\mu_g(S) = RT\ln(\rho_g(S)\Lambda_s^3 q_s^{-1}) = [RT\ln(\Lambda_s^3 q_s^{-1}) + RT\ln(N_A)] + [RT\ln(\rho_g(S)) - RT\ln(N_A)] = \mu_g^\infty(S) + RT\ln[S_g] \quad (1)$$

$$\mu_{solv}(S) = \mu_g^\infty(S) + N_A W(S|solvent) + RT\ln[S_{solv}] = \mu_{solv}^\infty(S) + RT\ln[S_{solv}] \quad (2)$$

where k is the Boltzmann constant, N_A is Avogadro's number, $\rho(S)$ is the number density of particles S, $[S] = \rho(S)/N_A$ is the molar concentration, Λ_s^3 is the momentum partition function, q_s is the molecular partition function, and $W(S|solvent)$ is the coupling work or the Gibbs free energy of the interaction of S with its environment, that is, a pure solvent in this case. The quantities $\mu_g^\infty(S)$ and $\mu_{solv}^\infty(S)$ are, respectively, the standard chemical potentials of S in the gas phase and the solvent.

The standard molar Gibbs free energy of solvation is defined as the free energy of transfer of one mole of S from an ideal gas state to an infinitely dilute solution. This free energy of transfer is the difference between the standard chemical potentials of S in the two phases:

$$\Delta G_{solv}^*(S) = \mu_{solv}^\infty(S) - \mu_g^\infty(S) \quad (3)$$

Substituting eq 2 into eq 3 yields

$$\Delta G_{solv}^*(S) = N_A W(S|solvent) \quad (4)$$

Thus, the standard free energy of solvation can also be defined as the work of addition of a particle of S to a fixed position in the solvent, per mole of solute.

Equation 4 can also be applied to the self-solvation of water. In this case, the substitution of H_2O for S into eqs 1 and 2 yields

$$\mu_g(H_2O) = \mu_g^\infty(H_2O) + RT\ln[H_2O_g] \quad (5)$$

$$\mu_{solv}(H_2O) = \mu_g^\infty(H_2O) + N_A W(H_2O|H_2O) + RT\ln[H_2O_{solv}] \quad (6)$$

where $[H_2O_{solv}]$ is the concentration of the pure liquid at a given T and P. At equilibrium

$$\mu_g(H_2O) = \mu_{solv}(H_2O) \quad (7)$$

This enables us to express the free energy of self-solvation of water as

$$\Delta G_{solv}^*(H_2O) = N_A W(H_2O|H_2O) = RT\ln([H_2O_g]/[H_2O_{solv}])_{eq} \quad (8)$$

Substituting the saturation liquid and vapor densities[33] of water at $T = 298.15$ into eq 8 ($[H_2O_g] = 1.281\ 10^{-3}$ mol/L, and $[H_2O_{solv}] = 55.34$ mol/L) yields $\Delta G_{solv}^*(H_2O) = -6.32$ kcal/mol.

3. Selection of the Standard State

Most tabulations of experimental and calculated free energies of solvation are based on Ben-Naim's definition[1,2] of solvation as the transfer of a solute from a hypothetical ideal gas at 1 M into a hypothetical ideal 1 M aqueous solution at infinite dilution. The condition of equality of concentrations in the two phases yields solvation free energy with no translational entropy corrections for the phase change. This quantity is directly related to the solute−solvent interactions, as defined in eq 4. Although this standard state convention is fully accepted for solvated species, it still causes some confusion when water is both a solvated species and a solvent. According to the widely adopted symmetrical standard state definition, the activity of a pure solvent at standard conditions is taken as unity.[34,35] For pure water [H_2O(l)] at $T = 298$ K, this corresponds to a concentration of 55.34 M. However, using this definition of the standard state to describe the self-solvation of water leads to a free energy of transfer that contains an additional term because of the difference in solute (water) concentrations between the two phases. This can be avoided by adopting a standard state of 1 M for water. Although choosing the same standard state for the solute and the solvent may seem unnatural, a 1 M standard state of water can be thought of as just a hypothetical reference state, as pointed out by Pliego.[28,29] Thus, it is correct to use either a 1 M water solution or pure water as reference states because they can be interconverted easily by the addition of the translational entropy. This entropic conversion factor often causes confusion in the literature, as discussed in the next section of this article.

4. Thermodynamic Cycles for Cluster/Continuum Models

4.1. Thermodynamic Cycles for the Determination of $\Delta G_{solv}^*(A^{m\pm})$.

The inability of dielectric continuum models to give accurate predictions of the solvation free energies of charged solutes can be overcome by treating a part of the solvent explicitly. In this case, the solvation free energy of an ionic solute can be calculated by using the thermodynamic cycles depicted in Scheme 1[10–14] or 2.[22–26] For the monomer cycle (Scheme 1), an ionic solute reacts with n distinct water molecules. Conversely, a cluster of n water molecules reacts

TABLE 1: Absolute Aqueous Solvation Free Energies (kcal/mol) of $H_3O^+(H_2O)_n$ and $OH^-(H_2O)_n$ Clustered Ions[a]

	$H_3O^+(H_2O)_n$		$OH^-(H_2O)_n$	
N	ref 8	corrected	ref 8	corrected
1	−90.2	−87.8	−89.3	−86.9
2	−81.7	−77.0	−82.3	−77.5
3	−76.7	−69.6	−78.3	−71.2
4	−75.4	−65.9	−77.1	−67.6
5	−75.4	−63.6	−77.3	−65.4
6	−76.9	−62.7	−77.4	−63.1

[a] Values from ref 8 have been corrected to include the nRT ln[H_2O] term.

TABLE 2: Absolute Aqueous Solvation Free Energies (kcal/mol) of $(H_2O)_n$ Clusters at T = 298.15 K

n	$\Delta G^{\circ}_{\mathrm{g,bind}}$[a]	$\Delta G^{*}_{\mathrm{solv}}((H_2O)_n)$[b]	$\Delta G^{*}_{\mathrm{solv}}((H_2O)_n)/n$
2	2.08	−10.03	−5.01
3	3.51	−13.26	−4.42
4	2.43	−14.06	−3.51
5	2.16	−15.70	−3.14
6_{cyclic}	4.07	−19.54	−3.26

[a] Free energy of forming water clusters in the gas phase calculated by Dunn et al.[37] by using the CBS-APNO level of theory. [b] Calculated by using the thermodynamic cycle shown in Scheme 3.

with the ionic solute in the cluster cycle (Scheme 2). In both cases, $\Delta G_{\mathrm{g,bind}}{}^{\circ}$ is the gas-phase free energy of complexation and $\Delta G^{*}_{\mathrm{solv}}(X)$ is the standard free energy of solvation for X = $A^{m\pm}$, H_2O, $(H_2O)_n$, and $A(H_2O)_n{}^{m\pm}$.

Note that the correct construction of a thermodynamic cycle requires that each reactant or product in the upper and lower legs of the cycle be in the same standard state. This is the key point of our discussion and one that many authors do not consider properly. Often experimental and calculated gas-phase free energies are defined with the standard state being that of an ideal gas at 1 atm ($\Delta G^{\circ}_{\mathrm{g}}$), wheres free energies of solvation are associated with the 1 M (gas) → 1 M (solution) process ($\Delta G^{*}_{\mathrm{solv}}$). In this article, we evaluate all of the thermodynamic quantities in Schemes 1–4 by using the 1 M ideal gas and the 1 M solution as standard states.

The free-energy change of 1 mol of an ideal gas from 1 atm (24.46 L mol^{-1}) to 1 M (1 mol L^{-1}) is given by[7,8]

$$\Delta G^{\mathrm{o}\rightarrow *} = -T\Delta S^{\mathrm{o}\rightarrow *} = RT\ln(V_0/V^*) = RT\ln(24.46) = 1.89\ \mathrm{kcal/mol}\ (T = 298.15\mathrm{K}) \quad (9)$$

The conversion from an ideal gas standard state of 1 atm to a standard state of 1 M yields

$$\Delta G^{*}_{\mathrm{g}} = \Delta G_{\mathrm{g}}{}^{\mathrm{o}} + \Delta G^{\mathrm{o}\rightarrow *} \quad (10)$$

Applying eq 10 to each gas-phase reactant and product yields the corrections given in the upper legs of thermodynamic cycles 1 and 2.

