Single-Ion Hydration Thermodynamics from Clusters to Bulk Solutions: Recent Insights from Molecular Modeling

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Abstract: The importance of single-ion hydration thermodynamic properties for understanding the driving forces of aqueous electrolyte processes, along with the impossibility of their direct experimental measurement, have prompted a large number of experimental, theoretical, and computational studies aimed at separating the cation and anion contributions. Here we provide an overview of historical approaches based on extrathermodynamic assumptions and more recent computational studies of single-ion hydration in order to evaluate the approximations involved in these methods, quantify their accuracy, reliability, and limitations in the light of the latest developments. We also offer new insights into the factors that influence the accuracy of ion-water interaction models and our views on possible ways to fill this substantial knowledge gap in aqueous physical chemistry.

Keywords: Single-ion hydration; molecular modeling; extrathermodynamic assumption; cluster ion; surface potential

1. Introduction

The relative magnitude of cation and anion contributions to hydration thermodynamics and local charge imbalances are the main driving forces behind physical and chemical processes in inhomogeneous electrolytes, which are responsible for the formation of the electric double layer at interfaces, selective ion adsorption and separation, diffusion through solutions and membranes, protein denaturation, or transport through ion channels in biological systems.

The importance of the subject and impossibility¹⁻³ of direct experimental measurement of single-ion thermodynamics in bulk solutions has motivated development of a multitude of approximate approaches intended to overcome the limitations given by the electroneutrality condition. These so-called extrathermodynamic assumptions (ETA) are based on physically

motivated intuitive ideas about ion-water interactions, typically involving some form of assumed symmetry to split neutral salt properties to cation and anion contributions, but different assumptions result in significantly different predictions.⁴⁻⁹ The estimated Gibbs free energies and enthalpies of hydration from various ETAs are spread over the range of 40-50 kJ/mol, *i.e.*, the energy corresponding to two typical hydrogen bonds, and could result in qualitatively different solvation structures. Moreover, some of these estimated values are still used to develop molecular models of ion-water interactions¹⁰ or form a part of *ab initio* computational techniques,^{11,12} so the potential errors can affect computer simulations and propagate to other studies.

A more promising way to determine single-ion hydration thermodynamics is based on molecular-scale understanding of ion-water interactions derived from first principles.¹³ Ultimately, this bottom-up approach would be based on quantum chemical calculations, and with a perfect representation of inter-particle interactions and large computational resources, this method will, in principle, arrive at the correct values. However, the current limitations on the size of the investigated system require the use of approximative techniques that may introduce uncertainties of their own. These size and time restrictions on the simulated system can be overcome with molecular simulations using effective classical force fields, whose speed makes it possible to study large-scale bulk solutions and interfacial systems needed to capture reliably the effects of the surface potential. The critical part of molecular modeling is the adequacy and accuracy of the used force fields, which should be comparable to high-level *ab initio*-predicted interactions and thoroughly validated against reliable experimental data. It follows that careful evaluation of experimental reference data, use of high-level quantum chemical methods, and various consistency checks are a prerequisite for accurate representations of ion-water interactions and reliable predictions of single-ion hydration thermodynamics.

In this article we evaluate the current approaches used to investigate ion hydration and include recent insights into the factors that adversely influence the accuracy of the ETAs, quantum chemical methods, and classical molecular force fields. We also suggest ways to either minimize these factors or correct their effect in order to achieve the related goals of accurate description of ion-water interactions and single-ion hydration thermodynamics. For simplicity, we restrict the discussion to systems in which ions only interact with water without interference from other species, such as in infinitely diluted solutions or in gas-phase clusters. Since the separation of cation and anion contributions can be done for any ion pair while the rest can be computed from known neutral salt values, we focus on simple atomic ions that do not exhibit complex behavior, *e.g.*, vibrational, rotational, and electronic degrees of freedom of molecular ions that may preclude stability in the gas phase.¹⁴ This scenario corresponds to the typical subject of other computational studies, in which quantum chemical methods often concentrate on the hydration of H^+ and OH^- ions, as they are light and can be treated at the same level as the surrounding H_2O molecules, and classical molecular simulations typically work with ions that do not form chemical bonds, such as alkali metal cations or halide anions.

After introducing the basic terminology, thermodynamic relations, and common conventions (Section 2), we will briefly review the most important experimental sources of information on the structure, dynamics, and thermodynamics of ions in gas and aqueous phases (Section 3). To set the essential background for the following discussion of computational methods, we will consider the justification and criticisms of several ETAs that are most often used as references for microscopic modeling (Section 4). Subsequently we discuss recent quantum and classical computational studies of ion hydration and analyze factors that can negatively impact their accuracy (Section 5). Finally, we summarize the current status of the subject and outline possible future developments that should lead to better understanding of ion hydration thermodynamics.

2. Thermodynamics of ion formation and hydration

The formation of ions in the bulk aqueous phase can be described by a thermodynamic cycle shown in Figure 1. In the first major step, a gaseous ion is formed from elements in their standard states, and in the second, the ion is immersed in pure water. Throughout this manuscript we follow the standard state definitions, conventions, and units used in the NBS compilation of thermodynamic properties.¹⁵ The standard state of pure substances is defined at the temperature of 298.15 K and the pressure of 100 kPa; the standard state of individual ions in aqueous solutions is defined at the temperature of 298.15 K and the concentration of 1 mol per 1 kg of water in the state of an ideal solution; the electron is treated classically and the units follow the SI conventions. The NBS tables also serve as our reference for reliable thermodynamic properties of formation.

Figure 1. The thermodynamic cycle of ion hydration following the conventions used in the NBS compilation.¹⁵ Shaded areas denote species in solution with the standard state of 1 mol per kg of solvent. The horizontal lines span reactions and reaction free energies, $\Delta_r G^\circ$, corresponding to the formation of ions in the gas phase (red), hydration of ions (blue), and formation of ions in bulk water (green). Note that the formal charge, z , is negative for anions.

2.1. Gas-phase ionization

The formation of gas phase atomic ions can be described by the following reaction

where $A(ss)$ denotes the element A in its standard state, z is the formal charge of the atomic ion, $e^-(g)$ denotes an electron in the gas phase, and n is the number of atoms in the standard state form of element A, *e.g.*, for $H_2(g)$ $n = 2$ and for $Na(cr)$ $n = 1$. Note that z is negative for anions. The enthalpy of reaction (1) is given as

$$D_r H^\circ = D_f H^\circ [A^z(g)] + z D_f H^\circ [e^-(g)] - D_f H^\circ [A_n(ss)]/n \quad (2)$$

By convention the enthalpy of an element in its standard state is equal to zero. We also adopt the so-called electronic convention (EC),¹⁶ according to which the electron is treated as a standalone element. Therefore, the formation enthalpy of an electron is also equal to zero and the reaction enthalpy is equal to the formation enthalpy of the ion. The actual value of the ion formation enthalpy can be calculated from the known ionization energy, IE , at 0 K and integrated heat capacities (enthalpy differences) between 0 and 298.15 K. In the first step of this thermodynamic cycle (Figure1), the atomic gas of the element A is formed,

$$D_r H^\circ = D_f H^\circ [A(g)] - D_f H^\circ [A_n(ss)]/n \quad (3)$$

In the second step, the atoms are cooled down to 0 K, ionized, and the charged products are heated back to 298.15 K:

$$D_r H^\circ = IE + (H_T^\circ - H_0^\circ)[A^z(g)] + z(H_T^\circ - H_0^\circ)[e^-(g)] - (H_T^\circ - H_0^\circ)[A(g)] \quad (4)$$

For cations the ionization energy is equal to their ionization potential while for anions it is equal to their electron affinity. To a very good approximation the atoms and atomic ions can be treated as classical ideal gas particles following the Boltzmann statistics leading to the integrated heat capacities $H_T^\circ - H_0^\circ$ equal to 6.197 kJ/mol. In reality, the electron does not behave like a classical particle, but follows more closely the Fermi-Dirac statistics, which leads to the electron value of $H_T^\circ - H_0^\circ$ equal to 3.146 kJ/mol.¹⁶ Ionic formation enthalpies taking into account the quantum

nature of the electron are denoted EC-FD (Fermi-Dirac). Despite the non-classical behavior of electrons, a common convention is to treat electrons as classical particles, resulting in $H_T^\circ - H_0^\circ$ equal to those of the atoms or ions; this convention is denoted as EC-B (Boltzmann) and leads to ionic formation enthalpies differing by 3.151 kJ/mol from the EC-FD values. Since a particular choice of the convention does not influence results related to ion hydration and because important reference resources use the EC-B convention, we adopt it throughout this article.

