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LETTERS

Quasi-Chemical Theory and the Standard Free Energy of $H^+(aq)$

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Quasi-chemical theory and electronic structure results on inner-sphere $H(H_2O)_n{}^+$ clusters are used to discuss the absolute hydration free energy of $H^+(aq)$. It is noted that this quantity is not thermodynamically measurable, and this leads to some relative misalignment of available tables of absolute hydration free energies of ions in water. The simplest quasi-chemical model produces a reasonable quantitative result in the range of −256 to −251 kcal/mol. The primitive concepts on which the model is based naturally identify the Zundel cation $H_5O_2{}^+$ as the principal chemical structure contributing to this hydration free energy. The specific participation of an Eigen cation $H_9O_4{}^+$ is not required in this model because the definition of that structure depends on outer-sphere arrangements, and a crude dielectric continuum model is here used for outer-sphere contributions.

I. Introduction

The aqueous hydrogen ion, $H^+(aq)$, is ubiquitous in chemistry and biology. Thermodynamic properties of this component are relevant to the molecular modeling of many biological processes and to understanding pK_a's on a molecular basis. However, the hydration free energy of $H^+(aq)$ is not thermodynamically measurable, as is well-known. Furthermore, calculations are more complicated for $H^+(aq)$ than for other cases (e.g., $Li^+(aq)$). Large discrepancies exist between experimental and calculational estimates for the hydration free energy of $H^+(aq)$, despite the evident utility of this information. An acknowledged range of experimental and theoretical values is −265 to −251 kcal/mol.[1−4] Because this absolute hydration free energy of $H^+(aq)$ serves as a reference value for hydration free energies of ionic species in water, different tabulations of absolute hydration free energies of ions in water typically differ by this same amount, roughly 10 kcal/mol.

On the calculational side, a basic difficulty is that the interaction of H^+ with the water solvent is intrinsically "chemical" (i.e., not easily described by simple force-fields to sufficient accuracy). Recognized structural diversity in the hydration of H^+ also complicates computational work. Therefore, ab initio molecular dynamics calculations, with substantial empirical ingredients, have played a dominant role in computational studies of $H^+(aq)$.[5−20] However, these calculations have required a vast allocation of computational resources, and still the information obtained is typically not sufficient to formulate confident estimates of the hydration free energy desired.

Because this single ion hydration free energy is not thermodynamically measurable, it might be questioned whether it is important to have an accurate value for it. An answer to this question is that this hydration free energy is not unknowable.[21] A precise value for it would test theories that have a goal of molecular understanding in addition to predicting experimental quantities, including thermodynamic ones.

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The recently developed quasi-chemical theory provides a systematic way of including the most important solvent contributions into calculations of the free energies sought in such cases.[22,23] The simplest quasi-chemical approach says something surprising about the hydration structures contributing to the case of H^+(aq) and yields a realistic value with surprisingly little computational effort. Describing that model and result is the goal of this letter.

Quasi-chemical developments can be completely formalized, but practical calculations are decidedly approximate. Therefore, the result produced here is not terminal. Simplicity of the theory and the reasonable value suggest that this approach would repay subsequent efforts to study natural corrections on this basis.

Quasi-chemical theory partitions the chemical potential of a solute in a solvent into (a) an inner-shell contribution, where chemical effects are deemed important, and (b) an outer-shell contribution, where chemistry is considered nonexistent and all the interactions between the inner shell and the rest of the system are described by conventional force-field or continuum dielectric models. The inner shell refers to a bonding region, typically the first solvation shell. In the present work, a continuum dielectric model supplies the outer term, and high-level electronic structure methods, the inner term.

For clarity, we will build our discussion for the case of D^+(aq). The tricky but ultimately avoided question of "which H^+?" is then side-stepped from the beginning. The calculations are carried out for the proton solute, however, and we do not address the issue of isotope effects for these free energies. The more primitive questions are difficult enough as they are.