The concentration corrections in the lower legs of cycles 1 and 2 can also be understood in terms of translational entropy corrections, as discussed below. The formation of a cluster of a solvated ion in liquid water does not involve any change in free energy. This can be expressed as

$$A^{m\pm}(\mathrm{aq}) + nH_2O(l)_{55.34\mathrm{M}} = [A(H_2O)_n]^{m\pm}(\mathrm{aq});\quad \Delta G^{l}_{\mathrm{aq,clust}} = 0 \quad (11)$$

$$A^{m\pm}(\mathrm{aq}) + (H_2O)_n(l)_{55.34/n\ \mathrm{M}} = [A(H_2O)_n]^{m\pm}(\mathrm{aq});\quad \Delta G^{l}_{\mathrm{aq,clust}} = 0 \quad (12)$$

The concentrations of H_2O and $(H_2O)_n$ in liquid water are 55.34 M and 55.34/n M, respectively. To combine reactions 11 and 12 with standard free energies of solvation defined by a standard state of 1 M, a correction term must be added. In cycle 1, the correction term is the free-energy change of n moles of H_2O gas from 55.34 M liquid state to 1 M

$$n\Delta G^{\mathrm{l}\rightarrow *}_{H_2O} = -nRT\ln(55.34) = -2.38n\ \mathrm{kcal/mol}\quad (T = 298.15\ \mathrm{K}) \quad (13)$$

For cycle 2, the correction term is the free-energy change of 1 mol of $(H_2O)_n$ gas from 55.34/n M liquid state to 1 M,

$$\Delta G^{\mathrm{l}\rightarrow *}_{(H_2O)n} = -RT\ln(55.34/n)\ (T = 298.15\ \mathrm{K}) \quad (14)$$

Thus, $\Delta G^{*}_{\mathrm{solv}}(A^{m\pm})$ from cycle 1 is given by[10]

$$\Delta G^{*}_{\mathrm{solv}}(A^{m\pm}) = \Delta G^{\mathrm{o}}_{\mathrm{g,bind}}(\mathrm{I}) + \Delta G^{*}_{\mathrm{solv}}([A(H_2O)_n]^{m\pm}) + n\Delta G_{\mathrm{vap}}(H_2O) \quad (15)$$

Here, $\Delta G_{\mathrm{vap}}(H_2O)$ is the vaporization free energy defined by

$$\Delta G_{\mathrm{vap}}(H_2O) = -G^{*}_{\mathrm{solv}}(H_2O) - RT\ln[H_2O] - \Delta G^{\mathrm{o}\rightarrow *} \quad (16)$$

$\Delta G^{*}_{\mathrm{solv}}(A^{m\pm})$ from cycle 2 can be written as

$$\Delta G^{*}_{\mathrm{solv}}(A^{m\pm}) = \Delta G^{\mathrm{o}}_{\mathrm{g,bind}}(\mathrm{II}) + \Delta G^{*}_{\mathrm{solv}}([A(H_2O)_n]^{m\pm}) - \Delta G^{*}_{\mathrm{solv}}((H_2O)_n) - \Delta G^{\mathrm{o}\rightarrow *} - RT\ln([H_2O]/n) \quad (17)$$

Note that eq 15 is exactly the equation that Pliego and Riveros[10] and Asthagiri et al.[13] derived by using a more formal description of the thermodynamics of solvation.

A number of reports with systematic errors in the computed solvation free energies have been published recently. The main source of error is the incorrect assignment of a standard state for water molecules or water clusters in the solvent phase. For example, Kelly et al.[7] employed thermodynamic cycle 1 (Scheme 1) to estimate the aqueous solvation free energies of solute−water clusters from the corresponding experimental gas-phase free energies of ion−water clusters and solvation free energies of bare ions. However, the concentration correction term, nRT ln[H_2O], was not included in their analysis. In a more recent publication,[8] these authors used H_2O(l) in the lower leg of thermodynamic cycle 1. They argued that the concentration of pure liquid should not appear in eq 15 because of the use of a standard state of ideal dilute solution, for which the activity of water is close to unity. Kelly et al.[7] subsequently used a value of $\Delta G^{*}_{\mathrm{solv}}(H_2O)$ = −6.32 kcal/mol to calculate the free energy of solute transfer from 1 M (gas) into 55.34 M (solution). Note that from our previous discussion, the correct value of the free-energy change for this process is $\Delta G^{*}_{\mathrm{solv}}(H_2O)$ + RT ln[H_2O] = −4.94 kcal/mol. To illustrate the significance of the concentration corrections, Table 1 lists published[8] and corrected experimental absolute solvation free energies (kcal/mol) for $H_3O^+(H_2O)_n$ and $OH^-(H_2O)_n$ clustered ions. Interestingly, the solvation free energy of the proton reported by Kelly et al.[8] is correct because it is based on the difference between the solvation free energies of cation−water and anion−water clusters. In this case, the standard state corrections cancel out.

Surprisingly, no concentration correction for water clusters using the cluster cycle (eq 14) was included in previous calculations of solvation free energies. Although this correction is smaller in magnitude than that given by eq 13, it is still significant. That is, it is greater than 1 kcal/mol in absolute value for $11 > n > 300$. For example, Zhan and Dixon[22] did not include concentration corrections in their high level ab initio calculations of the hydration free energy of the proton. Their calculated value (−264.3 kcal/mol) is ~1.6 kcal/mol less negative than the estimated value of −265.9 kcal/mol suggested by Tissandier et al.[30,36] However, the addition of concentration corrections (for $(\mathrm{H_2O})_4$ and $(\mathrm{H_2O})_{10}$ clusters) to Zhan and Dixon's calculations yields a value $\Delta G^{*}_{\mathrm{solv}}(\mathrm{H^+}) = -265.63 \pm 0.22$ kcal/mol that is closer to the value given by Tissandier et al.[30,36]

Finally, we would like to point out that Gutowski and Dixon[27] have recently employed a correction factor for $(\mathrm{H_2O})_n$ clusters in the form $-(\Delta G^{\mathrm{o}\rightarrow *} + \Delta G^{\mathrm{l}\rightarrow *}_{\mathrm{H_2O}})/n = -4.3/n$, which is quite different from that in eq 17. Note that this correction goes to zero when n goes to infinity, whereas the solvation phase correction factor defined by eq 14 would equal zero only when $n = [\mathrm{H_2O}] = 55.34$ M; that is, there is no change in the concentration of water molecules between the gas and liquid phases.

As an illustration of the validity of our approach, consider the gas-phase process in Scheme 2, where n is very large, $n = N_{\mathrm{A}}$, (Avogadro's number):

$$1\ \mathrm{ion}\ (\mathrm{A}^{m\pm}(\mathrm{g})) + 1\ \mathrm{cluster}\ ((\mathrm{H_2O})_{N_{\mathrm{A}}}) = 1\ \mathrm{ion}([\mathrm{A}(\mathrm{H_2O})_{N_{\mathrm{A}}}]^{m\pm});\quad [\mathrm{H_2O}] = 55.34\ \mathrm{M};\ \Delta G_{12\mathrm{b}} = \Delta G^{*}_{\mathrm{solv}}(\mathrm{A}^{m\pm})/N_{\mathrm{A}} \quad (12\mathrm{b})$$

If it is written per particle, then the free-energy change for reaction 12b is directly related to the solvation free energy, $\Delta G^{*}_{\mathrm{solv}}(\mathrm{A}^{m\pm})/N_{\mathrm{A}}$. Note that the concentration of water as reagent here is 55.34 M.

If one uses a standard state of 1 M for each component as in Schemes 1–4,

$$1\ \mathrm{M}\ (\mathrm{A}^{m\pm}(\mathrm{g})) + 1\ \mathrm{M}\ ((\mathrm{H_2O})_{N_{\mathrm{A}}}) = 1\ \mathrm{M}\ ([\mathrm{A}(\mathrm{H_2O})N_{\mathrm{A}}]^{m\pm});\quad [\mathrm{H_2O}] = \mathrm{N_A}\ \mathrm{M};\ \Delta G_{12\mathrm{c}} = \Delta G^{\mathrm{o}}_{\mathrm{g,bind}}(\mathrm{II}) - \Delta G^{\mathrm{o}\rightarrow *} \quad (12\mathrm{c})$$

then, the free-energy change is expressed as $\Delta G_{12\mathrm{c}} = \Delta G^{\circ}_{\mathrm{g,bind}}(\mathrm{II}) - \Delta G^{\mathrm{o}\rightarrow *}$. Note that the concentration of water as reagent using this standard state convention is N_{A} M. The Gibbs free-energy change for reaction 12c is related to the $\Delta G^{*}_{\mathrm{solv}}(\mathrm{A}^{m\pm})$ in reaction 12b by converting the concentration of water from N_{A} to 55.34 M. This is equivalent to changing the concentration of $(\mathrm{H_2O})_{N_{\mathrm{A}}}$ from 1 to $55.34/N_{\mathrm{A}}$ M. Using the conversion factor $RT \ln([\mathrm{H_2O}]/N_{\mathrm{A}})$ for this process leads to $\Delta G^{*}_{\mathrm{solv}}(\mathrm{A}^{m\pm}) = \Delta G^{\circ}_{\mathrm{g,bind}}(\mathrm{II}) - \Delta G^{\mathrm{o}\rightarrow *} - RT \ln [\mathrm{H_2O}]/N_{\mathrm{A}}$. This result can be obtained directly from the cluster cycle (eq 17) by equating $\Delta G^{*}_{\mathrm{solv}}((\mathrm{H_2O})_n)$ and $\Delta G^{*}_{\mathrm{solv}}([\mathrm{A}(\mathrm{H_2O})_n]^{m\pm})$ to 0 for very large n.