The translational entropy of simple monoatomic ions can be calculated from the Sackur-Tetrode equation for ideal gas,¹⁷

$$S_{tr}^\circ = R \ln \left[\frac{k_B T}{P^\circ} \frac{(2 \rho m k_B T)^{3/2}}{h^3} \right] + \frac{5}{2} R \quad (5)$$

In general, an additional contribution to ion entropy comes from the electronic partition function,

$$q_{el} = \prod_i^n (2J_i + 1) \exp[-e_i/k_B T] \quad (6)$$

However, for the main-group ions with closed shells only the ground electronic state has to be considered, in which case the electronic contribution to entropy can be neglected.¹⁷ As in the case of enthalpy, the electron can be treated either classically, in which case Eqn. (5) is used, or quantum mechanically. The entropy of the electron gas is 20.979 J/K/mol in EC-B convention and 22.732 J/K/mol in EC-FD convention.¹⁶

The Gibbs free energy of reaction (1) is determined from standard thermodynamic relations

$$D_r G^\circ = D_f G^\circ[A^z(g)] = D_f H^\circ[A^z(g)] - T \left(S^\circ[A^z(g)] + z S^\circ[e^-(g)] - S^\circ[A(st)]/n \right) \quad (7)$$

where we used the EC-B convention, which sets the formation Gibbs free energy of electron to zero and includes the electronic entropic contribution to $D_f G^\circ[A^z(g)]$ of the ion.¹⁸ Note that the comprehensive compilation of ionic properties by Marcus¹⁹ does not include the electron entropy

term $zS^\circ[e^-(g)]$ in $D_f G^\circ[A^z(g)]$; therefore, the tabulated values differ from other sources by about $6.1z$ kJ/mol.¹⁸

2.2. Ion hydration

The second main stage in the formation of hydrated ions according to the thermodynamic cycle in Figure 1 is the immersion of gaseous ions in bulk water. Thus, the ion formation properties in the aqueous phase can be written as,

$$D_f X^\circ[A^z(aq)] = D_f X^\circ[A^z(g)] + D_{aq} X^\circ[A^z] \quad (8)$$

where X can represent G , H , or S , and the subscript aq denotes the change of the thermodynamic quantity X upon hydration. Because the standard state for individual ions in aqueous solution is the hypothetical ideal solution at unit molality at 298.15 K, the second term on the right-hand side of Eqn. (8) contains a contribution corresponding to the compression of the ion gas from the standard state of 100 kPa at 298.15 K. It is sometimes desirable to express ionic hydration properties as resulting only from ion-water interactions by defining the hydration properties without the compression contribution as (note the * used in this definition)

$$D_{aq} X^*[A^z] = D_{aq} X^\circ[A^z] - \{X(ig, 1\text{bar}) - X(ig, 1\text{mol/kg})\} \quad (9)$$

Ion hydration is often quantified in terms of so-called conventional properties. We are aware of two such conventions: one defines them relative to the proton hydration properties (*i.e.*, transfer of a proton from gas to solution),⁸ and the other relative to the proton formation properties in a solvent (*i.e.*, formation of a proton in a solution from its standard state, $\frac{1}{2}\text{H}_2$).⁷ Since the latter convention seems to be more common and was used in the NBS compilation,¹⁵ we will adopt it in this article. The formation properties $D_f X^\circ[A^z]$ are therefore conventionally

defined relative to the formation of a hydrated proton in the standard state solution by setting $D_f X^{\circ, \text{con}}[\text{H}^+] = 0$. The conventional formation and hydration properties are consequently given as⁷

$$\begin{aligned} D_f X^{\circ, \text{con}}[\text{A}^z] &= D_f X^{\circ}[\text{A}^z] - z D_f X^{\circ}[\text{H}^+(aq)] \\ D_{aq} X^{\circ, \text{con}}[\text{A}^z] &= D_{aq} X^{\circ}[\text{A}^z] - z D_f X^{\circ}[\text{H}^+(aq)] \end{aligned} \quad (10)$$

The immersion of an ion in bulk water can be achieved by two distinct physical pathways: (i) the ion can be transferred from the gas phase through the liquid-vapor interface to a position in solution infinitely (in the limit) far away from the interface, and (ii) an infinite number of individual water molecules ($n \rightarrow \infty$) can be gradually added to the ion to form a cluster-ion of an infinite size, *i.e.*, bulk phase.

A controlled transfer of individual ions through the planar interface is not experimentally feasible but can be easily realized in computer simulation using the thermodynamic integration or similar methods. The thermodynamic changes occurring over the continuous path from gas to bulk solution can be theoretically divided into two distinct contributions: one coming from the interaction of an ion with the surrounding bulk water and the other coming from electrostatic interactions with a distant (planar) vapor-liquid interface. In this context the full hydration properties $D_{aq} X^{\circ}$ are called ‘real’, because they characterize a physically realizable process, while the properties coming from ion-bulk water interactions without accounting for the vapor-liquid surface contribution are called ‘intrinsic’, $D_{aq} X^{\circ, \text{int}}$. Conversion between the real and the intrinsic properties requires the inclusion of the surface potential contribution, f_X^{sp} , *i.e.*,

$$D_{aq} X^{\circ}[\text{A}^z] = D_{aq} X^{\circ, \text{int}}[\text{A}^z] + z e f_X^{\text{sp}} \quad (11)$$

where e is the unit of electrostatic charge.

Sometimes the term ‘absolute’ is used to characterize hydration properties, typically invoked as a synonymous for ‘intrinsic’,^{20,21} but it is also used to describe the results of cluster experiments,^{7,22,23} whose outcome has been extensively considered to measure ‘real’ properties,^{21,24-26} which naturally include the cluster surface potential.²⁰ To avoid confusion, here we will avoid the term ‘absolute’ in favor of ‘real’ and ‘intrinsic’. As these terms suggest, the intrinsic properties are not real in the sense that they cannot be realized in any physical process because ions have to cross the interface when transferred from gas to the aqueous phase. However, a bulk solution without an interface can be achieved in computer simulations in periodic boundary conditions involving the Ewald summation (or for that matter, any other lattice summation) treatment of long-range interactions.²⁶⁻²⁸ It follows that to determine real thermodynamics of ion hydration from computer simulations, it is critical to understand the planar vapor-liquid interface of pure water.

Note that the separation of the real properties into the intrinsic part and surface potential contribution is, to a large degree, artificial and various definitions of the surface potential have been introduced (Section 5.1). However, as long as the intrinsic and surface contributions are treated consistently, the real properties will not be affected.

The second pathway, from an isolated ion in the gas phase to a hydrated ion in bulk water, leads to gradually adding individual water molecules to form a cluster ion of increasing size. The thermodynamics of the gas-phase ion hydration and formation of cluster ions at finite temperatures and pressures can be expressed in terms of elementary stepwise (or incremental) reactions and their associated enthalpies and Gibbs free energies. The standard state (*i.e.*, $T^\circ = 298.15$ K and $P^\circ = 100$ kPa) enthalpy, $DH_{n-1,n}^\circ[A^z]$, and Gibbs free energy, $DG_{n-1,n}^\circ[A^z]$, of such a stepwise hydration reaction,

$$A^z(H_2O)_{n-1} + H_2O \rightleftharpoons A^z(H_2O)_n, \quad (12)$$

in which a cluster-ion comprising an ion A and $n-1$ water molecules binds an additional water molecule, can be expressed as follows,

$$DH_{n-1,n}^\circ[A^z] = H^\circ[A^z(H_2O)_n] - H^\circ[A^z(H_2O)_{n-1}] - H^\circ[H_2O] \quad (13a)$$

$$DG_{n-1,n}^\circ[A^z] = G^\circ[A^z(H_2O)_n] - G^\circ[A^z(H_2O)_{n-1}] - G^\circ[H_2O] \quad (13b)$$

The thermodynamic quantities listed on the right-hand side of Eqs. (13) correspond to individual reactants and products (*i.e.*, cluster-ions comprising n and $n-1$ water molecules, and a single water molecule, respectively) in the ideal gas state at standard conditions. The enthalpies of reactants and products appearing in Eqn. (13a) can be decomposed into the following components,

$$H^\circ = K^\circ + U + P^\circ V \quad (14)$$

where K° and U are the average kinetic and potential energies, V is the molar volume of the species at the standard pressure P° .

The real hydration properties, $D_{aq}X^\circ$, can be obtained by summing individual reaction steps for $n \rightarrow \infty$ and adding water vaporization enthalpy, Gibbs free energy, or entropy according to the following relation,⁷

$$D_{aq}X^\circ[A^z] = \lim_{n \rightarrow \infty} \left\{ \sum_{i=1}^n DX_{i-1,i}^\circ[A^z] + nD_{vap}X^\circ[H_2O] \right\} \quad (15)$$

Unlike the transfer of an ion through the bulk water interface, the gradual addition of water molecules and the formation of cluster-ions can be, to some extent, studied experimentally (*vide infra*). Unfortunately, the experimentally analyzed clusters are usually limited to sizes not exceeding the first or second hydration shells. As it turns out, this is not enough for reliable extrapolations to bulk hydration and computer simulations have to be used to gain additional insights into hydration of large cluster-ions.²⁹

3. Experimental study of single ion properties - reference data

Even though the bulk solution single-ion thermodynamics cannot be experimentally measured, there are numerous ways to gain empirical insight into the behavior of individual ions, and partially constrain the possible values of the hydration thermodynamic properties. Here we list experimental methods whose results are most frequently used for development and validation of computational models.

3.1. Cluster ions

Accurate description of ion hydration in gas phase is critical for the study of atmospheric processes in ionosphere,³⁰ seawater sprays,³¹ flames,^{32,33} or electric discharges,³⁴ and also for understanding aqueous electrolytes at supercritical conditions.^{35,36} Besides concrete applications, cluster ions also offer an experimental window into the problem of single-ion solvation. Gas phase ion hydration thermodynamics has been experimentally studied by mass spectrometric methods based on equilibrium measurements³⁷⁻⁴³ and collision-induced dissociation (CID).⁴⁴⁻⁴⁶ In the equilibrium measurements based on high-pressure mass spectrometry, ions generated by an ion source, such as electrospray,³⁷ electron capture,⁴³ or thermionic emission from a heated filament,⁴² enter a reaction chamber containing water vapor. After sufficient time needed for establishing the ion-water equilibria, the newly formed cluster-ions enter the low-pressure mass spectrometer and their size is analyzed. The equilibrium constant $K_{n-1,n}$ of the reaction described by Eqn. (12) can be then determined assuming that the measured intensities, I_n , corresponding to cluster ions of different sizes are proportional to the cluster-ion concentrations in the reaction chamber, *i.e.*,⁴²

$$K_{n-1,n} = \frac{I_n}{PI_{n-1}} \quad (16)$$

where P is the vapor pressure in the reaction chamber. The experiment is repeated at different temperatures and the reaction enthalpies and entropies are then determined from the van't Hoff plots.^{42,43} The experimental temperatures typically range from ~ 200 K, at which conditions large halide clusters are stable, to ~ 800 K at which small alkali metal clusters are prevalent. The experimental errors differ for each methodology and setup. The reported standard deviations of the experimental enthalpies and entropies for halide anions are around 5 kJ/mol or lower,⁴³ and up to 10 kJ/mol or higher for cations.⁴⁷ Besides the statistical noise and uncertainties regarding the relation between the measured intensities and the true equilibrium distribution, the reliability of the experimentally determined properties for small clusters ($n = 1, 2$) of light alkali metal ions can be negatively impacted by the need to extrapolate from high temperatures ~ 800 K to the standard temperature of 298.15 K.

