



HAL
open science

Improving the description of solvent pairwise interactions using local solute/solvent three-body functions. The case of halides and cabroxylates in aqueous environment

Florent Réal, Valérie Vallet, Michel Masella

► **To cite this version:**

Florent Réal, Valérie Vallet, Michel Masella. Improving the description of solvent pairwise interactions using local solute/solvent three-body functions. The case of halides and cabroxylates in aqueous environment. *Journal of Computational Chemistry*, 2019, 49, pp.1209-1218. 10.1002/jcc.25779 . hal-01987259

HAL Id: hal-01987259

<https://hal.science/hal-01987259v1>

Submitted on 15 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Improving the Description of Solvent Pairwise Interactions Using Local Solute/Solvent Three-Body Functions. The Case of Halides and Carboxylates in Aqueous Environment

Florent Réal,^[a] Valérie Vallet,^[a] and Michel Masella^[b]

We propose a general strategy to remediate force-field artifacts in describing pairwise interactions among similar molecules M in the vicinity of another chemical species, C , like water molecules interacting at short distance from a monoatomic ion. This strategy is based on introducing a three-body potential energy term that alters the pairwise interactions among M -type molecules when they lie at short range from the species C . In other words the species C is the center of a space domain where the pairwise interactions among the molecules M is altered. Here, we apply it to improve the description of the water interactions provided by

the polarizable water model TCPE/2013 in the vicinity of halides, from F^- to At^- , and of the prototypical carboxylate anion CH_3COO^- . We show the accuracy and the transferability of such an approach to investigate not only the hydration process of single anions but also of a salt solution NH_4^+/Cl^- in aqueous phase. This strategy can be used to remediate the drawbacks of any kind of force fields. © 2019 Wiley Periodicals, Inc.

DOI:10.1002/jcc.25779

Introduction

The structuring of water molecules lying in the vicinity of an ion (cation or anion) is highly improbable in pure liquid water, as it corresponds to unfavorable water/water interactions. For instance, we showed^[1] from high level quantum computations that the interaction energy ΔU^{ww} of water molecules interacting in the first hydration sphere of the highly charged heavy cation Th^{4+} to range in gas phase from +3 to +45 kcal mol⁻¹ when considering from 3 to 10 water molecules. Even if the hydration structures around halide anions are different (see Fig. 1), they are energetically not very favorable. For instance ΔU^{ww} ranges from -4.7 to -11.0 kcal mol⁻¹ when considering the most stable chloride hydrated clusters in gas phase comprising from 3 to 6 water molecules from our own quantum computations. The latter two values have to be compared to high end quantum binding energy (BE), estimates for the most stable water trimer and hexamer, -15.7 and -46.1 kcal mol^{-1,2]} respectively. The hydration energy of an ion thus results from a competition between strongly favorable ion/water and strongly unfavorable water/water interactions. To accurately model ion hydration processes both the latter kind of interactions should be thus described at an equal level of accuracy.

Most of the water models proposed to date, from standard additive ones like SPC/E,^[3] TIP3P,^[4] and TIP4P,^[5] to much more sophisticated ones, like the model HBB2-pol^[6] or the Drude oscillator based model SWM4-DP,^[7] were all developed to accurately reproduce water properties in finite size systems or in bulk phases where the above ion hydration structures are not observed. This explains that the water models used commonly to investigate ion hydration processes, like SPC/E and TIP3P, are usually not able to accurately model water interactions in the vicinity of an ion. For instance the water energy ΔU^{ww} corresponding to the cluster $[Th(H_2O)_{10}]^{4+}$ (see Fig. 1) computed using the above mentioned force fields is larger than its

quantum counterpart by about +110 (SPC/E and TIP3P), +80 (TIP4P) and +67 (SWM4-DP) kcal mol⁻¹. This represents an error ranging from 100 to 180 k_BT at ambient conditions.

The standard approach to remediate the potential bias induced by erroneously quantified water interactions in the vicinity of an ion is to assign the ion/water force-field parameters to reproduce the binding energies of ion/water clusters and/or the hydration free energies of ions (see among others Refs. (8–11)). This approach thus leads to large cancellations of errors and that does not ensure such kind of force fields to be well suited to model ion/water interactions in a different chemical environment (for instance to model the chelation of an ion at the interface of a macromolecule or the ion solvation process in a solvent mixture).