II. Quasi-Chemical Theory

The development here applies to any extraneous solute in aqueous solution. Consider specifically a distinguished hydrogen ion, D^+. The quasi-chemical form

$$\beta\mu^{\mathrm{ex}}_{D^+(aq)} = -\ln(1 + \sum_{m\geq 1} K_m \rho_{H_2O}{}^m) - \ln\langle\langle e^{-\beta\Delta U_{D^+}} \textstyle\prod_j (1 - b_{D^+j})\rangle\rangle_0 \qquad (1)$$

describes the contributions of the solute–solution interactions to the chemical potential of the species D^+. This excess chemical potential is partitioned into an inner-shell (bonding) contribution (the first term on the right side of eq 1) and an outer-shell contribution (the remainder). The inner-shell region is defined by an indicator function b_{D^+j}, which is equal to 1 if water molecule j is within the bonding region of the distinguished D^+ and zero (0) otherwise. The outer-shell contribution would be the hydration free energy under the hypothetical constraint that no inner-sphere bonding is permitted. The inner-shell contribution is associated with the equilibrium for chemical equations

$$D^+ + mH_2O \rightleftharpoons D(H_2O)_m{}^+ \qquad (2)$$

for the formation of inner-shell complexes *in situ*. The coefficients K_m are equilibrium ratios for these equations. The advantage of the quasi-chemical formulation is that a reasonable initial approximation is to use $K_m \approx K_m{}^{(0)}$, the equilibrium ratio for the case in which the effects of the external medium on K_m are neglected as if the cluster were present in an ideal gas. The harmonic approximation to $K_m{}^{(0)}$ is available from electronic structure calculations. $K_m{}^{(0)}$ is obtained under conditions of standard temperature (298.15 K) and pressure (P_o= 1 atm), and hence the reference density is just $\rho_o = 1$ atm/RT. It is then understood that the factors of ρ_{H_2O} that appear in eq 1 are referenced relative to this density, and their contribution is accounted for by adjusting the free energies by the amount $-mRT\ln(\rho_{H_2O}/\rho_o) = -mRT\ln(1354)$. In other words, we specify a pressure of 1354 atm $= \rho_{H_2O}RT$, where $\rho_{H_2O} = 1$ gm/cm^3.[24,25] Note that eq 1 immediately gives us the excess chemical potential and thus measures the reversible work of coupling the solute with the solvent. This corresponds to the Ben-Naim[26] definition of solvation, and it is usual to think of this as the transfer of the solute from an ideal gas to an ideally diluted solution at the same density. ρ_o appearing above is solely a handy device to compute the equilibrium constants using standard electronic structure tools. One could in principle choose $\rho_o = \rho = 1$ gm/cm^3 but then compute the equilibrium constants at densities corresponding to the density of water (i.e., at 1 gm/cm^3) or specify a pressure of 1354 atm in electronic structure programs.

It is convenient here to define the volume of b_{D^+j} as a ball centered on the ion with a radius midway between the first and second peaks in the OH radial distribution function for water.[27] In principle, the suitability of this definition of the inner-sphere region can be given a variational check. The final net hydration free energy should be independent of this inner–outer-sphere partitioning of contributions. It has been argued that when this insensitivity is observed the inevitable approximations are reasonably balanced.[22]

We will treat the outer-sphere contribution with a primitive dielectric model[28,29] and combine those contributions with corrections to $K_m{}^{(0)}$ accounting for medium effects on the *in situ* equilibrium ratios. Thus, we introduce $\tilde{K}_m = K_m{}^{(0)}\exp[-\beta(\mu^{\mathrm{ex}}_{D(H_2O)_n{}^+} - n\mu^{\mathrm{ex}}_{H_2O})]$ and write

$$\beta\mu^{\mathrm{ex}}_{D^+(aq)} \approx -\ln(1 + \sum_{m\geq 1} \tilde{K}_m \rho_{H_2O}{}^m) \qquad (3)$$

The quantities $\mu^{\mathrm{ex}}_{D(H_2O)_n{}^+}$ are obtained with the primitive dielectric model. The leading term (1) in eq 3 corresponds to the bare ion. Similarly, the outer sphere terms treat the bare ion, including electrostatic and packing contributions. No accounting for the implied packing interactions is attempted because these contributions are expected to be roughly 100 times smaller than the chemical energies of first importance here.