The dissociation energies of bonds between water molecules and cluster-ions were also investigated through the collision-induced dissociation of metal cation clusters.⁴⁴⁻⁴⁶ In this approach ion-water clusters are generated by an associative reaction between metal ions and water vapor, accelerated, mass selected, and decelerated to a desired kinetic energy. The resulting cluster-ions are guided to a gas cell filled with a collision gas (typically Ar or Xe) where the collision reaction products along with unreacted clusters are led to a detector. The relative intensities of the reacted and unreacted ions are converted to absolute cross sections, which are subsequently used to calculate the bond dissociation energies. Even though the calculation of the thermodynamic quantities from the CID studies involves statistical modeling and is less straightforward than from the equilibrium methods, the CID experiments made possible the investigation of the $\text{Li}^+\text{-H}_2\text{O}$ dimer dissociation,⁴⁶ which could not be reliably measured in

previous studies.⁴² The estimated errors for the Li⁺ cluster-ion thermodynamics range between 5 to 10%.

The experimental results have been used as anchoring points for the extrapolation of hydration properties to bulk conditions,^{7,29} as well as for the development and validation of classical molecular force fields.^{21,48-52} The small size of cluster ions, comprising typically less than 10 water molecules, also provides a more direct insight into the specific details of ion-water interactions than that in bulk aqueous systems, which makes these systems a valuable source of information for force field optimization.

3.2. Bulk solutions

The fundamental experimental information on ion hydration thermodynamics comes typically from calorimetric measurements performed on charge-neutral salts. The enthalpies, entropies, and Gibbs free energies of formation of salts in aqueous solutions have been measured with high accuracy and tabulated.¹⁵ Any accurate theoretical method or computer simulation model should satisfy the constraints on the charge-neutral sums of cation and anion values as well as on the relative differences within cation and anion groups given by these experimental values.

Useful empirical correlations found between ion hydration entropies and enthalpies can be used to further constrain the theoretical or computational models. The plot of adjusted values of $TDS_{aq}^{con,\circ}$ as a function of $DH_{aq}^{con,\circ}/z$, Figure 2, reveals a characteristic quasi-linear relationship between the two quantities. These linear trends, an example of entropy-enthalpy compensation,⁵³ have long been recognized and used to devise extrathermodynamic estimates of single-ion hydration thermodynamics.^{8,54} If real instead of conventional quantities were plotted in Figure 2, the separation between cation and anion lines would reflect the charge asymmetry of water

molecules because any charge-symmetric solvent would solvate the positive and negative ions identically,⁵⁵ and the corresponding trend lines would coincide. We compare the effect of different estimates of real hydration properties on the (entropy) S vs. (enthalpy) H plot in later sections.

Figure 2. Conventional single-ion hydration entropy, as a function of hydration enthalpy. The plotted quantities are conventional values shifted so that proton hydration enthalpy and Gibbs free energy are equal to those recommended by Conway:⁵ $D_{aq}H^{o,con*} = -1104$ kJ/mol, $D_{aq}G^{o,con*} = -1066$ kJ/mol, and $TD_{aq}S^{o,con*} = D_{aq}H^{o,con*} - D_{aq}G^{o,con*}$. Monovalent cations are shown in blue, divalent cations in green, and halide anions in red.

X-ray diffraction and neutron scattering techniques can, in principle, provide detailed structural information in the form of ion-water pair distribution functions or estimates of the effective ion radius and coordination number (see discussion in the article by Chialvo & Vlcek in this volume⁵⁶). The results of numerous X-ray diffraction studies have been assembled in a compilation by Ohtaki and Radnai.⁵⁷ Effective ionic radii have been used to correlate hydration thermodynamic properties⁵⁸ and often serve as a reference for molecular model development.⁵¹ Unfortunately, the ionic radii and coordination numbers derived from X-ray diffraction depend on the model used to interpret the raw data, which is complicated by unknown variables, such as ion pairing.^{59,60} The resulting values of ion coordination numbers therefore frequently differ by tens of percent.⁶¹ Finer discrimination between different contributions to the scattering signal and more reliable information about the structure of water surrounding ions can be achieved by neutron diffraction with isotopic substitution⁶¹ if suitable isotopes are available. The structure of the first hydration shell has also been investigated by the X-ray absorption fine structure (EXAFS) spectroscopy.^{62,63} Indirect information about the structure of electrolyte solutions can be obtained from the statistical mechanical relations between thermodynamic fluctuation properties and solute-solvent pair distribution functions expressed through the Kirkwood-Buff integrals for electrolytes.^{64,65} The data has been used as a reference for development of molecular models of concentrated solutions.⁶⁶ In general most of the experimental structural information is interpreted through a microscopic model, either theoretical or computational, and therefore the results may be biased by the deficiencies of the model.

Transport properties can be related to solvation thermodynamics through semi-quantitative correlations with excess entropy introduced by Rosenfeld⁶⁷ and later applied to tracer diffusivities.⁶⁸ Similar relations were derived specifically for predicting diffusion coefficients by Dzугutov.⁶⁹ Since diffusion coefficients are known for individual cations and anions,¹⁹ these

correlations provide important constraints on the values of single-ion hydration entropies, thus making diffusion coefficients an excellent source of accurate unambiguous reference data.

3.3. Vapor-liquid interface

The surface tension of the aqueous vapor-liquid interface (71.99×10^{-3} N/m at 298.15 K) along with its temperature and pressure dependence have been measured by standard thermodynamic methods,⁷⁰ and the values provide a suitable reference for validation of molecular models. The structure of the interface has been indirectly investigated by a range of spectroscopic techniques,⁷¹ including the methods of non-linear optics, such as Vibrational Sum Frequency Spectroscopy (VSFS),⁷² Sum Frequency Generation (SFG),⁷³ and Second Harmonic Generation (SHG) spectroscopy whose interpretation by molecular simulations suggest that water molecules at the interface are oriented such that one OH bond points towards the vapor phase.⁷²

When investigating the surface potential, it is critical to distinguish between the so-called electrochemical surface potential and a surface potential measured by electron diffraction or electron holography. As discussed by Kathmann *et al.*,⁷⁴ the diffraction and holography techniques use high energy electrons as probes that can penetrate close to atomic nuclei and sample thus the electrostatic potential over the full space of the water sample, including both inter- and intra-molecular regions. Surface potentials determined by these methods are positive, in the approximate range between +3 and +5 V,^{75,76} and are compatible with quantum chemical simulations.⁷⁴ An alternative idea of the so-called electrochemical potential has been often considered within the context of electrochemical experiments. The value of this potential was estimated in several independent studies with the resulting values ranging between 25 mV and 125 mV.⁷⁷⁻⁸⁰ However, the methodological issues related to the experimentally based surface

potential definitions have to be dealt with care when comparing the results with computational model predictions (see Section 5.1).

4. Extrathermodynamic assumptions and empirical correlations

The first attempts to determine single-ion solvation properties before the advent of large-scale molecular simulations relied on physical intuition and simplified theoretical considerations embodied in various extrathermodynamic assumptions (ETA). These assumptions were critically reviewed by Conway,⁵ who recommended the following values of proton hydration properties: $DG_{aq}^{\circ}[\text{H}^+] = -1066 \text{ kJ/mol}$, $DH_{aq}^{\circ}[\text{H}^+] = -1104 \text{ kJ/mol}$, $DS_{aq}^{\circ}[\text{H}^+] = -131 \text{ J/K/mol}$ (hydration properties in Figure 2 were adjusted according to this estimate). Out of necessity, these methods neglect the complexity of the ion hydration structure as well as the unknown surface potential of water, both of which influence the behavior of real systems. In most cases the idea is to identify a state of an electrolyte solution in which the contributions of anions and cations to the total thermodynamic properties can be expected to be nearly equal, and consequently, split the experimentally accessible neutral salt properties into even contributions.⁸¹ Despite the inherent simplifications that lead to the neglect of the details underlying the molecular interactions, oftentimes these approaches still serve as a basis for estimating proton hydration properties that are used as reference values for the development of molecular models, and consequently, they impact the outcome of many computer simulations. The resulting predictions of hydration free energies and enthalpies based on different extrathermodynamic assumptions often differ from each other by more than 20 kJ/mol, *i.e.*, a physically significant amount equivalent to the energy of one or more hydrogen bonds. Here we will take a closer look at the ETAs that are still

currently used as reference for computational methods, consider their justification and tests of their underlying assumptions.