4.2. Thermodynamic Cycle for the Formation of Water Clusters. The formation of a cluster of n water molecules can be described as a simple rearrangement of liquid water into solvated water clusters with no change in free energy:

$$n\mathrm{H_2O}(l)_{55.34\mathrm{M}} = (\mathrm{H_2O})_n(l)_{55.34/n\ \mathrm{M}};\ \Delta G^{*}_{\mathrm{aq,clust}} = 0 \quad (18)$$

For the 1 M ideal gas and solution standard states, the concentration correction is given by

$$\Delta G^{*}_{\mathrm{aq,clust}} = \Delta G^{\mathrm{l}\rightarrow *}_{(\mathrm{H_2O})n} - n\Delta G^{\mathrm{l}\rightarrow *}_{\mathrm{H_2O}} = nRT \ln[\mathrm{H_2O}] - RT \ln([\mathrm{H_2O}]/n) = RT \ln(n[\mathrm{H_2O}]^{n-1}) \quad (19)$$

Thus, the corrected solvation free energy of a water cluster (Scheme 3) is expressed as

$$\Delta G^{*}_{\mathrm{solv}}((\mathrm{H_2O})_n) = -\Delta G^{\mathrm{o}}_{\mathrm{g,bind}} + (n-1)\Delta G^{\mathrm{o}\rightarrow *} + n\Delta G^{*}_{\mathrm{solv}}(\mathrm{H_2O}) + RT \ln(n[\mathrm{H_2O}]^{n-1}) \quad (20)$$

Table 2 lists the estimated solvation free energies of water clusters. The theses were calculated by using $\Delta G^{\circ}_{\mathrm{g,bind}}$ values for $(\mathrm{H_2O})_n$, $n = 2-6$, calculated by Dunn et al.[37] [at the CBS-APNO level of theory] and the experimental solvation free energy of water [$\Delta G^{*}_{\mathrm{solv}}(\mathrm{H_2O}) = -6.32$ kcal/mol].[33] Note that the solvation free energy of $(\mathrm{H_2O})_n$ clusters [per molecule] rapidly decreases with increasing n to approximately half the solvation free energy of a free water molecule because of the formation of hydrogen bonds between water molecules inside the clusters.

4.3. Thermodynamic Cycle for the Determination of pK_{a}. Our methodology can be applied to any reaction in aqueous solutions. For example, the selection of a consistent thermodynamic cycle for the calculation of acidity constants (pK_{a}) in aqueous solutions has been the subject of discussion in recent years.[28,29,39] By definition, pK_{a} is given by

$$\mathrm{HA(aq)} = \mathrm{A^-(aq)} + \mathrm{H^+(aq)};\ \mathrm{p}K_{\mathrm{a}} = -\log K_{\mathrm{a}} = \Delta G_{\mathrm{aq,deprot}}/(RT \ln 10) \quad (21)$$

Combining eq 21 with eq 11 yields

$$\mathrm{HA(aq)} + (n+m)\mathrm{H_2O(l)} = [\mathrm{A}(\mathrm{H_2O})_m] - (\mathrm{aq}) + [\mathrm{H}(\mathrm{H_2O})_n] + (\mathrm{aq});\ \mathrm{p}K_{\mathrm{a}} = \Delta \mathrm{G}'_{\mathrm{aq,deprot}}/RT \ln(10) \quad (22)$$

The free-energy change for reaction 22 is independent of the values of n and m when the activity of liquid water in the solution phase is unity. However, a correction term, $((n + m)RT \ln[\mathrm{H_2O}])$ must be added when the 1 M aqueous solution is used as standard state. In this case, the pK_{a} can be calculated by using the thermodynamic cycle shown in Scheme 4,

$$\mathrm{p}K_{\mathrm{a}} = 1/(RT \ln 10)(\Delta G^{\mathrm{o}}_{\mathrm{g,deprot}} + G^{\mathrm{o}\rightarrow *} + \Delta G^{*}_{\mathrm{solv}}([\mathrm{A}(\mathrm{H_2O})_m]^-) + \Delta G^{*}_{\mathrm{solv}}([\mathrm{H}(\mathrm{H_2O})_n]^+) - \Delta G^{*}_{\mathrm{solv}}(\mathrm{HA}) + (n+m)\Delta G_{\mathrm{vap}}(\mathrm{H_2O})) \quad (23)$$

Note that eq 23 is equivalent to the one derived by Pliego in ref 28. However, it is different from the equations used by Kelly et al.[9] and da Silva et al.[39] Because of this, the methodologies employed by these authors in refs 9 and 39 give systematic errors in the computed pK_{a}.

5. Computational Methods

The structures of neutral/protonated water clusters and Cu(II)−water clusters were optimized by using the B3LYP[40,41] variant of density functional theory (DFT). The standard 6-311G++(d,p) basis set with diffuse functions was employed in the light atoms. The standard Los Alamos effective core potential LACVP[42] uncontracted to form a triple-ζ valence basis set, LACV3P,[43] and diffuse function was employed in Cu. In addition, single-point energy calculations were performed by using more extended basis sets (i.e., the aug-cc-pVTZ(-f) basis set[44] for the light atoms and the LACV3P+ basis set augmented by two f-polarization functions[45] ($\alpha_{\mathrm{f}} = 4.97$ and 1.30) for Cu).

Frequency calculations were carried out with the smaller 6-31G** basis set. The standard Gibbs free energy of each species (X) in the gas phase was calculated by using the standard rigid rotor-harmonic oscillator approximation without scaling.

Three continuum solvent models were evaluated in this study: the COSMO model[46] as implemented in Turbomole,[47] the Poisson−Boltzmann (PB) model as implemented in Jaguar,[48] and the Jaguar version[48] of the SM6 model.[7] The electronic energies in the solvent reaction fields were calculated at the B3LYP/6-311++G(d,p) level, except for the SM6 model in which the largest allowed basis set was 6-31+G(d,p). Solvation calculations for ionic clusters were carried out using the COSMO model with all of the geometries fully optimized in the solvent reaction field. COSMO calculations were performed with the recommended solvation parameters optimized for neutral solutes:[49] solvent probe radius of 1.3 Å, solvent dielectric constant of 78.4, and atomic radii of 1.30 Å for hydrogen and 1.72 Å for oxygen. The Bondi radius[50] scaled by 1.17 (2.223 Å) was used for copper. Note that the results of the calculations are not sensitive to the choice of this parameter if the metal ion is completely surrounded by water molecules. The nonelectrostatic component (cavity term) of the solvation free energy was estimated by using the empirical relation given in ref 51.

6. Results and Discussion

As previously discussed, the free energy of solvation of an ionic species $A^{m\pm}$ can be calculated by using either the monomer cycle (eq 15) or the cluster cycle (eq 17). However, the two methods give significantly different results when coupled with the continuum solvent models. Note that the difference between the reactions in the cluster and monomer cycles (Schemes 1 and 2) gives the reaction of formation of water clusters (Scheme 3), which we discuss first to provide an explanation for the inconsistency between the two cycles.

6.1. Solvation of Water and Water Clusters. The calculated self-solvation free energies of water are, respectively, −8.80, −8.83, and −6.67 kcal/mol using the PB, the SM6, and the COSMO models. The latter value compares favorably with the experimental value of −6.32 kcal/mol.[33] The calculated gas-phase cluster free energies and solvation free energies of water clusters are summarized in Table 3. The residual errors of theoretical calculations in closing cycle 3 are also listed in Table 3. The magnitude of this error is a measure of deviation between the two thermodynamic cycles. As shown in Figure 1, the residual error increases almost linearly with the number of hydrogen bonds. One source of error is the inaccuracy of the calculated gas-phase free energies. Note that an extension of the basis set from 6-311G++(d,p) to aug-cc-pVTZ(-f) or using MP2/CBS electronic binding energies from ref 52 increases the residual error even further. The COSMO model provides the most accurate estimate for the $\Delta G^{*}_{\text{solv}}(H_2O)$ and gives the lowest error among the three continuum models tested in this study. However, even in this case, the residual error is still large (up to 41.1 kcal/mol for $(H_2O)_{18}$). One of the main sources of these errors (Figure 1) is the failure of the continuum solvation methods to describe accurately the solvation of water clusters. Continuum models are predicated upon the assumption that the solute (cluster) is a rigid species undergoing only harmonic vibrational motion. Because of this, changes in the internal partition function of a hydrogen-bonded solute induced by the presence of the solvent are generally not taken into account by continuum solvent models. In solution, however, there might be a potential of mean force among molecules in the cluster, resulting in high mobility and diffusion of water molecules.[10] Indeed, the calculated gas-phase entropy loss per mole of water upon the formation of $(H_2O)_{18}$ (29.5 eu) is significantly larger than the experimental entropy change associated with the gas (1 M) to liquid (1 M) transition (14.1 eu). Thus, the solvation free energy of $(H_2O)_{18}$ will be greatly underestimated in this case. One can presumably decrease this error by tuning the default solvent-accessible surface area contributions, which are primarily optimized for small and rigid molecules. However, we have not pursued this ad hoc approach and have used the default solvation parameters with each model.