Recently, we proposed the water many-body model TCPE/2013^[12] whose parameters were in particular assigned to reproduce the energies ΔU^{ww} of the water molecules belonging to first hydration sphere (comprising from 3 to 10 water molecules) of the heavy cation Th^{4+} . This model is shown to accurately model pure water systems (gas-phase clusters and liquid water under a large domain of temperature and pressure conditions^[12]). It was applied to study the hydration processes of organic cations (like methylated ammonium cations^[13,14] and guanidinium^[15]) and of anions (like halides, from fluoride, F^- to astatide, At^- ^[16] and linearly alkylated carboxylates^[17]). We

[a] F. Réal, V. Vallet

CNRS, UMR 8523 - PhLAM - Physique des Lasers Atomes et Molécules, Université de Lille, F-59000 Lille, France

[b] M. Masella

Laboratoire de Biologie Structurale et Radiobiologie, Service de Bioénergétique, Biologie Structurale et Mécanismes, Institut Joliot, CEA Saclay, F-91191 Gif sur Yvette Cedex, France
E-mail: michel.masella@cea.fr

Contract Grant sponsor: French National Research Agency; Contract Grant number: ANR-11-LABX-0005-0

© 2019 Wiley Periodicals, Inc.

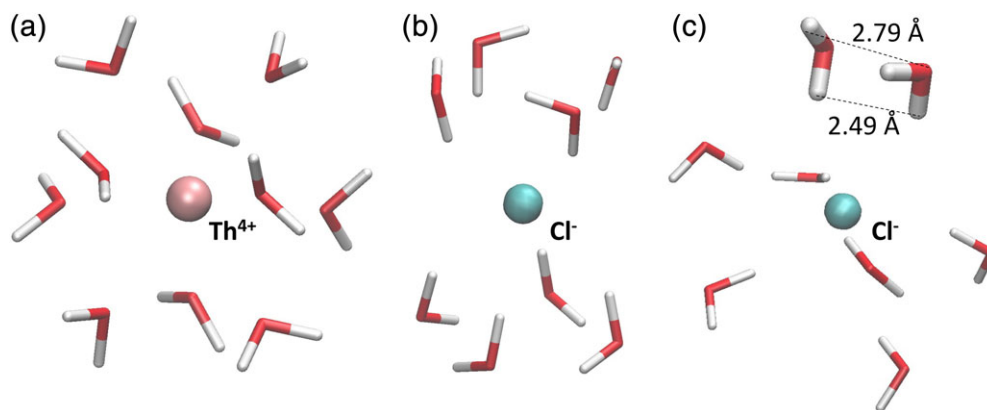


Figure 1. Examples of first hydration shell structures in gas phase for the highly charged heavy cation Th^{4+} interacting with 10 water molecules (note this structure to correspond to an extremum of the cation/water potential energy surface *in vacuum*) (a), the chloride anion in gas phase (b) and in aqueous phase (c) (as extracted from a MD bulk simulation reported in Ref. 16). For chloride in bulk water, the anion and the two highlighted water molecules correspond to the structure \mathbf{S}_3 discussed in the present study. [Color figure can be viewed at wileyonlinelibrary.com]

provide Supporting Information Appendix S1 as a comparison between the TCPE/2013 predictions regarding small gas-phase water clusters and bulk liquid water and those derived from the above mentioned water models.

Compared to recent ion/water modeling approaches, highly specialized,^[18,19] or showing some degree of transferability (and based on a many body polarization term used in conjunction with an ion/water pairwise interaction energy term^[20–22]), we modeled hydrated halide clusters using the water TCPE/2013 model and an ion/water potential including both a many-body polarization and a short range anisotropic many-body term to account for halide/water charge-transfer effects.^[12,23] That approach was shown to reproduce the water interaction energies in small halide/water clusters comprising up to eight water molecules compared to high end quantum computations at the complete basis set limit, within less than 1 kcal mol⁻¹ on average.^[16] However halide first hydration shells in aqueous phase result from an equilibrium between ion hydrated clusters that encompass from 7 to 10 water molecules and whose structures are more disordered than the gas-phase structures used to assign our force-field parameters; see for instance the Cl^- /first hydration shell structure extracted from a simulation of Cl^- in aqueous phase shown in Figure 1. Anticipating our results, we show TCPE/2013 to be less accurate to describe such kind of large sized hydrated halide clusters. This arises from an inaccurate description of the water pairwise interactions corresponding to a particular water dimer conformation. In particular that yields the proton hydration enthalpy, $\Delta H_{\text{hyd}}(\text{H}^+)$, extrapolated from halide or carboxylate/water nanodroplet data, to be from 3 to 8 kcal mol⁻¹ weaker than the well accepted experimental range of values, while our TCPE/2013-based $\Delta H_{\text{hyd}}(\text{H}^+)$ estimate extrapolated from methylated ammonium/water nanodroplets is in much better agreement with experiment.^[13,17]