4.1. TATB

Probably the most frequently referenced ETA is one due to Marcus,⁶ commonly known under its abbreviation TATB, which assumes that the hydration enthalpies and Gibbs free energies of a large cation, tetraphenylarsonium (TA), and a large anion, tetraphenylborate (TB), in bulk water are roughly equal. This assumption leads to the proton hydration Gibbs free energy $D_{aq}G^{\circ}[\text{H}^+] = -1056 \text{ kJ/mol}$ and corresponding enthalpy $D_{aq}H^{\circ}[\text{H}^+] = -1103 \text{ kJ/mol}$.^{6,58,82} It is not completely clear, from the way the ETA was introduced, whether TATB estimates the real or the intrinsic hydration quantities. Some authors consider the values to be intrinsic,²⁰ but others use them as if they represented real properties.⁸³ However, the assumption that charge asymmetric water molecules will respond symmetrically to large cations and anions is certainly not guaranteed. The reliability of the TATB was investigated by Schurhammer *et al.*⁸⁴ using molecular dynamics simulations with two simple molecular models (TIP3P⁸⁵ and TIP5P⁸⁶) of water. The results revealed significant differences between interactions of water with the cation and anion, especially for the more charge-asymmetric TIP3P water model. Similar conclusions were reached in a simulation study by Schamberger and Clarke,⁸⁷ and the outcome of spectroscopic experiments which do not support the idea of equivalent solvation of the TA and TB ions.^{88,89}

Note that the TATB-based cation and anion hydration Gibbs free energy values given in the comprehensive compilation by Marcus¹⁹ do not add to the accurately measured experimental values for the corresponding neutral salts.¹⁵ Even though the definitions given in the compilation

would lead to the correct values for the properties of the neutral salt, the listed final values of $D_{aq}G^\circ$ were not apparently calculated using those definitions. As a result, the values for monovalent anions are more positive by about 5-6 kJ/mol and values for divalent cations are more negative by about the same amount. This deviation was noticed in earlier publications,^{26,51,90} but the tabulated quantities are frequently used uncorrected. We consider these deviations a result of numerical errors (transferred from earlier publications) rather than different conventions, as sometimes suggested.^{26,51}

4.2. Equal entropy assumption

Another ETA proposed by Schmid and co-workers⁸ in 2000 is based on the assumption of equal entropies for the hydrated H^+ and OH^- ions, which leads to $S^\circ[H^+(aq)] = S^\circ[OH^-(aq)] = -5.45 \text{ JK}^{-1}\text{mol}^{-1}$. The enthalpy of proton hydration is then determined from the self-consistent relations introduced by Krestov.⁵⁴ The resulting values of proton hydration properties are $D_{aq}G^\circ[H^+] = -1052 \text{ kJ/mol}$, *i.e.*, comparable with that from the TATB, and $D_{aq}H^\circ[H^+] = -1078 \text{ kJ/mol}$.⁸ As in the case of the TATB, the authors did not specify whether these values included the surface potential contribution. Even though the authors justify their assumption using arguments about gas phase cluster-ion properties (which include the surface potential contribution²⁰), the resulting values have been treated as intrinsic quantities and used as a basis for the development of an alkali halide-water force field by Joung and Cheatham,⁵¹ and more recently by Li *et al.*⁹¹ The authors also attempted to derive single-ion hydration thermodynamics by assuming the linear relationship between hydration enthalpies and entropies discussed in Section 3.2 (Figure 4), and arrived at values of $D_{aq}H^\circ[H^+]$ between -

1108 kJ/mol and -1139 kJ/mol. We are not aware of any direct attempts to test the basic assumptions of this ETA beyond confirming the approximate linearity of the H - S relation in classical molecular simulations.²⁹

4.3. The cluster-pair extrapolations

An alternative approach to estimating single-ion hydration thermodynamics is based on the experimentally accessible properties of small cluster-ions. The experiments, outlined in Section 3.1, provide information about clusters involving typically less than 10 water molecules, which means that only the first hydration shell is probed directly. Extrapolations are therefore required to estimate the corresponding bulk solution properties.

The extrapolations are based on the notion that the difference between the hydration thermodynamics of the cation, $A^+ (H_2O)_n$, and the anion, $B^- (H_2O)_n$, clusters comprising n water molecules tends to zero as the cluster size increases,⁹² *i.e.*,

$$\lim_{n \rightarrow \infty} \left\{ DX_{aq}^\circ [A^+ (H_2O)_n] - DX_{aq}^\circ [B^- (H_2O)_n] \right\} = 0 \quad (17)$$

where DX_{aq}° stands for either real standard hydration Gibbs free energy, DG_{aq}° , or enthalpy,

DH_{aq}° . This relation can be further rearranged using Eqn. (10) to express the proton formation thermodynamic properties, $DX_f^\circ [H^+ (aq)]$, as a difference between the sums of stepwise cluster

cation and anion hydration, $DX_n^\circ = \sum_{i=1}^n DX_{i-1,i}^\circ$, and corresponding conventional properties, $DX_{aq}^{\circ, \text{con}}$,

as follows,⁷

$$\frac{1}{2} \left\{ \lim_{n \rightarrow \infty} \left(DX_n^\circ [A^+] - DX_n^\circ [B^-] \right) - \left(DX_{aq}^{\circ, \text{con}} [A^+] - DX_{aq}^{\circ, \text{con}} [B^-] \right) \right\} = DX_f^\circ [H^+ (aq)] \quad (18)$$

where the values for the stepwise sums are obtained from cluster ion mass spectrometry experiments.³⁷

In essence the extrapolation effectively assumes that the cluster-size dependence of the hydration thermodynamics observed for small clusters will extrapolate monotonically into the region not sampled, and consequently, relies on the absence of ‘surprises’ in the range between small clusters and bulk (*i.e.*, infinite-size cluster).⁷ Even though the authors claim that their extrapolations do not involve any ETA, we will demonstrate that, in fact, they do assume a behavior that is by no means guaranteed.

There exist several variants of the extrapolation procedure differing in how the experimentally measured data points are combined. The original and most cited method relies on the so-called cluster-pair-based approximation (CPA),⁷ which has also been considered to provide the most accurate proton hydration free energies and enthalpies.^{12,24,26,93-95} According to the CPA, the estimate for increasingly larger and infinite clusters is achieved by scaling the first term in Eqn. 18,

$$\frac{1}{2} \left\{ \frac{DX_n^\circ[A^+] - DX_n^\circ[B^-]}{c_{n,n}(A^+, B^-)} - \left(DX_{aq}^{\circ, \text{con}}[A^+] - DX_{aq}^{\circ, \text{con}}[B^-] \right) \right\} = DX_f^{\circ, \text{CPA}}[H^+(aq)] \quad (19)$$

where

$$c_{n,n}(A^+, B^-) = \frac{DX_n^\circ[A^+] + DX_n^\circ[B^-]}{DX_{aq}^{\circ, \text{con}}[A^+] + DX_{aq}^{\circ, \text{con}}[B^-]} \quad (20)$$

Note that the last quantity includes only sums of cation and anion contributions, and therefore can be determined unambiguously. According to the original publication, the extrapolation will be most accurate for ion pairs (real or hypothetical) whose prediction of $DX_f^{\circ, \text{CPA}}[H^+(aq)]$ is constant in the experimentally accessible range of clusters.⁷ The assumption that this constancy

will hold as the cluster size increases is the central factor for the validity of the CPA. The ideal cluster pair can be identified by a procedure described by Tissandier and co-workers.⁷

The original CPA method predicts $D_{aq}G^{\circ}[\text{H}^+] = -1104.5 \text{ kJ/mol}$ and $D_{aq}H^{\circ}[\text{H}^+] = -1150.1 \text{ kJ/mol}$,⁷ and as pointed out by its authors, one of the most distinctive predictions is that the proton hydration enthalpy is 50 kJ/mol more negative than other contemporary estimates.^{8,82,96} Since these extrapolated values have been used as a benchmark for the development of a wide range of molecular^{25,26,97} and continuum^{11,12} solvation models, any errors introduced by the CPA will be transferred to the computational studies.

New variations around this approximation have been developed to extrapolate small-cluster data to bulk solutions. Tuttle *et al.*,²² developed a cluster-pair correlation method in which the values of proton hydration thermodynamics are determined from the common intersection of plots of $0.5\left\{D_{aq}X^{con,\circ}[\text{B}^-(\text{H}_2\text{O})_n] - D_{aq}X^{con,\circ}[\text{A}^+(\text{H}_2\text{O})_n]\right\}$ against $0.5\left\{D_{aq}X^{con,\circ}[\text{B}^-] - D_{aq}X^{con,\circ}[\text{A}^+]\right\}$ for different values of n , whose outcome values $D_{aq}G^{\circ}[\text{H}^+] = -1103.7 \text{ kJ/mol}$ and $D_{aq}H^{\circ}[\text{H}^+] = -1149.9 \text{ kJ/mol}$ were almost identical to the original CPA. Donald and Williams later modified the cluster pair correlation method and complemented it with more extensive experimental datasets, arriving at $D_{aq}G^{\circ}[\text{H}^+] = -1102.1 \text{ kJ/mol}$ and $D_{aq}H^{\circ}[\text{H}^+] = -1151.9 \text{ kJ/mol}$,²³ The authors also noticed a non-negligible dependence of the calculated hydration enthalpy on the size of the clusters .

The assumptions underlying the cluster-pair extrapolation approaches have been recently examined using theoretical manipulation of the CPA equations and molecular simulation involving cluster sizes larger than those available from experiments.²⁹ The theoretical arguments

discussed in Section 5.4 show that the basic assumption of fast convergence of the hydration properties of cations and anions is not justified, and the numerical results indicate that the single-ion hydration properties extrapolated to bulk solutions can be significantly biased, especially in the case of hydration enthalpies and entropies. Despite these findings the extrapolated values are still used as the reference of choice.⁹⁸

5. Atomistic simulations

Classical and quantum chemical atomic-level computer simulations can be considered first principle methods in that they do not impose any macroscopic assumptions that might bias the results. There are, however, many specific issues that these methods must confront. In the case of truly *ab initio* quantum chemical methods, the biggest issue is their large computational expenses, which prevent studies at the space and time scales needed for reliable investigation of thermodynamic properties in systems with long-range interactions. In the case of classical molecular simulations, which can span sufficiently large scales, the critical issue is the accuracy of the underlying effective force fields describing inter-particles interactions. Here we review important aspects of the computational modeling approaches, indicate the sources of potential errors, and suggest ways to correct them.