TABLE 3: Calculated Gas-Phase Clusterization Free Energies and Solvation Free Energies of Water Clusters and the Total Residual Error of Closing Thermodynamic Cycle Shown in Scheme 3 Using Three Different Continuum Solvation Models[a]

		$\Delta G^{*}_{\text{solv}}((H_2O)_n)$			residual error		
n	$\Delta G^{\circ}_{\text{g,bind}}$	Jaguar[b]	COSMO[c]	SM6[d]	Jaguar[b]	COSMO[c]	SM6[d]
2	2.52	−15.51	−11.60	−15.40	−0.07	−0.42	0.09
3	4.71	−15.33	−10.73	−14.57	6.59	4.79	7.43
4	2.63	−18.05	−12.04	−17.28	6.17	3.63	7.03
5	2.06	−21.27	−14.48	−21.15	6.76	2.87	7.01
6	2.55	−24.11	−16.38	−24.32	8.84	3.76	8.78
8	8.11	−21.86	−15.16	−23.94	25.54	15.15	23.67
10	9.00	−29.25	−19.23	−30.17	27.97	16.64	27.31
12	13.85	−27.94	−17.61	−28.09	43.08	27.80	43.24
14	13.76	−32.82	−21.01	−34.55	47.09	29.01	45.71
16	19.28	−31.68	−20.01	−32.91	62.74	40.25	61.91
18	18.70	−36.48	−23.25	−39.46	66.35	41.15	63.82

[a] All energies are in kcal/mol. Electronic energies are calculated at the B3LYP/6-311++G(d,p) level [b] The Poison−Boltzmann continuum solvation model in Jaguar.[48] The calculated value for $\Delta G^{\circ}_{\text{solv}}$ (H_2O) is −8.80 kcal/mol. [c] The COSMO solvation model[46] in Turbomole[47] that gives the electrostatic contribution to the solvation free energy. Nonpolar contributions were estimated by using the empirical relation given in ref 51. The calculated value for $\Delta G^{*}_{\text{solv}}$ (H_2O) is −6.67 kcal/mol. [d] The SM6 solvation model of Kelly et al.[7] The calculated value for $\Delta G^{*}_{\text{solv}}$ (H_2O) is −8.83 kcal/mol.

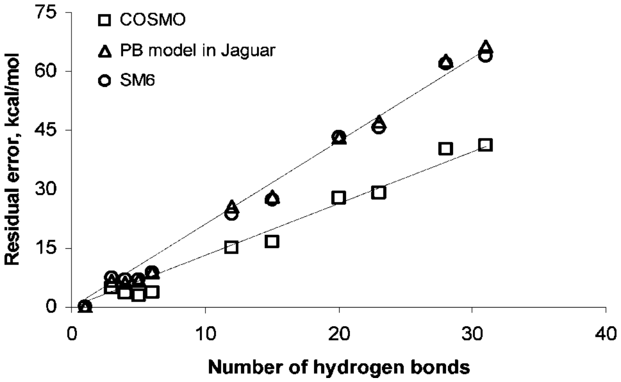


Figure 1. Correlation of the residual error for closing the thermodynamic cycle depicted in Scheme 3 with the number of hydrogen bonds in a water cluster. Calculations are performed by using three different continuum solvation models: COSMO, the Poisson−Boltzmann (PB) model implemented in Jaguar, and SM6. The line is drawn through the data points with the COSMO model and the PB model in Jaguar.

6.2. Solvation of Ions. As previously discussed, the ability of mixed cluster/continuum models to describe ion solvation has also been the subject of several investigations.

Pratt and co-workers[12–14] were the first to use rigorous statistical thermodynamic considerations to combine hybrid solvation models with a monomer cycle. They found that the best estimates of the solvation free energies are obtained when the size of the cluster (n) is selected variationally to produce

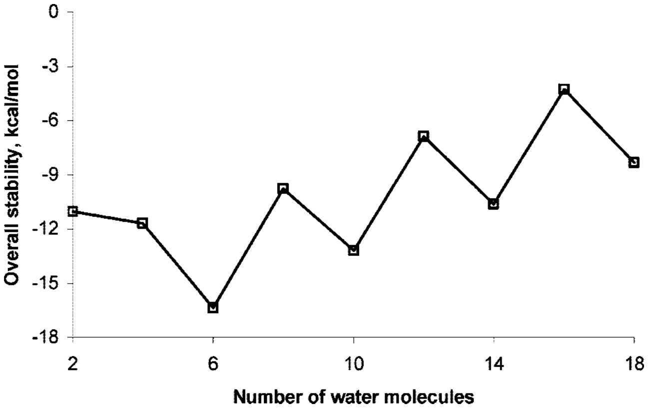


Figure 2. Dependence of the overall stability of $(H_2O)_n$ clusters in the aqueous phase defined as the sum of the gas-phase, $\Delta G^{\circ}_{g,bind}$, and solution phase, $\Delta G^{*}_{solv}((H_2O)_n)$, contributions (listed in Table 3) on the number of water molecules in the cluster. Solvation calculations are performed with the COSMO//B3LYP/6-311++G(d,p) method.

the lowest solvation free energy. For ions with well-defined coordination numbers, the optimum n is often equal to the number of solvent molecules in the first coordination shell. These authors also provided a detailed discussion of standard states pertinent to a monomer cycle. A closely related approach has been subsequently employed by Pliego and Riveros.[10,11]

The combination of a cluster/continuum model with a cluster cycle (Scheme 2) provides an alternative approach for the solvation free energy of ions. The underlying premise behind this methodology is that the interactions between $[A(H_2O)_n]^{m\pm}$ and bulk water are similar to those between $(H_2O)_n$ and bulk water in the limit of large n.[22] Thus, it is critical in this case to ensure that calculations are well converged as the number of explicit water molecules increases. This could significantly increase the computational cost due to the need to locate the low-energy isomers of relatively large solute−water clusters.

The selection of the number of explicit water molecules (n) is another important factor when using a cluster/continumm approach with a cluster cycle. The results of calculations shown in Figure 2 suggest that clusters with even numbers of water molecules ($n = 4$ to 18) break down into two subgroups with quite different sums of $\Delta G^{\circ}_{g,bind}$ and ΔG^{*}_{solv} $((H_2O)_n)$. This is due to different patterns of hydrogen bonds for the most stable $(H_2O)_n$ water clusters with n and $n + 2$ (Figure 3).[53–57] Thus, for the determination of the solvation free energies by using the cluster cycle we recommend to employ water clusters from the lowest-energy subgroup ($n = 6$, 10, 14, 18...).

6.2.1. Calculations of $\Delta G^{*}_{solv}(H^{+})$. Direct experimental measurements can only provide relative values for the solvation free energies of ions. These are often tabulated with respect to the solvation free energy of the proton. Thus, the accurate estimation of the absolute solvation free energy of the proton is of fundamental importance and has been the subject of numerous theoretical and experimental studies.[2,8,13,22,25,26,36,58–61] The key issue is that the solvation free energy of the proton cannot be measured directly. Because of this, assumptions are often made to separate the solvation free energy of a salt into contributions from the cation and anion. As a result, there is a large spread (>13 kcal/mol) in the reported values of the proton solvation free energy. Camaioni and Schwerdtfeger[30] have recommended using $\Delta G^{*}_{solv}(H^{+}) = -265.9$ kcal/mol, a benchmark value derived by Tissandier et al.[30,36] by using the cluster pair approximation and recently reproduced to within 0.2 kcal/mol by Kelly et al.[8]

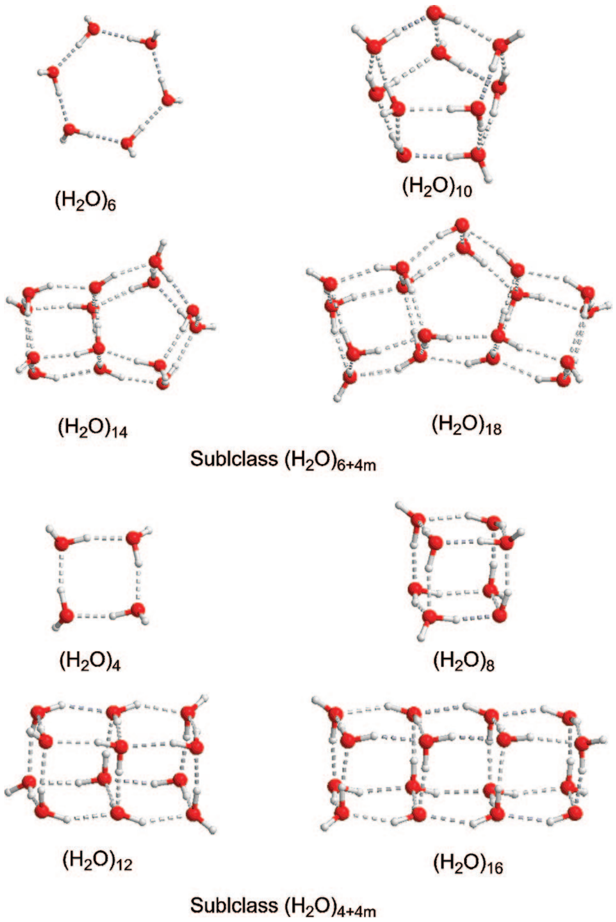


Figure 3. Most stable geometries of $(H_2O)_n$, $n = 4$ to 18, as obtained from B3LYP calculations using the 6-311++G(d,p) basis set. $(H_2O)_n$ clusters with $n = 6 + 4m$ and $4 + 4m$ and $m = 1$ to 3, broken down into two subclasses with different arrangements of the hydrogen bonds.