Consider the Movie. It is interesting to consider the movie that might be made from an ab initio molecular dynamics simulation of a D^+ ion at infinite dilution in liquid water. We expect to see exchanges

$$D^+ + H_2O \rightleftharpoons H^+ + DOH \qquad (4)$$

From the point of view of the quasi-chemical treatment here, the condition of the D^+ on the right is recombination with a hydroxide ion OH^-, and that is not accounted for. Such a contribution from recombination with a hydroxide ion would be flagged by a term involving ρ_{OH^-}. Formally, we might require that the clusters involving the distinguished D^+ have a net 1+ charge, or we might require the ligands to be dynamically immutable and $\rho_{OH^-} \rightarrow 0$. In fact, the model is the same for the D^+ case as for other extraneous ions (e.g., Li^+ or Be^{2+} in which the acidity of the aquo complexes is a significant question). The same issue would arise for those other extraneous ions. Any of these formalities beg the same physical questions: What chemical configurations contribute and how do we identify charged chemical species in solution when electronic charge is distributed? From the point of view of traditional statistical mechanics of solutions, it would be satisfactory to implement

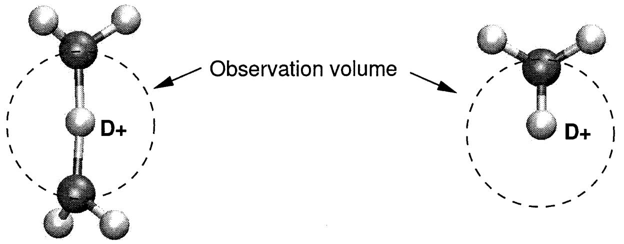

Figure 1. Quasi-components in proton hydration. The observation volume from the perspective of the distinguished proton, D^+, is indicated.

the theory on an atomic basis and to consider all possibilities for the formation of clusters, charged or neutral, that might form on a D solute. That would be much more complicated than the present simple model, and we do not pursue more complicated treatments here.

III. Protonated Water Cluster Geometries

To apply this model, we study inner-sphere clusters formed on a D^+ (Figure 1). Gas-phase minimum-energy structures of protonated water clusters $H(H_2O)_n{}^+$ were found at the B3LYP/6-311+G(d) level.[30] Random configurations were first optimized with a simplex algorithm[31] using the OSS2 water potential developed by Ojamae, Shavitt, and Singer.[32] The resulting minimum-energy clusters were reoptimized in Gaussian 98 at the B3LYP/6-311+G(d) level.[30]

The radial distribution of OH distances in water has its first peak at about 1.0 Å and a second peak at about 2.0 Å.[27] The only clusters with all oxygens within 2.0 Å of a distinguished proton are the hydronium and Zundel cations. The Eigen cation is recognized as an arrangement of outer-sphere material. This is consistent with previous work where protonated clusters were shown to contain the excess proton within either a hydronium or Zundel cation surrounded by waters.[33,34] On this basis, we truncate the sum of eq 3 after including the $m = 2$ (Zundel) term.

The individual terms in eq 3 were evaluated by adopting the harmonic approximation and utilizing widely available tools. In all cases considered, the $m = 2$ (Zundel) term dominated the $m = 1$ (hydronium) term by 5−6 kcal/mol.

By embedding the B3LYP/6-311+G(d) results for geometry and partial charges inside a molecular volume of atom-centered spheres (radii $R_O = 1.576$ Å and $R_H = 1.172$ Å) with a water dielectric continuum external to this molecular volume, we obtain the hydration free energy $\mu^{ex}_{H^+(aq)} \approx -255$ kcal/mol, which is within the wide range of -251 to -265 kcal/mol of experimental and theoretical solvation free energies.[2] Increasing the $R_H = 1.26$ Å value increased this energy by about 2 kcal/mol.

In a separate series of calculations, we optimized clusters at B3LYP/6-31+G(d,p), at which level the harmonic approximation was also applied. The electronic energies, however, were obtained at B3LYP/aug-cc-pVTZ (i.e., with an augmented, correlation-consistent basis set). A virtue of this level of theory is that basis set superposition errors are greatly minimized, and a better prediction is made of just the gas-phase properties of a single water molecule. With this level, too, the $m = 2$ (Zundel) term dominated, and the final solvation free energy of the proton is predicted to be -256 kcal/mol.

IV. Discussion

The range of values from -256 to -251 kcal/mol is in the lower end of the range of values from -265 to -251 kcal/mol that is quoted in the literature. Thus, it is helpful to compare our work with other theoretical and theoretical/experimental estimates.