5.1. Liquid-vapor interface

The question of how to interpret and determine the surface potential created by anisotropic arrangement of water molecules at the vapor-liquid interface has recently motivated a large number of studies.^{24,99-104} The full surface (or phase) potential, $\mathcal{F}_G^p$, felt on average by a test charge randomly inserted in the liquid phase (subscript *l*), whose reference zero is set in the vapor phase (subscript *v*), is defined as²⁶

$$f_G^{sp} = -\frac{1}{e_0} \int_{z_v}^{z_l} dz \int_{z_v}^{z_l} dz r(z) \quad (21)$$

where e_0 is permittivity of vacuum, z is the perpendicular distance along a trajectory going from vapor to liquid, and $r(z)$ is the charge density at z . An insightful analysis by Kathmann *et al.* related the average full electrostatic potential calculated from *ab initio* simulations according to Eqn. (21) to the results of electron diffraction experiments in which high energy electrons probe the full volume of the interface including areas close to atomic nuclei.⁷⁴ The electrochemical potential was then connected to the average potential calculated outside the atomic van der Waals radii.

The charge density in Eq. (21) can be expanded into multipole terms and the full potential can be written as,^{26,105}

$$f_G^{sp} = f_G^{sp,D} + f_G^{sp,Q} + \dots = -\frac{1}{e_0} \int_{z_v}^{z_l} dz P_z(z) + \frac{1}{e_0} \{Q_{zz}(z_l) - Q_{zz}(z_v)\} + \dots \quad (22)$$

where $f_G^{sp,D}$ and $f_G^{sp,Q}$ are dipolar and quadrupolar contributions to the full surface potential, respectively, given by integration of the z -component of macroscopic polarization $P_z(z)$ and difference of the average density of the zz -component of the quadrupole density Q_{zz} in liquid and vapor phases. The higher multipolar terms in Eqn. (22) were truncated. Cendagorta and Ichiye,¹⁰⁵ equated the electrochemical surface potential to the one felt by an H^+ test probe sampling regions outside the van der Waals radii of water molecule atoms and shown that deep in the bulk aqueous phase it is approximately equal to the dipolar contribution $f_G^{sp,D}$ to the full surface potential. A clear trend has been observed in this and other studies showing that more charge symmetrical water models, such as the TIP5P⁸⁶, create lower surface potential than models more asymmetric, such as the TIP3P⁸⁵, TIP4P,¹⁰⁶ or SPC/E.¹⁰⁷ Such a finding should not be very surprising,

because surface potential can only appear in the systems of charge asymmetric molecules (*i.e.*, not invariant to the change of charge sign).¹⁰⁴

The charge asymmetry effects do not apply only to the liquid-vapor interface but also to the interface between liquid water and a cavity. As a result, similar trends have been observed in the hydration free energies of ion solvation by different water models, as exemplified on the large ions of the TATB system mentioned earlier.⁸⁴ This fact has been used to define the so-called net potential, f_G^{net} , which represents electrostatic potential in the center of an uncharged solute^{108,109}

$$f_G^{net} = -\frac{1}{e_0} \int_{z_v}^{z_c} \int_{z_v}^{z^t} dz^t dz^c r(z^c) \quad (23)$$

where the integration path leads from the vapor phase through the liquid phase to a sufficiently large cavity (~ 6 Å). It has been argued that its value is close in magnitude to potentials derived from electrochemical measurements.²⁴

Even though the exact relationship between the surface potentials measured in simulations and estimated from electrochemical experiments has not been fully resolved, any uncertainty related to the surface potential definition can be avoided by working exclusively with real hydration quantities. Such a choice will sidestep the differences in charge distribution in classical and *ab initio* systems and allow us to treat cluster-ions and bulk solutions on a consistent basis. In this approach, the surface potential is simply a well-defined technical tool that converts bulk simulations with the lattice sum treatment of long-range Coulombic interactions into real quantities with the vapor phase potential set to zero.²⁷

In order to calculate real entropies and enthalpies of hydration, the corresponding surface contributions can be obtained from the temperature dependence as $f_S^p = \left(\partial f_G^p / \partial T \right)_p$ and $f_H^p = f_G^p + T f_S^p$. For example, the Gibbs free energy and enthalpy of the planar surface potential

at 298.15 K and $P = 100$ kPa are $\mathcal{F}_G^p = -57.7$ kJ/mol/e (-0.598(2) V) and $\mathcal{F}_H^p = -36.05$ kJ/mol/e (-0.374 V), respectively.²⁹

5.2. Boundary conditions and finite size corrections

Finite-size simulations of individual ions in bulk water require special considerations regarding periodic boundary conditions and the non-electroneutrality of the resulting system. Unlike the case of finite-size clusters, for which unequivocal direct summation of Coulombic interactions is possible, bulk solvation properties calculated in periodic boundary conditions are highly sensitive to the way solvent Coulombic interactions are summed up,^{27,110,111} how periodic images of ions are treated,^{112,113} and how long-range solvent polarization is accounted for.²⁶ The set of corrections needed for the calculation of ion solvation thermodynamics has been systematically analyzed and classified by Reif and Hunnenberger.¹¹⁴ The majority of present-day molecular simulations of electrolyte solutions use lattice-sum methods to treat long-range Coulombic interactions, such as the Ewald summation or particle-mesh methods. For tinfoil boundary conditions, *i.e.*, $e_{RF} \rightarrow \infty$, the reference potential within the simulation box is set to zero in these lattice techniques.²⁷ To obtain real hydration properties consistent with finite cluster simulations, the values calculated from bulk simulations with a particular model of water have to be corrected by adding the full surface potential of the planar vapor-liquid interface, Eq. (21).²⁶⁻²⁸ This theoretical observation has been verified by direct computer simulations of an ion transfer through the vapor-liquid interface.¹¹⁵ The full surface potential $\mathcal{F}_G^p$ therefore defines one type of intrinsic hydration properties, while other choices, such as $\mathcal{F}_G^{p,D}$ or $\mathcal{F}_G^{net}$ would define different sets of properties. In the following we will consider the intrinsic properties as defined by the full

potential of Eq. (21), unless stated otherwise, because it is the simplest choice when dealing with molecular simulations with lattice summation of Coulombic interactions.

An alternative approach to the calculation of bulk hydration properties from finite-size simulations relies on an approximative continuum treatment of the solvent medium.^{11,12} In these methods a small cluster is treated explicitly by a computationally expensive quantum chemical method and the effect of the surrounding solvent is included in the form of an effective dielectric response.¹¹⁶ However, as discussed in the previous section, the surface potential of a small charged cluster can be significantly different from that of a macroscopic aqueous phase. For this reason, single-ion properties calculated using the continuum solvation methods are susceptible to the same errors as the cluster-pair extrapolation methods and the resulting thermodynamic properties of ion hydration should be considered only on a relative basis rather than as real values.

5.3. Small cluster ions

Due to the small size of gas-phase cluster-ions, which typically include only the first hydration shell, their computational studies have often relied on high-level *ab initio* methods. Perhaps the most common way these calculations are used in force field development and validation is as a reference for the adjustment of interaction parameters to reproduce polymerization energies of selected locally optimized configurations. Although methodologically simple, the optimization based on minimum energy configurations may suffer from a bias caused by overweighting more compact structures and underweighting a wide range of higher-energy structures that can contribute significantly to the cluster hydration entropy. In contrast, and from the point of hydration thermodynamics, more useful data are obtained from quantum molecular dynamics (MD) or Monte Carlo (MC) simulations, where samples are

collected from equilibrium distributions at finite temperatures,^{117,118} making it possible to analyze entropic effects. At present, such simulations cover MD trajectories spanning tens of picoseconds or generate thousands of MC cycles, which are sufficient for basic estimation of the cluster thermodynamics. In these applications classical/quantum hybrid schemes have been used to increase sampling efficiency.¹¹⁸⁻¹²⁰ Due to the high computational requirements underlying quantum calculations, the larger number of desired samples requires lower levels of the quantum chemical methods for the calculation of interaction energies. In the case of anions forming strong hydrogen bonds with water molecules, it is also important to include nuclear quantum mechanical effects, such as proton tunneling,¹²¹ in the form of corrections or by running full path integral simulations, which further increases the computational costs.