The cluster pair approximation is based on the assumption that the difference between the absolute solvation free energies for positively and negatively charged ion−water clusters goes to zero as the cluster becomes infinitely large. The solvation free energy of the proton is determined by comparing the difference in the clustering free energies of cation−anion pairs containing clustered water molecules (up to six water molecules in the Kelly's et al.[8] analysis) with the difference between conventional solvation free energies of the ion-pairs containing no water molecules. Warren et al. in a recent publication advocated using solvation free energies of ions on the basis of this approximation as a benchmark set for parametrization of ion force fields. However, they and several others[13,61,62] have argued that the value of Tissandier et al. is not the absolute value for the solvation free energy, but rather, this value also includes an additional contribution from the electrostatic potential of the liquid phase relative to that in the gas phase (potential of the phase). This statement is supported by liquid simulation results using classical potentials.[13,61,62] This statement has been criticized[3,8] because of the conceptual difficulty in defining such a potential for clusters of just a few water molecules that needs to be considered to be a part of intermolecular interactions between a solute and a solvent ΔG^{*}_{solv} $(A^{m\pm})$. There is a general agreement that the potential of the phase is not present in pure continuum solvent calculations and bulk solvent simulations performed under periodic boundary conditions. More importantly for our present discussion, how-

TABLE 4: Solvation Free Energy of the Proton (kcal/mol) Calculated Using the Monomer Cycle and the Cluster Cycle

	monomer cycle							cluster cycle						
					$\Delta G^{\circ}_{\mathrm{solv}}(\mathrm{H}^+)$(I)							$\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+)$(II)		
n	$\Delta G_{\mathrm{g,bind}}{}^{\circ}$ (I)[a]	BSIE[b]	$\Delta\Delta G^{*}_{\mathrm{solv}}$(I)[c]	SScor (I)[d]	(el)[e]	(nonel)[f]	(full)	$\Delta G_{\mathrm{g,bind}}{}^{\circ}$ (II)[a]	BSEI[b]	$\Delta\Delta G^{*}_{\mathrm{solv}}$ (II)[c]	SScor (II)[d]	(el)[e]	(nonel)[f]	(full)
1	−156.9	0.6	−82.2	−4.3	−242.8	0.0	−242.8	−156.9	0.6	−82.2	−4.3	−242.8	0.0	−242.8
2	−185.4	2.6	−58.0	−8.5	−249.3	−1.4	−250.7							
4	−209.2	5.8	−27.7	−17.1	−248.2	−4.3	−252.5	−211.8	1.0	−46.6	−3.4	−260.8	0.1	−260.7
6	−215.5	8.4	−10.2	−25.6	−242.9	−7.3	−250.2	−218.0	0.2	−40.9	−3.2	−261.9	0.0	−261.9
10	−214.8	14.0	20.6	−42.7	−222.9	−13.7	−236.6	−223.8	−0.2	−38.5	−2.9	−265.4	0.1	−265.3
14	−215.0	20.6	55.0	−59.8	−199.2	−20.0	−219.2	−228.8	0.0	−34.9	−2.7	−266.4	0.0	−266.4
best estimate							−252.5[g]							−266.7[h]

[a] Electronic binding energies are calculated at the B3LYP/6-311G++G(d,p) level. Harmonic frequency analysis is performed using the 6-31G(d,p) basis set. [b] Basis set incompleteness error (BSIE) calculated as the change in the electronic binding energy with increasing the basis set size from 6-311G++(d,p) to aug-cc-pVTZ(-f). [c] Bulk solvent free-energy change: $\Delta\Delta G^{*}_{\mathrm{solv}}(\mathrm{I}) = \Delta G^{*}_{\mathrm{solv}}([\mathrm{H}(\mathrm{H_2O})_n]^+) - n\Delta G^{*}_{\mathrm{solv}}(\mathrm{H_2O})$ and $\Delta\Delta G^{*}_{\mathrm{solv}}(\mathrm{II}) = \Delta G^{*}_{\mathrm{solv}}([\mathrm{H}(\mathrm{H_2O})_n]^+) - \Delta G^{*}_{\mathrm{solv}}((\mathrm{H_2O})_n)$. [d] Standard state correction: $\mathrm{SScor(I)} = -nRT\ln[\mathrm{H_2O}] - n\Delta G^{\circ\rightarrow *}$ and $\mathrm{SScor(II)} = -RT\ln([\mathrm{H_2O}]/n) - \Delta G^{\circ\rightarrow *}$. [e] Total solvation free energy including only electrostatic contribution to solvation from COSMO/B3LYP/6-311G++(d,p). [f] Nonelectrostatic contribution to solvation using the cavity-formation term as described in ref 51. [g] The minimal value of $\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+)$(I) with respect to n. [h] $\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+)$ extrapolated to $n \rightarrow \infty$ assuming exponential decay of $\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+)$ with n.

TABLE 5: Solvation Free Energy of the Cu^{2+} Ion (kcal/mol) as Calculated Using the Monomer Cycle and the Cluster Cycle

	monomer cycle							cluster cycle						
					$\Delta G^{*}_{\mathrm{solv}}(\mathrm{Cu}^{2+})$(I)							$\Delta G^{*}_{\mathrm{solv}}$ (Cu^{2+})(II)		
n	ΔG $_{\mathrm{g,bind}}{}^{\circ}$ (I)[a]	BSIE[b]	$\Delta\Delta G^{*}_{\mathrm{solv}}$ (I)[c]	SScor (I)[d]	(el)[e]	(nonel)[f]	(full)	$\Delta G_{\mathrm{g,bind}}$ $^{\circ}$ (II)[a]	BSEI[b]	$\Delta\Delta G^{*}_{\mathrm{solv}}$ (II)[c]	SScor (II)[d]	(el)[e]	(nonel)[f]	(full)
4	−271.6	1.6	−177.2	−17.1	−464.3	−4.3	−468.7							
6	−304.3	4.8	−137.7	−25.6	−462.8	−7.4	−470.2	−306.8	−3.5	−168.4	−3.2	−481.9	0.0	−481.9
8	−333.0	9.3	−101.9	−34.2	−459.8	−10.4	−470.2							
10	−343.7	11.8	−80.6	−42.7	−455.2	−13.5	−468.7	−352.7	−2.3	−139.7	−2.9	−497.6	0.3	−497.3
18	−362.5	24.9	0.9	−76.9	−413.6	−26.2	−439.8	−381.2	−2.5	−120.6	−2.6	−506.9	0.1	−506.8
best estimate							−470.2[g]							−509.0[h]

[a] Electronic binding energies are calculated at the B3LYP/6-311G++G(d,p) level. Harmonic frequency analysis is performed using the 631G(d,p) basis set. [b] Basis set incompleteness error (BSIE) calculated as the change in the electronic binding energy with increasing the basis set size from 6-311G++(d,p) to aug-cc-pVTZ(-f). [c] Bulk solvent free-energy change: $\Delta\Delta G^{*}_{\mathrm{solv}}(\mathrm{I}) = \Delta G^{*}_{\mathrm{solv}}([\mathrm{Cu}(\mathrm{H_2O})_n]^{2+}) - n\Delta G^{*}_{\mathrm{solv}}(\mathrm{H_2O})$ and $\Delta\Delta G^{*}_{\mathrm{solv}}(\mathrm{II}) = \Delta G^{*}_{\mathrm{solv}}([\mathrm{Cu}(\mathrm{H_2O})_n]^{2+}) - \Delta G^{*}_{\mathrm{solv}}((\mathrm{H_2O})_n)$. [d] Standard state correction: $\mathrm{SScor(I)} = -nRT\ln[\mathrm{H_2O}] - n\Delta G^{\circ\rightarrow *}$ and $\mathrm{SScor(II)} = -RT\ln([\mathrm{H_2O}]/n) - \Delta G^{\circ\rightarrow *}$. [e] Total solvation free energy including only electrostatic contribution to solvation from COSMO/B3LYP/6-311G++(d,p). [f] Nonelectrostatic contribution to solvation using the cavity-formation term as described in ref 51. [g] The minimal value of $\Delta G^{*}_{\mathrm{solv}}(\mathrm{Cu}^{2+})$(I) with respect to n. [h] $\Delta G^{*}_{\mathrm{solv}}(\mathrm{Cu}^{2+})$ extrapolated to $n \rightarrow \infty$ assuming exponential decay of $\Delta G^{*}_{\mathrm{solv}}(\mathrm{Cu}^{2+})$ with n.