In the present study, we show how to remediate such kind of force-field drawbacks by means of a three-body energy term that only alters the original TCPE/2013 water/water potential energy surface, PES, at short range from anionic centers. This three-body term is built by considering the specific case of chloride, Cl^- . We organize the Section “Results and Discussion” of the present

manuscript to show first how we identify the physical origin of the drawbacks, then how we build a physically founded three-body potential energy term, and lastly we demonstrate the three-body term transferability in studying the hydration of the full halide series, from F^- to At^- and of the organic carboxylate anion CH_3COO^- , as well as in investigating ion pairing in a $\text{Cl}^-/\text{NH}_4^+$ diluted salt solution (at the 0.05 M scale).

Methods and Computational Details

Quantum computations

To compute all the necessary quantities at the best level of theory, here the second-order perturbation theory (MP2), we used for the lighter elements of the periodic tables, i.e., the oxygen, hydrogen, carbon, fluorine, and chlorine aug-cc-pVTZ basis sets.^[24] The heavier halides for which scalar relativistic effects are important, are described by small-core relativistic pseudopotentials that replace 10, 28, and 60 core electrons of Br, I, and At, respectively, with the associated aug-cc-pVTZ-PP basis sets.^[25] The density fitting approximation at Hartree-Fock and MP2 levels, was used to fasten the calculation except for systems containing bromide, because no auxiliary basis set is available.^[26,27] In the DF-MP2 calculations (or standard MP2 calculations for Br- clusters), the 1 s orbitals of each oxygen, carbon, nitrogen, fluor atoms as well as the 1 s, 2 s, 2p ones for Cl^- , the 3 s, 3p, 3d ones for Br^- , the 4 s, 4p, 4d ones for I^- and the 5 s, 5p, 5d ones for At^- are frozen. The BEs and interaction energies of the water molecules belonging to the first coordination sphere, ΔU^{www} , were computed thanks to the MOLPRO quantum chemistry package.^[28]

The water and the halide/water force field

The rigid and polarizable water model TCPE/2013^[12] includes four different components: a repulsive U^{rep} , a Coulombic U^{qd} , a polarization U^{pol} (based on an induced point dipole moment approach), and a short-range anisotropic many-body U^{hb} energy term. The halide/water interaction energy term ΔU^{iw} is also a sum of the first three last terms to which is added a specific short-range many-body potential U^{shb} to accurately model

strong hydrogen bond interactions. Its analytical form is close to the water/water U^{hb} one. These two many-body potentials are denoted U^{mbp} below. Both ΔU^{ww} and ΔU^{iw} functions (measuring the interaction energies with respect to, wrt, individual unbound gas-phase molecules), obey

$$\Delta U^{ww/iw} = U^{rep} + U^{qq'} + U^{pol} + U^{mbp}. \quad (1)$$

The repulsive U^{rep} , Coulombic $U^{qq'}$, and polarization U^{pol} terms are defined as:

$$U^{rep} = \sum_{i=1}^N \sum_{j=1}^{N^*} A_{ij} \exp(-B_{ij} r_{ij}), \quad (2)$$

$$U^{qq'} = \sum_{i=1}^N \sum_{j=1}^{N^*} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}^2}, \quad (3)$$

$$U^{pol} = \frac{1}{2} \sum_{i=1}^{N_\mu} \frac{\mathbf{p}_i^2}{\alpha_i} - \sum_{i=1}^{N_\mu} \mathbf{p}_i \cdot \mathbf{E}_i^q - \frac{1}{2} \sum_{i=1}^{N_\mu} \sum_{j=1}^{N_\mu^*} \mathbf{p}_i \mathbf{T}_{ij} \mathbf{p}_j. \quad (4)$$