To overcome the size and time limitations of current quantum mechanical methods, classical simulations with quantum-mechanically and empirically derived force fields may serve as a reasonable approximation.^{21,48-52} At the same time, small cluster ion systems with their strong electric fields and large anisotropy of molecular interactions present a significant challenge for effective classical molecular models and can therefore serve as a benchmark for development and evaluation of such models. *Ab initio* results are usually employed to develop polarizable models,^{90,102,122-128} but have alternatively been used as a part of a training set for simple non-polarizable force fields.⁵¹ Empirical models, typically represented by a simple potential model, have been frequently optimized to match experimental cluster-ion hydration thermodynamics. This approach was used by Smith and Dang, who optimized their ion force-field parameters compatible with the polarizable water model (RPOL) to match incremental hydration enthalpies of Na⁺ and Cl⁻ ions.¹²⁹ Likewise, Lamoureux and Roux adjusted the ion-water parameters based on their SWM4-DP model to reproduce the empirical enthalpies of ion monohydrates and found that the resulting model was able to predict reasonably well selected *ab initio* energies of larger

clusters.²¹ Shevkunov used experimental cluster-ion thermodynamic properties to design a non-polarizable force field specifically for the description of Cl⁻-water clusters,¹³⁰ while Lukyanov *et al.* performed an extensive systematic evaluation of the capability of a set of simple polarizable and non-polarizable models to predict cluster-ion binding hydration Gibbs free energies, enthalpies and entropies.⁴⁸ The analysis has been recently extended by Zidi using a fluctuating charge polarizable model.¹³¹ Finally, Grossfield *et al.* calculated the Cl⁻ cluster binding enthalpies for the flexible polarizable AMOEBA force field and found a close agreement with the high pressure mass spectrometry experiment.⁹⁰

We have recently compared the performance of different types of classical force fields,¹¹⁹ including non-polarizable SPC- and SPC/E-based models, a force field with a single polarizable site per particle based on the RPOL model of water, and a force field based on the BK3 model of water with three polarizable sites and Gaussian charges. A somewhat surprising finding was the ability of the simple non-polarizable models to describe hydration thermodynamics of alkali metal cluster ions with quality comparable with the more sophisticated polarizable models. Unfortunately, hydration of halide anions proved to be significantly more challenging for the non-polarizable models, in which the strong hydrogen-bonding interactions formed between anions and water hydrogens were not sufficiently well described even with the RPOL model and required the all-atom polarizability of the BK3 model.

In Figures 3 and 4 we include a new comparison of the step-wise hydration enthalpies predicted by the polarizable AMOEBA force field with experimental results. Here we used the force field parameter set included with the TINKER software package. For reference we also include results obtained with the non-polarizable force field by Joung and Cheatham.⁵¹ Unlike the non-polarizable force field, AMOEBA can reproduce the hydration enthalpies for most anions nearly quantitatively. Small but noticeable systematic deviations can be observed in

Figure 4 for ion-water dimers ($n = 1$), where hydration enthalpies are exaggerated for the lightest F^- anion. More significant deviations between models and experiment can be seen in Figure 3 for clusters of light alkali metal cations. Here the functional dependence of hydration enthalpies on the number of water molecules is experimentally concave but molecular-based predicted ones are convex or nearly linear. The same discrepancies between experiment and simulations were found for all models investigated in the previous study.¹¹⁹ Dzidic and Kebarle,⁴² who noticed similar deviations in their simple electrostatic model, suggested that covalent bonding may be missing from the interaction model. However, comparison with quantum chemical calculations¹¹⁹ as well as CID experiments⁴⁴⁻⁴⁶ suggests that the data originating from this specific set of high pressure MS experiments⁴² (also used in the original CPA extrapolations) may be affected by systematic errors. It is still unclear whether the discrepancy is the result of experimental errors or deficiencies of the computational models, but the issue needs to be resolved before the experimental data can be used with confidence as a reference for molecular model development. Even though it appears that, after additional parameter optimization, the AMOEBA force field will be capable of nearly quantitative description of the cluster-ion thermodynamics, it is clear that certain effects will be neglected or underrepresented, such as proton transfer¹³² and tunneling¹²¹ in strong hydrogen bonds $F^- \dots H^+ \dots OH^-$, or electronic charge transfer.¹³³

Figure 3. Incremental hydration enthalpies of alkali metal ions. HPMS experiment⁴² (black squares), CID experiment^{45,46} (black open circles), polarization corrected SPC/E (blue diamonds), AMOEBA (red triangles), and DFT (green stars).¹¹⁹ The standard errors of the classical simulation results are lower than 0.2 kJ/mol.

Figure 4. Incremental hydration enthalpies of halide ions. HPMS experiment⁴³ (black squares), polarization corrected SPC/E (blue diamonds), AMOEBA (red triangles), and MP2-level *ab initio*¹³⁴ (green stars). The standard errors of the classical simulation results are lower than 0.2 kJ/mol.

5.4. Large cluster ions and transition to bulk hydration

Because no direct experimental measurements are available for the thermodynamics of large cluster ions, the study of the transition from small clusters to bulk solutions must rely on computational modeling. Moreover, because the clusters may include hundreds or thousands of

water molecules, the only practical approach is to use classical simulations with effective interaction potentials. While there have been numerous studies of small and medium size ion-water clusters addressing different challenges of the molecular based interpretation of ion hydration phenomena,^{111,131,135,136} only a few of them attempted to address the transition from small clusters to bulk solutions. The first attempts to study this transition were conducted by Peslherbe and coworkers,¹³⁷ who used a liquid drop model to augment simulated small clusters, where water surrounding the cluster is treated as a dielectric sphere. Coe used simulations of medium-sized clusters in which the solvent was represented by the Stockmayer model, which consists of a van der Waals repulsive sphere and a point dipole.¹³⁸ Unfortunately, neither of these studies considered the implications of the water molecule charge asymmetry, which is responsible for the formation of surface potential¹⁰⁴ that can significantly influence ion solvation thermodynamics.

A more realistic representation of water-ion interactions was used in a recent simulation study to investigate cluster-size dependence of hydration Gibbs free energies and enthalpies. The cluster sizes covered in the study ranged from a single solvent molecule to infinitely large clusters. As discussed by Asthagiri and co-workers,²⁰ cluster ions naturally include a contribution from the liquid-vapor surface potential; therefore, to treat the full range of cluster sizes including bulk solution on a consistent basis, real hydration properties had to be compared. The methodology used to study cluster-size dependence of hydration properties was based on the formal similarity of expressions defining the relation between real and conventional properties, Eqn. (10), and the expression defining the relation between real and intrinsic properties, Eqn. (11). Consequently, the relation for the proton formation energy in bulk solution, Eqn. (18), can be rewritten using intrinsic properties instead of conventional to arrive at the relation for the surface potential,²⁹

$$\frac{1}{2} \left\{ \left(DX_n^\circ[A^+] - DX_n^\circ[B^-] \right) - \left(DX_{aq}^{\circ, \text{int}}[A^+] - DX_{aq}^{\circ, \text{int}}[B^-] \right) \right\} = e f_X^{\text{sp}}(n) \quad (24)$$

where on the right side is the contribution of the surface potential to the hydration property X . The difference between estimated values of $D_f X^\circ[H^+(aq)]$ and f_X^{sp} as a function of n (Eqns. 18 and 24) results in a vertical shift equal to the difference between the conventional and intrinsic properties. However, the overall shape of the curves will be identical because neither conventional nor intrinsic bulk values depend on n ; consequently, any trends and deviations detected in the estimation of f_X^{sp} will be present in the estimate of $D_f X^\circ[H^+(aq)]$. This re-definition of the original Eqn. (18) allows us to calculate the limiting value of $f_X^{\text{sp}}(n)$ for $n \rightarrow \infty$, which in this case corresponds to the full surface potential of a planar vapor-liquid interface. The ability to directly calculate the limiting value from independent simulations is a valuable consistency check of the extrapolations. The same substitution of intrinsic for conventional quantities can be applied to the original CPA expressions, given by Eqns. (19) and (20),⁷ as well as to the related cluster-pair correlation expressions.^{12,22,23}

This re-formulation also shows that the cluster extrapolation techniques effectively assume that the planar liquid-vapor surface potential is equal to the averaged cation and anion surface potentials of small clusters. However, such an assumption is clearly unjustified because the surface properties of small clusters consisting of only the first hydration shell are determined by direct ion-water interactions, whereas the surface potential of the planar liquid-vapor interface is determined only by pure water interactions. This proves that the cluster-pair extrapolations cannot be generally valid for arbitrary systems. The results of actual simulations with the model system shown in Figure 5 demonstrate that, indeed, the surface potential contributions significantly change when going from small clusters to bulk solution. An advantage of using the

same molecular model for cluster, bulk, and surface potential simulations is the consistency of the results and the ability to compensate possible errors of the ion-water interactions by subtracting the ion-specific short-range contributions in Eqn. (24). The more critical issue is the accuracy of the water model and its description of the vapor-liquid interface. In this regards, the SPC/E model used to test the CPA method has been considered to describe well the orientational distribution of water molecules near the liquid-vapor interface as obtained from experiments and *ab initio* simulations.^{24,72,139}

A similar test of the cluster-size dependence of the hydration properties was later performed by Pollard and Beck^{103,140} using the AMOEBA polarizable force field, quantum DFT, and MP2-level *ab initio* potentials in the simulation of the $\text{Na}^+ - \text{F}^-$ cluster pair. Their results indicate the same type of changes of hydration properties for larger clusters as those observed for the simple non-polarizable model. In their modified approach the authors used the net potential, Eqn. (23), instead of the full surface potential defined by the model, along with tabulated conventional values of ion hydration properties instead of the corresponding intrinsic values measured in bulk simulations. Unfortunately, the reference numerical values may be affected by the use of single-ion hydration properties taken from Ref ¹⁹. As mentioned in Section 4.1, the cation and anion values do not sum up to the neutral salt values because of the inconsistent use of gas and liquid phase formation Gibbs free energies.