ever, is that irrespective of the outcome of the ongoing discussion on the absolute solvation free energy of the proton,[3,8,13,30,36,61,62] our cluster/continuum calculations can be properly compared with the set of experimental data interpreted by using the cluster pair approximation. Indeed, the potential of the phase, if included in the Tissandier et al. analysis, would also be included in eqs 15 and 17 for calculation of $\Delta G^{*}_{\mathrm{solv}}$ $(\mathrm{A}^{m\pm})$ as a part of the gas-phase clustering free energy. As mentioned above, continuum dielectric calculations treat $[\mathrm{A}(\mathrm{H_2O})_n]^{m\pm}$ as a rigid cluster with no change in solute−solvent interaction (partition function) inside the cluster (including the part of the interaction corresponding to the potential of the phase). Thus, it is warranted to make a direct comparison between the calculations of ion−water clusters (cluster/continuum calculations) and the ion solvation free energies assigned using the gas-phase experiments on ion−water clusters (cluster−pair approximation).

Table 5 list the free energies of solvation of the proton $(\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+))$ and the various gas- and solvent-phase contributions calculated by using the monomer and cluster cycles (Schemes 1 and 2). Hodges et al.[63] have carried out an extensive search of the conformational space of protonated water clusters. They combined a basin-hopping algorithm with the potentials developed by Kozack and Jordan[64] and Hodges and Stone.[65] We used the five structures with the lowest gas-phase energies for $n \geq 6$ located by Hodges et al.[63] as initial structures in our geometry optimizations. These were carried out at the B3LYP/6-311G++(d,p) level of theory in the gas phase and COSMO solvent reaction field. Geometries and electronic energies of all $\mathrm{H}(\mathrm{H_2O})_n{}^+$ complexes optimized in the gas phase and in the solvent are provided in the Supporting Information.

The $\Delta G^{*}_{\mathrm{solv}}(\mathrm{H}^+)$ for each cluster size is computed by using the lowest-energy structure in the solvent reaction field. Table 4 highlights the effect of basis set on the calculated electronic energies. The effect of extending the basis set from 6-311G++(d,p) to aug-cc-pVTZ(-f) is significant for the monomer cycle (Scheme 1). In this case, the difference in the binding energy increases with the size of the cluster. Conversely, the effect of the basis set size on the calculated binding energies for the cluster cycle (Scheme 2) is small and becomes negligible for larger n. Note also that the cavity contributions to the solvation free energies are significant and increase linearly with n for the monomer cycle but are negligible for the cluster cycle (Table 4).

The B3LYP method used in conjunction with large basis sets is known to underestimate the binding energies of water clusters compared with the more accurate but computationally more demanding calculations at the MP2 and CCSD(T) level. However, the error given by B3LYP for the difference in total binding energies between $\mathrm{H}^+(\mathrm{H_2O})_n$ and $(\mathrm{H_2O})_n$ clusters is expected to be much smaller. Indeed, the gas-phase free-energy change of −210.8 kcal/mol calculated at the B3LYP/aug-cc-

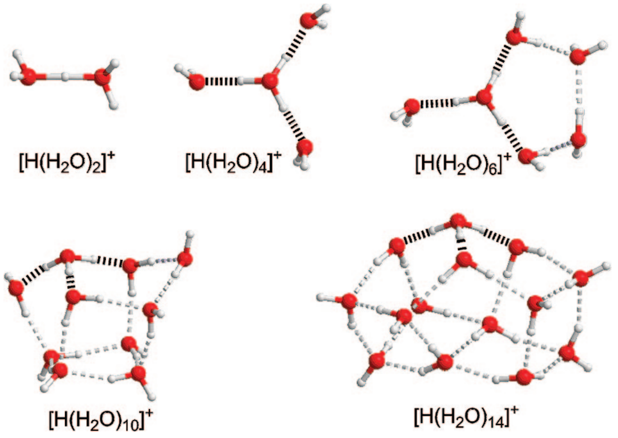


Figure 4. Most stable structures of $[H(H_2O)_n]^+$ found in our calculations after COSMO optimization at the B3LYP/6-311G++(d,p) level.

pVTZ(-f)//6-311G++(d,p) level is in excellent agreement with the value of −211.1 kcal/mol calculated in ref 22 for the same process at the CCSD(T) level with extrapolation to complete basis set limit and corrections for core-valence correlation and relativistic effects.

The bulk solvent shift, $\Delta\Delta G^*_{\text{solv}}$ (II), calculated with the B3LYP-COSMO method for $n = 4$, is −46.6 kcal/mol. It can be compared with the −51.3 kcal/mol for the same process in ref 22 using the MP2-SVPE method. This difference is likely to arise from a different parametrization of the two solvation models. The COSMO model overestimates the hydration free energy of water by 0.3 kcal/mol, whereas the SVPE model used in ref 22 overestimates it by 2.6 kcal/mol (by 0.9 kcal/mol after including the cavity contribution[51]). We emphasize that it is critical to model accurately the solvation free energy of water for the accurate estimation of ΔG^*_{solv} ($A^{m\pm}$) because the interaction between $[A(H_2O)_n]^{m\pm}$ and bulk water is mainly due to interactions between water molecules.

The best estimate of ΔG^*_{solv} (H^+) is obtained by analyzing its dependence on the number of water molecules in the solute−water cluster (Figure 5). For the monomer cycle, ΔG^*_{solv} (H^+) exhibits a minimum at $n = 4$, followed by a gradual increase. The minimum value of −252.5 kcal/mol for ΔG^*_{solv} (H^+) provides the best estimate for the solvation of the proton using the monomer cycle (Scheme 1). Note that the calculated ΔG^*_{solv} (H^+) are sensitive to the nonelectrostatic contributions (cavity term). The calculations performed without cavity terms yield the lowest solvation energy of −249.3 kcal/mol for the $[H(H_2O)_2]^+$ cluster.

Figure 5 shows that the cluster cycle (Scheme 2) gives calculated proton solvation free energies that monotonically decrease and level off as n increases. The change in ΔG^*_{solv} (H^+) is significant from $n = 1$ to $n = 6$ (~19 kcal/mol), moderate from $n = 6$ to $n = 10$ (~3.4 kcal/mol), and relatively small from $n = 10$ to $n = 14$ (~1.1 kcal/mol). The results are reasonably converged at $n = 14$. This enables us to estimate ΔG^*_{solv} (H^+) by extrapolating the calculated energies to $n \rightarrow \infty$ by using the exponential function

$$\Delta G^*_{\text{solv}}(n) = \Delta G^*_{\text{solv}}(n \rightarrow \infty) - (a)\exp(-(b)n) \qquad (24)$$

where a and b are the fitting parameters. This yields a ΔG^*_{solv} ($n \rightarrow \infty$) of −266.7 kcal/mol, which is our best estimate of the proton hydration free energy using the cluster cycle. This estimate is very close to the value (−265.9 kcal/mol) recommended by Tissandier et al.[36] Conversely, the difference between the monomer cycle estimate and the recommended value of ΔG^*_{solv} (H^+) is ~14 kcal/mol. The overall results of our calculations suggest that the monomer cycle does not produce accurate estimates of solvation free energies. This may be the result of an unbalanced reaction scheme involving n separate water molecules on the reactant side and a solute−water cluster on the product side (Scheme 1) having problems similar to those observed for the water cluster formation cycle (Scheme 3 and Table 3). The reaction scheme for the cluster cycle (Scheme 2) is more balanced with clusters of similar size on both the reaction and product sides. Because of this, calculation errors associated with the treatment of solvation effects in hydrogen-bonded clusters largely cancel out. In this case, our results suggest that high-level correlated ab initio methods, extended basis sets, and surface-area-dependent nonpolar solvation contributions are not needed to obtain accurate solvation free energies (see Table 4).