The quasi-chemical theory has something definite to say about the solution structures that contribute to the free energy of $H^+(aq)$ and the description of outer shell contributions on the basis of coarse dielectric models. (A variational check is available to confirm the definition and balance of inner and outer shell contributions.) In particular, the model here emphasizes that the Eigen cation structure need not be explicitly included as an inner shell contributor to the free energy of $H^+(aq)$ although the Eigen cation structure would appear naturally in consideration of $H_3O^+(aq)$. That consideration would belong to a more ambitious iterated quasi-chemical scheme. We do not pursue such an approach here because additional concerns will have to be resolved. The foremost such concern is the rigid-rotor harmonic-oscillator approximation. Gomez and Pratt[37] have already shown that anharmonic effects are not negligible for a cluster as simple as H_3O^+. These effects should be more pronounced for weakly hydrogen-bonded outer-sphere complexes such as the Eigen cation. Anharmonic vibrations would likely lower (i.e., make more negative) the solvation free energy of the proton, $\Delta G_{solv}(H^+)$.

In contrast, earlier theoretical efforts have endeavored to build progressively larger clusters to converge to some estimate, but haven't proceeded beyond harmonic approximations associate with minimum energy configurations.[2,38] A further contribution is the entropy required to sequester water molecules in a complex. This contribution is supplied approximately in the present treatment by the explicit factors of water density in eq 3. The cluster treatments do not answer the question what is the density of the solvent and so do not address this fundamental issue. Another entropic contribution is the conformational entropy distinct from naive anharmonicity of a single energy minimum. Finally, we note that convergence with respect to cluster size through a series of finite-sized clusters is generally convergence to a different result than the conventional absolute hydration free energy. This is due to the surface polarization of a cluster that provides a substantial contribution that does not vanish for large clusters.

Other estimates of $\Delta G_{solv}(H^+)$ have been based on a combination of experimental and theoretical inputs. These have typically used thermodynamic cycles (see refs 3 and 39). Although this is a reasonable approach, in such cases, a skew in any one number affects all others, and ultimately, a molecular-level understanding is not provided. To see this, consider the calculations by Liptak and Shields[3] and by Riveros and co-workers.[39] If we take their analysis of the dissociation of acetic acid to the acetate ion and a proton, we note a misalignment of about 7 kcal/mol for the solvation free energy of the acetate ion between these two studies. However, both groups quote very similar values for the solvation free energy of acetic acid, the pK_a of acetic acid, and $\Delta G_{solv}(H^+)$. The differences in this instance is due to the values for the gas-phase thermochemistry part of the thermodynamic cycle. Riveros and co-workers[39] adopt their value from the literature, whereas Shields and co-workers[3] calculate theirs using a very high level of theory. A subsequent paper by Shields and co-workers[40] further strengthens the case for $\Delta G_{solv}(H^+)$ around -264 kcal/mol, a value that is also close to the estimate based on using experimental information on ion−water clusters.[4] If this value does indeed stand in disparate circumstances, then theory has a clear marker to achieve. As already discussed, we believe a significant step in improving the present calculations would be to understand anharmonic effects, and following these iterated quasi-chemical[23,36] procedures would be a natural corollary.

V. Conclusions

Tabulations of absolute hydration free energies of ions differ by approximately 10 kcal/mol because of the ambiguity of the absolute hydration free energy of H^+(aq). Computational physical chemistry might reduce this 10 kcal/mol relative misalignment by exhaustive study of an alternative case that is simpler for computation (e.g., Li^+(aq) rather than H^+(aq)). For the H^+(aq) case, the model discussed here is surprisingly simple and produces estimates of the absolute hydration free energy of H^+(aq) in the range of -256 to -251 kcal/mol, in reasonable agreement with experimental and theoretical estimates. The model is well embedded in organized statistical thermodynamics, so the approximations are available for investigation.

The quasi-chemical approach provides a single consistent framework for treating inner- and outer-shell contributions, acknowledging that different approximations are appropriate in the different regions. Thus, traditional tools of computational chemistry are applied to inner-shell bonding problems, though these methods would be inappropriate for the statistical issues arising from the outer-sphere contributions. Similarly, dielectric models are used for outer-shell electrostatic contributions, though they would be problematic for issues of nearest neighbors of hydrated ions.

The primitive concepts on which the model is based naturally identify the Zundel cation $H_5O_2^+$ as the principal chemical structure contributing to this hydration free energy. However, the direct participation of the Eigen cation $H_9O_4^+$ is not evident because the definition of that structure depends on outer-shell arrangements, which this model treats highly approximately. A recent extension of these quasi-chemical ideas suggests an alternative procedure for the treatment of outer-shell effects;[36] it seems likely that the Eigen structure would reappear in those more ambitious treatments. However, other issues need to be addressed as this work proceeds further. In particular, the harmonic approximation for the inner-shell clusters deserves testing.[37]

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