Figure 5. The estimate of surface potential contributions $\phi_G^{sp}(n)$ and its enthalpic contribution $\phi_H^{sp}(n)$ as a function of cluster size at $T=298.15\text{K}$. Black circles: cluster-pair values; red dashed line: planar surface potential ϕ_X^{sp} ; green dashed line: the CPA estimate of the surface potential. Reprinted with permission from Vlcek, L.; Chialvo, A. A.; Simonson, J. M. *J. Phys. Chem. A* **2013**, *117*, 11328-11338. Copyright 2013, American Chemical Society.²⁹

The changes in surface potential contributions with changing size of the clusters are schematically illustrated in Figure 6, which suggests a possible speculative explanation of the behavior seen in Figure 5. In small clusters the dipoles are oriented to conform to the strong electric field of the central ion, but in large clusters the water-water interactions are the main factor determining their orientation. In classical simulations the majority of water molecule dipoles at the liquid-vapor interface of pure water are directed toward the liquid phase,¹⁰⁵ *i.e.*, they are pointing toward the hydrated ion. The ion-surface dipole interactions in a cluster of decreasing size thus become gradually more energetically favorable for cations because of the alignment of dipoles with the ionic electric field. This effect should be seen as a negative slope of the enthalpy as a function of $n^{-1/3}$ in Figure 5. While the interaction energy (enthalpy) will be more favorable, the re-alignment will also cause increasing order of the surface dipoles, and thus decrease in entropy. Some form of partial entropy-enthalpy compensation and the resulting muted effect on the Gibbs free energy can be therefore expected,⁵³ which is indeed observed in Figure 5.

Figure 6. Schematic depiction of electric fields and surface dipole moments in small (left) and large (right) cationic (top) and anionic (bottom) cluster ions. Black arrows represent electric fields created by ions and green arrows represent orientation of surface dipole moments.

5.5. Bulk solutions

The improving capabilities of the quantum chemical computational methods have prompted a number of *ab initio* studies aiming to determine the bulk solution single-ion hydration properties. Most of the early studies used the supermolecule-continuum approach in which a small cluster comprising an ion and a few ($n = 1$ to 6) water molecules is surrounded by a dielectric continuum representing water.¹⁴¹⁻¹⁴³ Tawa *et al.* used this technique to estimate the hydration Gibbs free energy of a proton,¹⁴⁴ followed by the investigation of alkali halide ions,¹⁴⁵ with the resulting value $D_{aq}G^{\circ}[\text{H}^+] = -1097$ kJ/mol. Mejias *et al.* used the continuum solvation model to calculate the proton hydration enthalpy and reported $D_{aq}H^{\circ}[\text{H}^+] = -1150$ kJ/mol.¹⁴⁶ Zhan and Dixon used high-level *ab initio* methods coupled with the continuum solvent to determine hydration Gibbs free energies for H^+ and OH^- ions,^{147,148} with the resulting value of $D_{aq}G^{\circ}[\text{H}^+] = -1098$ kJ/mol.

The accuracy of these hybrid continuum techniques relies on the assumption that the surface potential of the small cluster will be the same as of the bulk solution, which is essentially the assumption in cluster-pair extrapolations. Therefore, it is not surprising that these methods predict hydration free energies and enthalpies in good agreement with the values determined from the CPA. However, as discussed in the previous section, the still remaining issue is how these values translate to real bulk solvation properties when the surface potential contributions

are properly accounted. We would argue that despite their high accuracy in the description of small clusters, the above-mentioned quantum chemical results are affected by the unaccounted changes of the surface potential.

More recently Leung *et al.* used *ab initio* molecular dynamics simulations to estimate the hydration Gibbs free energies for Li^+ , Cl^- , and Ag^+ ions,¹⁴⁹⁻¹⁵¹ employing the thermodynamic integration method and bulk simulations in periodic boundary conditions with 32 and 64 water molecules. The long-range Coulombic interactions were calculated using the Ewald summation, which implies that the resulting free energies corresponded to the intrinsic properties defined by Eqn. (11). To avoid large-scale simulations needed to determine the full *ab initio* surface potential of water, the authors used instead the quadrupolar and dipolar contributions to the surface potential of the classical SPC/E model, and compared their results to the TATB-based values of Marcus¹⁵² and CPA-based values of Tissandier *et al.*⁷ The results for the calculated $D_{aq}G^\circ$ of the combined neutral $\text{Li}^+ + \text{Cl}^-$ pairs differed by up to 20 kJ/mol from the experimental values.

Even though the explicit inter-particle interactions of these quantum chemical methods can be considered as based on first principles (excluding the approximations involved in the computational techniques), they still involve simplifying assumptions in the treatment of the surface potential. An alternative to a direct quantum chemical simulation is to use effective classical force fields, whose lower computational requirements make large-scale simulations of interfacial systems possible.

Force fields based on fitting *ab initio* data are typically derived from small cluster systems as discussed in Section 5.4, and then applied to bulk simulations. In principle, such force fields can be used to estimate single-ion bulk hydration thermodynamics. For instance, the AMOEBA force

field predicts $D_{aq}G^{\circ}[\text{H}^{+}] = -1056.5 \text{ kJ/mol}$.⁹⁰ However, this value is intrinsic, because it does not include the unknown surface potential contribution. Real hydration properties values were calculated by Lamoureux and Roux using the SWM4-DP, which predicts $D_{aq}G^{\circ}[\text{H}^{+}] = -1085.5 \text{ kJ/mol}$.

Most current force fields for aqueous solutions of electrolytes are empirical in nature, as they have been developed to reproduce some tabulated macroscopically averaged reference properties derived from experiments. Almost invariably, these references have included single-ion hydration thermodynamic properties based on one of the extrathermodynamic assumptions as described in Section 4, and often also invoke the radius of the hydration shell. Consequently, different sets of force fields exist for different reference ETAs, and any inaccuracy of these reference values are transferred to the corresponding simulation studies. Moreover, the ETAs were not always treated consistently. For instance, the TATB values have been used as a reference both for intrinsic¹⁵³ and real properties.⁸³ Since the hydration free energies are closely related to the size of the ion, the resulting models also differ significantly in the structural properties. More recently Li *et al.* combined reference values for alkali metal cations derived from TATB ETA and halide anions derived from the equal-entropy ETA,⁹¹ a combination that makes the resulting models unable to reproduce the neutral salt properties.

The largest group of the empirical models conforms to the same type of ion-water interactions, and consist of the Lennard-Jones (LJ) potential acting between the ion and water oxygen, complemented by point charge (PC) interactions between the ion and water oxygen and hydrogens.^{25,26,66,83,91,97,153-160} We will denote this force field form as LJPC. Individual LJPC force fields differ from each other only by the use of different water molecule models and/or ion-oxygen Lennard-Jones parameters. The importance of the LJPC form stems from its

computational efficiency for which it is chosen for large-scale biochemical and geochemical simulations. Any deficiencies and artifacts of the LJPC form should be therefore well understood to avoid unnecessary prediction errors. Polarizable models by Dang,¹⁶¹ Warren and Patel,²⁶ and the SWM4-DP model of Lamoureux and Roux²¹ also conform to the LJPC form, but add an explicit polarizability through the fluctuating charge or shell model methods.

Almost invariably, these empirical models were optimized to reproduce only a single thermodynamic function (either DG_{aq}° ,^{25,26,97,154} or DH_{aq}° ¹⁵⁵), which obscured their inability to reproduce the full set of common thermodynamic properties – Gibbs free energy (G), enthalpy (H) and entropy (S) of hydration. This fact has only become apparent when Horinek and co-workers²⁵ attempted to develop their simple non-polarizable model of the LJPC form based on matching simultaneously DG_{aq}° and DS_{aq}° according to the CPA reference values, and found that the models and the CPA ETA values are incompatible. This was later further demonstrated by plotting TDS_{aq}° against DH_{aq}° as illustrated in Figure 7.²⁹ The blue and red dots in the plot correspond to different combinations of the size and energy parameters of the LJ interaction between ions and water oxygen. Note that only by correcting the CPA values as suggested in the previous section, the models and reference data get to a better agreement, and while the agreement is nearly quantitative for cations, a small residual systematic shift in hydration entropies is still observed for anions. Both cation and anion data points are grouped along trend lines similar to those seen in experiments, but the anion line has a different slope, which leads to larger deviations for small anions F^- and Cl^- . Given the strong correlation between hydration entropies and diffusivities,⁶⁸ it is not surprising that simple models also systematically under-predict anion diffusion coefficients.¹⁶² In addition, this asymmetric shift means that no further manipulation of the force field parameters will result in the correct G , H , S set of properties for

ion pairs involving small anions F^- and Cl^- (*i.e.*, no red dots in Figure 6 overlap the cross symbols of the anions). Even without the knowledge of accurate single-ion properties we know beforehand that the interactions of the small anions with water cannot be described accurately by the LJPC force fields. Such a result could be expected in the light of small cluster-ion results shown in Figure 4, where it is clear that hydrogen bonds between water and light anions are poorly reproduced. The assumption that only anions need significant corrections is supported by the cluster-cation results in Figure 3 showing that cation-water interactions are described in qualitative agreement with more sophisticated polarizable models.

To test whether the deficiency of anion-water interactions can be corrected, we added a new non-Coulombic interaction between the anions and the water hydrogen sites. For simplicity and consistency with the rest of the force field, the anion-hydrogen interaction has the form of the LJ potential and is designed to modulate the hydrogen point-charge interaction. As such, we do not impose any constraints on the LJ energy and size parameters. To efficiently navigate in the four-dimensional parameter space (two and two LJ parameters for oxygen and hydrogen interactions), we used the perturbation method,¹⁶³ which allowed us to find new parameters using only one equilibrium simulations for each ion using the force field of Joung and Cheatham⁵¹ as a reference system.. The resulting hydration thermodynamic properties obtained with the adjusted LJPC force field, shown in Figure 7 as red and blue circles, nearly coincide with the corrected CPA values and sum up to correct neutral salt properties. The simulation methodology was described in our previous publication.²⁹

The idea of modifying anion-water hydrogen interactions by adding a special LJ term to the LJPC form was also proposed by Alexandre and co-workers¹⁶⁴ as a way of improving the predictions of solubility in concentrated solutions of NaCl. These observations indicate that an

additional interaction term between anions and water hydrogens may also improve the chemical potential of aqueous electrolytes, which is poorly described by models of the LJPC form.^{165,166}

Figure 7. Real bulk single ion hydration entropy ($-T\Delta S_{aq}^{\circ}$) versus enthalpy ($-\Delta H_{aq}^{\circ}$) from molecular simulations (dots: data from Tables III-VI by Horinek and co-workers²⁵ with our values of f_X^{sp} , circles: results obtained with modified models including anion-hydrogen LJ potential), the original CPA values (squares), and the corrected CPA values (crosses). Cations are shown in blue, anions in red, and the gray dashed lines denote free energy isolines,

$$\Delta G_{aq}^{\circ} = \Delta H_{aq}^{\circ} - T\Delta S_{aq}^{\circ}$$

6. Summary and discussion

We have reviewed various theoretical and computational approaches designed to determine ion-water interactions and the resulting single-ion hydration thermodynamic properties. An overview of the most relevant estimates of hydration Gibbs free energies and enthalpies is compiled in Table I.