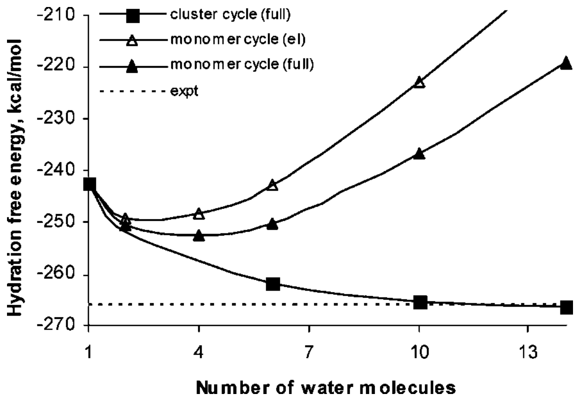


Figure 5. Solvation free energy of the proton as a function of the number of water molecules in the cluster. The monomer cycle is shown in Scheme 1, and the cluster cycle is shown in Scheme 2. Solvation calculations are performed with the COSMO method giving the electrostatic contribution (el) and by including the nonelectrostatic cavity formation contribution (full) to the solvation free energy. The later term appears to be negligible for the cluster cycle, and thus, only the cluster cycle (full) data points are shown.

6.2.2. Calculations of ΔG^*_{solv} (Cu^{2+}). The next example compares the performance of the two thermodynamic cycles for predicting the solvation free energy of a Cu(II) ion. The solvation of transition metal ions is particularly difficult to model because of the pronounced ligand field stabilization effects and significant extent of the charge transfer from the ligands to the metal.[27,66,67] We have studied the electronic and geometric structures of various hydrated Cu(II) complexes, $[Cu(H_2O)_n]^{2+}$, as a function of the metal coordination number (4 to 6) and the cluster size ($n = 4$ to 18). The lowest-energy structures of the $[Cu(H_2O)_n]^{2+}$ complexes in the aqueous phase for $n = 4$, 6, 8, 10, and 18 are depicted in Figure 6. More detailed analysis of the role of the first and second shells of water on the structure and energetics of $[Cu(H_2O)_n]^{2+}$ will be reported in a separate article.[68]

Table 5 and Figure 6 summarize the calculated hydration free energies of Cu^{2+} as a function of n. Comparative analysis of the results obtained using the monomer and the cluster cycles reveals the same qualitative differences as noted for the solvation of the proton. Again, the cluster approach is intrinsically less sensitive to the use of the extended basis set and the inclusion of nonpolar solvation contributions. The best estimate of the ΔG^*_{solv} (Cu^{2+}) with the monomer cycle (Scheme 1) is −470.2 kcal/mol, which is the shallow minimum around $n = 6$ to 8. The results for the cluster cycle (Scheme 2) show that the convergence of ΔG^*_{solv} (Cu^{2+}) as a function of n is much slower

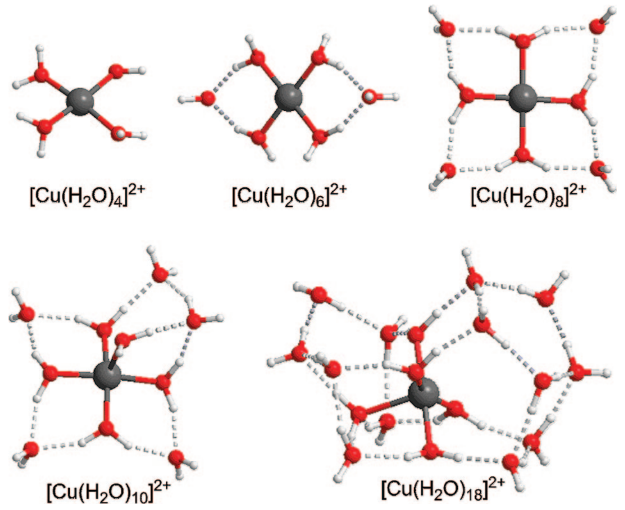


Figure 6. Most stable structures of $[Cu(H_2O)_n]^{2+}$ found in our calculations after COSMO optimization at the B3LYP/ LACV3P+/6-311G++(d,p) level.

than that of ΔG^*_{solv} (H^+). There is a very large change in hydration free energy from $n = 6$ to 10 (~15.4 kcal/mol) and a significant change from $n = 10$ to 18 (~9.5 kcal/mol). Although we cannot claim that the calculated hydration free energy of Cu(II) has fully converged at $n = 18$, we can estimate the limit of ΔG^*_{solv} (Cu^{2+}) when $n \rightarrow \infty$ by using the exponential fit (eq 24). This leads to a value of −509.0 kcal/mol, which is our best estimate of the ΔG^*_{solv} (Cu^{2+}) with the cluster cycle.

Similar to the results obtained for the proton, the value of $\Delta G^*_{\text{solv}}(Cu^{2+})$ calculated with the cluster cycle is within the experimental uncertainty (507.0 ± 4 kcal/mol). Conversely, the value of $\Delta G^*_{\text{solv}}(Cu^{2+})$ calculated with the monomer cycle underestimates the experimental value by more than 35 kcal/mol. Again the inability of the monomer cycle to give adequate estimates can be attributed to systematic errors resulting from an unbalanced reaction scheme involving n separate water molecules on the reactant side and a solute−water cluster on the product side (Scheme 1). Note the decrease in the $\Delta G^*_{\text{solv}}(Cu^{2+})$ calculated with the cluster cycle as more water molecules are added to the outer shells of the ion−water clusters. This can be attributed to the fact that there is still a significant charge transfer between the ligands and the metal center beyond the first coordination shell, as illustrated in Figure 8 by using charges from natural atomic orbitals (NAO).[69] For soft divalent d- and f-block[27] metal ions, this is likely to be a general phenomenon. Continuum solvent models and classical molecular dynamics simulations with nonpolarizable potentials are not able to describe the charge-transfer effect. Thus, the solvation free energies for transition metal ions will be underestimated when they are calculated by using cluster/continuum models with only a single (first) hydration shell treated explicitly. Note that charge transfer is expected to die out quickly with increasing distance from the metal center, thus justifying the use of eq 24 to estimate the bulk limit solvation free energy of metal ions in solutions.

6.2.3. Comparison with Published Results.

The monomer cycle was used by Asthagiri et al.[13,14] in the framework of the quasi-chemical theory and by Pliego et al.[10,11] within a conceptually similar cluster-continuum model. Tawa et al.[25] and Mejías et al.[26] were among the first investigators to use the cluster cycle to calculate the solvation free energy of an ionic solute, although no standard state correction expressed by eq 14 was applied. Calculations performed at the higher level of theory using a cluster cycle were reported by Zhan et al.[22] Table 6 compares the results of these calculations with respect to their accuracy in predicting solvation free energies of a few simple ions. Classical liquid simulation results from polarizable and nonpolarizable force fields are also included for the comparison.[13,61,62] In addition to the experimental data based on Tissandier's proton hydration free energy of −265.9 kcal/mol, we also list the data compiled by Marcus using the proton hydration free energy of −254.3 kcal/mol.[2] The latter ion-cluster data are consistent with the tetraphenylarsonium tertaphenylborate (TATB) assumption[60,70] commonly adopted by the molecular dynamics simulation community.

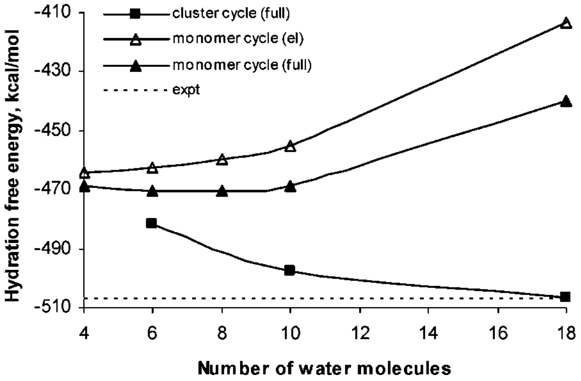


Figure 7. Solvation free energy of Cu^{2+} as a function of the number of water molecules in the cluster. The monomer cycle is shown in Scheme 1, and the cluster cycle is shown in Scheme 2. Solvation calculations are performed with the COSMO method giving the electrostatic contribution (el) and by including the nonelectrostatic cavity formation contribution (full) to the solvation free energy. The later term appears to be small for the cluster cycle, and thus, only the cluster cycle (full) data points are shown.

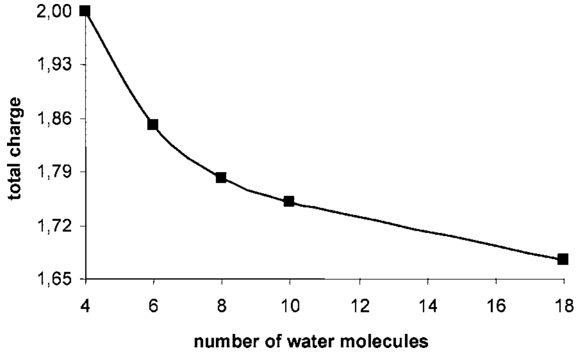


Figure 8. Dependence of the natural atomic orbital (NAO) charge confined by the Cu^{2+} and the four equatorial water molecules on the total number of water molecules in $[Cu(H_2O)_n]^{2+}$. This indicates a significant charge transfer from the metal ion to the second and outer hydration shells.