Here, r_{ij} is the distance between atoms i and j , q_i are the static charges located on the N atomic centers, and A_{ij} and B_{ij} are adjustable parameters. \mathbf{p}_i is the induced dipole moment of the polarizable center i (all the N_μ nonhydrogen atoms) whose isotropic polarizability is α_i . \mathbf{E}_i^q is the static electric field generated on the center i by the surrounding charges q_j and \mathbf{T}_{ij} is the dipolar tensor. Both the static electric field and the dipolar tensor include a short range Thole's-like damping function.^[1,12,23] As the repulsive term, these damping functions are smoothly zeroed between 4.5 and 5.0 Å using a fifth order B-spline polynomial. The dipoles \mathbf{p}_i obey

$$\mathbf{p}_i = \alpha_i \cdot \left(\mathbf{E}_i^q + \sum_{j=1}^{N_\mu^*} \mathbf{T}_{ij} \cdot \mathbf{p}_j \right). \quad (5)$$

In the above equations, the superscript * indicates the sum to include only atom pairs separated by more than two chemical bonds (as for the U^{rep} and $U^{qq'}$ sums).

The terms U^{mbp} is a short-range anisotropic many-body energy term introduced to accurately model water/water hydrogen bond (HB) networks or strong hydrogen bond ones (SHB)

$$U^{mbp} = \sum f(r)g(\theta). \quad (6)$$

The sum runs over all HB/SHB pairs, r and r_e are the HB/SHB length and its equilibrium value, respectively. θ is a set of specific intermolecular angles. For SHBs, θ reduces to the sole angle $\psi^1 = \angle X^- \cdots H - O$. For HBs, it is a set of two angles (ψ^1, ψ^2), namely $\angle O \cdots H - O$ and the angle between the bisector of the water angle $\angle HOH$ and the hydrogen of the second water molecule involved in a HB, respectively. The functions f and g are defined as

$$f(r) = D_e \exp\left(-\frac{(r-r_e)^2}{\gamma_r}\right), \quad (7)$$

$$g(\Theta\{\psi^l\}) = \prod_l \exp\left(-\frac{(\psi^l - \psi_e^l)^2}{\gamma_\psi^l}\right). \quad (8)$$

For a given HB (SHB), the intensity of its U^{mbp} term is modulated by the chemical environment of the water molecule (anion) accepting the water hydrogen. This is achieved by taking D_e as a linear function of the local density n_b of the water oxygen (HB) or of the O–H bonds (SHB) in the vicinity of hydrogen acceptor species, i.e., $D_e = d_e(1 - \xi n_b)$, d_e and ξ being two adjustable parameters. The local density n_b is computed as

$$n_b = \sum \exp\left(-\frac{(r-r_e)^2}{\gamma_{rt}'}\right), \quad (9)$$

in which, r and r_e are defined as for function f . γ_{rt}' is a parameter adjusted to take into account only water molecules in the first hydration sphere of the hydrogen acceptor species and the sum runs over all the molecules surrounding it (apart from the local one considered explicitly in the present function f). U^{mbp} is a short-range energy term which is smoothly zeroed for distances r included between 5.75 and 6.25 Å. We discussed this energy term as mainly mimicking charge-transfer effects in SHBs^[23] even if it also accounts for halide/water dispersion. Regarding U^{hb} , its relation with water/water dispersion is shown in Supporting Information Figure S2.

At the exception of the isotropic polarizability (whose value is set to match gas-phase experimental or high-end quantum computation data^[16,23]), all the model parameters are assigned to reproduce geometrical and energetic properties of small clusters (comprising up to eight water molecules) as computed from high-end quantum computations.^[12,16,23]

Regarding the carboxylate CH_3COO^- , the interactions between water molecules and its anionic head are handled using the ΔU^{iw} potential energy described for halides. However, water/methyl interactions are modeled by substituting U^{mbp} by a basic dispersion term

$$U^{disp} = - \sum_{i=1}^{N_{\text{water oxygen}}} \sum_{j=1}^{N_{\text{methyl carbon}}} \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6, \quad (10)$$

here σ_{ij} is an adjustable parameter expressed in $(\text{kcal mol}^{-1} \text{Å})^{1/6}$. NH_4^+ /water interactions are modeled accordingly, i.e., we use the above dispersion term instead of a specific U^{mbp} one (the above second sum then runs on ammonium centers). The carboxylate methyl and ammonium dispersion parameters are provided in our former studies.^[13,17]