Table I: Summary of important estimates of proton hydration Gibbs free energies and enthalpies.

Method	$DG_{aq}^{\circ}[\text{H}^+]$ [kJ/mol]	$DH_{aq}^{\circ}[\text{H}^+]$ [kJ/mol]	type
ETA, average by Conway (1981) ⁵	-1066	-1104	(intrinsic)
ETA, TATB by Marcus (1987) ^{6,19}	-1056	-1103	(intrinsic)
ETA, equal entropy by Schmid (2000) ⁸	-1052	-1078	(intrinsic)
ETA, CPA by Tissandier (1998) ⁷	-1104.5	-1150.1	small clusters
<i>Ab initio</i> Tawa (1998) ¹⁴⁴	-1097	-	small clusters
<i>Ab initio</i> Mejias (2000) ¹⁴⁶	-	-1150	small clusters
<i>Ab initio</i> Zhan and Dixon (2001) ¹⁴⁷	-1098	-	small clusters
<i>Ab initio</i> da Silva (2009) ¹⁴²	-1130	-	small clusters
Classical, AMOEBA (2003) ⁹⁰	-1056.5	-	intrinsic
Classical, SWM4-DP (2006) ¹⁶⁷	-1085.5/-1033.4	-	real/intrinsic
Corrected CPA, SPC/E (2013) ²⁹	-1089.0	-1103.5	real

Corrected (2014) ¹⁰³	CPA,	AMOEBA,	Marcus	-1097.5	-1138.7	real
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In the case of the ETA estimates we inserted the word ‘intrinsic’ in parenthesis, because these methods do not specify what type of surface potential is used to define the reported properties. As we have highlighted, there are different definitions of the surface potential that correspond to different probes used to measure it (*i.e.*, electron, proton, or finite-size ion). Moreover, the surface potential values are also sensitive to the type of water molecule representation. We see no compelling reason to think that the ETA methods were designed with classical molecular models and their full surface potentials in mind, as they are often applied. In fact, it seems more likely that the difference between the ‘intrinsic’ values of the TATB and ‘real’ values of the CPA are a result of a fortuitous coincidence rather than a well-defined real-intrinsic relation. This feature becomes even clearer when the ‘real’ values of the CPA are corrected for the cluster-size dependence of the surface potential,²⁹ in which case the enthalpy values nearly coincide and the Gibbs free energies become too close to be explained by a surface potential contribution. A more reasonable choice seems to be treating the values as intrinsic with respect to the net potential defined in Eq. (23),¹⁰³ which eliminates a larger part of the model dependence. The uncertainty of the ETA estimates is further compounded by typographical errors, and their inconsistent use.

The two corrected CPA values in Table I differ from each other by non-trivial amounts. It is unclear to us what the precise reason for the observed difference is, but aside from the difference between the molecular models used in the studies, the usage of the full vs. net surface potentials can play a significant role. We note that the full surface potential in the study by Vlcek *et al.* is essential, as it guarantees consistency of the bulk and cluster results.²⁹ Another possible factor

contributing to the observed difference is the reliance on an ETA-based bulk proton hydration free energy¹⁶⁸ in the studies by Pollard and Beck,^{103,140}

The frequently debated issue of the surface potential and what it represents in different experiments and simulations can be bypassed by working with real hydration properties. Unlike intrinsic properties, the real ones seamlessly transition between gas and liquid systems, and can be connected to observable physical quantities without their artificial separation into intrinsic and surface contributions (*e.g.*, ion-water dimer energy). In this respect, we believe that real properties should be targeted when developing and comparing models of ion-water interactions.

The uncertainties surrounding the ETA estimates suggest that the most likely path towards accurate determination of single-ion thermodynamics will lead through the use of computational methods. As pointed out in previous sections, the present-day computational methods still suffer from limitations, such as the neglect of surface potential effects in cluster-continuum approaches or imperfections in classical force field parameterization. In the case of *ab initio* methods, the results are also strongly dependent on the technique and overall simulation setup. Despite these errors, the cluster-continuum results seem to be close to the uncorrected CPA method, supporting the view that they are influenced by the same approximations related to the cluster-size dependence of the surface potential.

Our analysis of the accuracy of classical force fields on the system of small cluster ions indicates that simple non-polarizable models may not be adequate for the description of gas phase hydration, especially when strong hydrogen bonds between water and anions are involved. However, it seems that clusters large enough to include more than one hydration shell are still described reasonably well. More complex polarizable models, such as AMOEBA, can in principle be capable of reproducing both small cluster and bulk hydration, but as our test study shows the currently available parameters are not always well optimized (this is especially true for

clusters involving large cations Rb^+ and Cs^+ ions). At the same time we have shown that with proper parameterization even simple non-polarizable models based on point charge electrostatics and Lennard-Jones potential can, in principle, provide a consistent simultaneous description of bulk hydration Gibbs free energies, enthalpies, and entropies, but only if an additional non-Coulombic term is added to the anion-hydrogen interaction.

7. Outlook

It is our view that estimates based on extrathermodynamic assumptions have reached their limit of accuracy by constraining the values of ion hydration free energies and enthalpies within about 20-30 kJ/mol (Table I), and further refinement will only be possible using the bottom-up approach of computational methods.

To achieve accuracy at the level of thermodynamic fluctuations ($\sim k_B T$), we must confront systematically the factors influencing the resulting single-ion hydration properties, and correct their effects. The three main contributors to real hydration properties come from short-range ion-water interactions that include the nearest one or two hydration shells, long-range interactions with bulk water usually described as dielectric polarization effects, and ‘infinite’ range effects of the surface potential contributing to real properties. At present no computational method is capable of reproducing all of these contributions at our desired level of accuracy. While the short-range interactions in small cluster-ions can be accurately described by high-level *ab initio* calculations, extension of these results to bulk solutions is only possible through some form of a hybrid methodology. The popular cluster-continuum methods need to be augmented by a correction accounting for the surface potential contribution and its cluster-size changes, as discussed in previous sections. A less approximate approach with explicit treatment of water molecules is used in hybrid QM/MM (quantum mechanics/molecular mechanics) simulations,¹²⁰

or in perturbation schemes in which classical molecular dynamics or Monte Carlo simulations are used to sample the configurational space with the interactions subsequently refined by quantum mechanical corrections. Given the large effect that surface potential can have on the real hydration properties, it is still an open question to what extent the results of QM/MM methods are influenced by the quality of the classical MM model and its description of the vapor-liquid interface, in addition to how the QM/MM interface itself influences the results. A purely classical alternative to these hybrid simulations is the use of highly optimized effective polarizable force fields. All of these hybrid and classical techniques have their own merits and are being actively pursued.

Our own interest and the main topic of this article is the accurate description of ion-water interactions by practical molecular models. A natural direction in improving classical force fields is their optimization to reproduce the best available *ab initio* data while satisfying constraints given by accurate structural, thermodynamic, and dynamic experimental data. This generally requires complex, polarizable, and possibly even reactive interaction models. The comparison of some of the more complex models in this and previous studies shows that there is still substantial room for improvement.

There is also a great deal of demand for simple non-polarizable force fields that can be used in fast large-scale simulations. Because of their simplicity, it is not always possible to match well the accurate and detailed *ab initio* potentials; consequently, the models are usually optimized to reproduce macroscopic reference properties, one of which is almost invariably some ETA estimate of the free energy of hydration. Given the discussed uncertainty about these values, we subscribe to the suggestion by Pollard and Beck¹⁴⁰ that the currently available properties should be avoided in the development of empirical models. In the meantime other approaches based on less controversial experimental data in combination with *ab initio* simulation of small clusters

can be used to avoid these issues. As mentioned before, one of the natural requirements is the consistency of the hydration Gibbs free energy, enthalpy, and entropy of neutral salts, possibly complemented by average coordination numbers, and diffusion coefficients.

An interesting problem that still waits for its resolution is the microscopic origin of the changes in the vapor-liquid interface in growing cluster ions. We have provided a tentative qualitative explanation of the effects, but a more detailed study will be needed to understand how they translate to real properties of ion hydration that will, for instance, provide corrections to cluster-continuum methods. A related practical task is the calculation of model-specific surface potentials and their components. While surface potentials have been calculated for a large number of molecular models, the enthalpic and entropic contributions are accurately known for only a few of them.

In this article we have only dealt with ion hydration at ambient standard state conditions. Single-ion properties at much higher temperatures or pressures, such as supercritical aqueous solutions, which are more relevant in geochemistry and technological applications, are still largely unexplored and will require additional computational studies. We have also left aside the question of complex molecular ions that are either not stable in the gas phase or strongly polarized upon transfer to water. In such cases alternative thermodynamic cycles have to be considered to quantify the thermodynamic effects of ion hydration.

ACKNOWLEDGMENT

This research was supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, Chemical Sciences, Geosciences, and Biosciences Division.

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