A close examination of Table 6 reveals several important points: (1) Our results are consistent with all of the reported values when they are compared using the same thermodynamic cycle. (2) Solvation calculations using the cluster cycle are in excellent agreement with the values recommended by Tissandier et al.[36] (3) There is also a very reasonable agreement between independent classical liquid simulation results and the values suggested by Marcus.[2] These two sets of data can be reconciled by assuming a contribution from the potential of the phase (see section 6.2.1) present in the cluster/continuum calculations (using both the monomer and the cluster cycle) and the data from Tissandier but absent in the classical liquid simulations and the data from Marcus. Indeed, taking into account the total liquid−vacuum interfacial potential of −11.5 to −12.7 kcal $mol^{-1}e^{-1}$, estimated for various water models,[62,71–73] yields a

TABLE 6: Comparison of the Theoretical Values of Hydration Free Energy for Ionic Solutes Obtained Using the Monomer Cycle, the Cluster Cycle, and Classical Liquid Simulations with Experiment (kcal/mol)

	monomer cycle			cluster cycle			classical liquid simulations[c]			expt	
ion	Asthagiri[13,14]	Pliego[10]	this work	Zhan[22]	Zhan (cor)[b]	this work	Asthagiri[13]	Grossfield[61]	Warren[62]	Marcus[2]	Kelly[8]
H^+	−254.6	−257.7[a]	−252.5	−264.3	−265.6	−266.7		−254.4[d]		−254.3	−265.9
OH^-	−105.3	−93.1		−106.4	−107.1		−121.1; −123.8	−116.8[e]		−116.3[h]	−104.7
Li^+	−120.5			−127.0	−128.5				−102.3−105.4[f]	−116.9	−128.4
K^+	−75.2							−74.5	−56.2−69.5[f]	−74.6	−86.0
Cu^{2+}	−473.6		−470.2			−509.0				−483.7	−507.0[j]

[a] Converted to the $\Delta G^*_{\text{solv}}(H^+)$ given the calculated value of $\Delta G^*_{\text{solv}}(H_3O^+)$ and the known experimental difference[33] between the solvation free energies for H^+ and H_3O^+. [b] Computational results of Zhan et al.[22] corrected for the standard state change according to eq 14. [c] Not adjusted for the potential of the phase. [d] Converted to the $\Delta G^*_{\text{solv}}(H^+)$ given the calculated value of $\Delta G^*_{\text{solv}}(K^+)$ (−74.5 kcal/mol) and the known difference, $\Delta G^*_{\text{solv}}(H^+) - \Delta G^*_{\text{solv}}(K^+) = -179.9$ kcal/mol.[61] [e] Converted to the $\Delta G^*_{\text{solv}}(OH^-)$ given the calculated value of $\Delta G^*_{\text{solv}}(Cl^-)$ (−84.6 kcal/mol) and the known difference, $\Delta G^*_{\text{solv}}(OH^-) - \Delta G^*_{\text{solv}}(Cl^-) = -30.3$ kcal/mol. There is a typographical error in Table 8 of ref 61 for $\Delta G^*_{\text{solv}}(OH^-)$. [f] The variation in the solvation free energy calculated by using five ion model sets. [g] Adjusted to correspond to the 1 M (gas) → 1 M (solution) process. [h] Adjusted according to the $\Delta G^*_{\text{solv}}(H^+)$ of −254.3 kcal/mol and the known sum, $\Delta G^*_{\text{solv}}(H^+) + \Delta G^*_{\text{solv}}(OH^-) = -370.7$ kcal/mol. [i] An uncertainty of experimental data is no less than 2 kcal/mol for singly charged ions and 4 kcal/mol for doubly charged ions.[8] [j] Taken from ref 2 and adjusted according to the $\Delta G^*_{\text{solv}}(H^+)$ value of −265.9 kcal/mol.

remarkable agreement (within 1 kcal/mol) among cluster cycle calculations, best liquid simulations using polarizable force fields,[61] and experiment. The only serious discrepancy is for the monomer cycle, which produces solvation free energies that are significantly underestimated compared to the values of Tissandier et al.[36]

One important test of the accuracy of the two cluster/continuum methods is the ability to reproduce the difference between $\Delta G^*_{\text{solv}}(Cu^{2+})$ and $\Delta G^*_{\text{solv}}(H^+)$, which is directly measurable. The cluster cycle yields 24.4 kcal/mol, which is in excellent agreement with the experimental value of 24.9 kcal/mol. Conversely, the calculations with the monomer cycle performed by us and by Asthagiri et al.[14] lead to a mean absolute error of 9.9 and 10.7 kcal/mol, respectively.

These results are consistent with the statement we made earlier that coupling the monomer cycle with continuum solvent calculations leads to systematic errors in the calculated $\Delta G^*_{\text{solv}}(A^{m\pm})$ values that are too positive. The fundamental problem here is that continuum dielectric calculations treat hydrogen-bonded complexes as rigid clusters with no change in the internal partition function caused by the solvent.

The boundary defining a separation between inner and outer solvent molecules in the monomer cycle is obtained by applying a variational check to the right-hand side of eq 15 (the value of n that yields the lowest $\Delta G^*_{\text{solv}}(A^{m\pm})$). Note that eq 15 is, in principle, exact. $\Delta G^*_{\text{solv}}(A^{m\pm})$ has a minimum with respect to some finite n only because the calculated value of $\Delta G^*_{\text{solv}}([A(H_2O)_n]^{m\pm})$ using continuum models is underestimated and the calculational error increases with increasing cluster size. Because this minimum of $\Delta G^*_{\text{solv}}(A^{m\pm})$ with respect to n is an artifact of continuum calculations, the boundary from applying this variational check has no real physical meaning.

There is no such boundary in the cluster approach because the dependence of the right-hand side of eq 17 on n is expected to be monotonic (apart for some oscillations with cluster size), converging to some limit at large n. This provides a reasonable picture of solvation thermodynamics, especially for multiply charged ions (such as Cu^{2+}) in which water molecules in the second hydration shell have a significant influence on the calculated $\Delta G^*_{\text{solv}}(A^{m\pm})$.

A much better overall performance of the cluster cycle can be attributed for the most part to its tendency to compensate for systematic errors present in gas- and solvation-phase calculations by considering the difference in free energies for clusters of similar size. This makes the cluster approach much less sensitive to such factors such as the deficiency of continuum solvation models, the incompleteness of the basis sets, the approximate nature of DFT functionals, the inclusion of anharmonic corrections to the vibrational frequencies, the nonpolar contributions to solvation, and so forth.

The difference in solvation free energy between the two approaches is particularly striking for Cu^{2+}. The full solvation of the first and the second shells around Cu^{2+} is needed for an accurate prediction of the solvation free energy with the cluster approach. This can be attributed to significant charge transfer involving the first and the second solvation shell. Conversely, the stabilizing effect of the second coordination sphere cannot be properly described with the monomer cycle suffering from uncompensated errors associated with the solvation of ion−water clusters.

This study provided a critical analysis of the monomer and the cluster cycle results and raised several important issues regarding the choice of the most appropriate calculation method. We hope this paper will spur further research into the development of accurate methods for calculation of solvation free energies of ionic solutes.

7. Conclusions

We have presented a simple methodology that leads to thermodynamically consistent equations for the calculation of solvation free energies using mixed cluster/continuum models. The approach is based on the use of consistent thermodynamic free-energy cycles with the same standard state for each species involved in the reactions. Ignoring this requirement leads to systematic errors in the computed free energies.

We analyze two different thermodynamic cycles for calculating the solvation free energies of ionic solutes: the cluster cycle with an n water cluster as a reagent (Scheme 2) and the monomer cycle with n distinct water molecules as reagents (Scheme 1). Using the cluster cycle leads to a mean absolute error of 0.8 kcal/mol for H^+ and 2.0 kcal/mol for Cu^{2+} when compared with the experimental values suggested by Tissandier et al.[30,36] Conversely, calculations using the monomer cycle yield solvation free energies that are underestimated by >10 kcal/mol for H^+ and >30 kcal/mol for Cu^{2+}. This is likely due to systematic errors present in the solvation energy calculations for hydrogen-bonded clusters that are not compensated for in the monomer cycle but largely cancel out in the cluster cycle. We find that the stabilizing effect resulting from the inclusion of water molecules beyond the first coordination shell is significant and amounts to 5 kcal/mol for H^+ and 27 kcal/mol for Cu^{2+}. Thus, accurate estimations of solvation free energies for these systems require the explicit inclusion of at least the first and second hydration shells.

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Supporting Information Available: Synopsis Cartesian coordinates and absolute energies for all $H(H_2O)_n{}^+$ complexes optimized in the gas phase and in the field of the continuum solvent (COSMO model with water as a solvent) at the B3LYP/6-311++G(d,p) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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