The TCPE/2013 model is rigid. No intramolecular relaxation term is needed to model halide/ NH_4^+ /water systems. Moreover, all the above energy terms converge to zero for large interatomic distances. The sum $\Delta U^{ww} + \Delta U^{iw}$ thus yields the halide/water cluster BEs. For the carboxylate CH_3COO^- , we add to the latter two intermolecular terms an intramolecular relaxation one as discussed in Ref. 17. In the following we denote \mathbf{FF}^{16} the global force field corresponding the halide/water model proposed in Ref. 16 and the water/water model TCPE/2013.^[12]

Molecular dynamics and potential of mean force

We detail here briefly our molecular dynamics (MD), protocols that correspond to those used in our former studies.^[13–15,17] More details can be found in Supporting Information. Bulk phase systems (comprising all 1000 water molecules) are simulated in the NPT (constant-temperature, constant-pressure) ensembles using periodic boundary conditions. Droplet systems (comprising 200, 400, and 600 water molecules) were simulated in the NVT (constant-temperature, constant-volume) ensemble, with the droplet embedded in a cavity to prevent evaporation phenomena (the droplet is large enough to minimize its effect on the droplet dynamics). The water intramolecular degrees of freedom are restrained during the simulations that are all performed at the 10 ns scale.

The potential of mean force (PMF), corresponding to the elongation of an ion pair r distance in aqueous phase or to the elongation of the r distance between an ion and the droplet center of mass (COM), are computed from a standard Umbrella Sampling scheme of 20 windows (bulk phase) and 40 windows (droplets). The window duration is 10 ns. The target distances r_{target} are equally spaced among the windows and the r distance is constrained to the value r_{target} in a particular window using a harmonic potential whose constant is set to 5.0 kcal mol⁻¹. The PMFs are computed from the latter simulations by means of the Umbrella Integration method^[29] and they all account for the entropic contribution $2k_{\text{B}}T \ln(r)$.

To compute the statistical averages, we sampled the last 9 ns segment of our MD simulations each 1 ps. The statistical ensembles thus comprise all 9000 points.

Definition of ion first hydration shell clusters and of their interaction energies

We classically define the first hydration shell of a mono atomic ion as the water molecules lying within less than the distance corresponding to the location r_{min} of the first minimum after the first peak of the ion/water oxygen radial distribution function computed from a bulk simulation. We define the ion coordination number N_c as the number of water molecules belonging to the ion's first hydration shell. For the organic anion CH₃COO⁻, we set the anion center to one of its oxygens.

We define the quantity $\bar{E}_{\text{method}}^k$ to be the mean interaction energy of ion first hydration shell clusters comprising k water molecules as extracted each 1 ps from a bulk phase ion MD simulation segment of 500 ps. Here "method" refers to quantum (QM) or force-field (MM) computations. Denoting w_k the weight (population) of the sized k clusters along the MD segment, the latter mean energies allows us to define the mean total difference $\Delta E_{\text{QM/MM}}$ in the interaction energy of ion first hydration shell clusters as follows

$$\Delta E_{\text{QM/MM}} = \sum_k w_k \delta \bar{E}_k = \sum_k w_k (\bar{E}_{\text{QM}}^k - \bar{E}_{\text{MM}}^k). \quad (11)$$

Similarly we define the energy components $\bar{E}_{\text{method}}^k$ as the above energies $\bar{E}_{\text{method}}^k$ to which the difference in the mean water/water interaction energies in the k -clusters is subtracted. From the $\bar{E}_{\text{method}}^k$ we compute the quantity $\Delta \bar{E}_{\text{QM/MM}}^k$:

$$\Delta \bar{E}_{\text{QM/MM}} = \sum_k w_k \delta \bar{E}_k = \sum_k w_k (\bar{E}_{\text{QM}}^k - \bar{E}_{\text{MM}}^k), \quad (12)$$

that measures the difference in the intensity of the sole anion/water interactions in the ion's first hydration shell clusters from both quantum and force-field computations.

Note that a 500 ps segment can not be considered as a long enough MD trajectory allowing to exhaustively sample the PES of the molecular systems here considered. We provide as Supporting Information a plot showing the fluctuations of the quantity $\sum_k w_k \bar{E}_{\text{MM}}^k$, i.e., the mean ion/first hydration shell interaction energy computed for all the continuous 500 ps segments that can be extracted from a 4 ns MD trajectory of Cl⁻ solvated in bulk water. These fluctuations can be as large as 2 kcal mol⁻¹, a value that matches the order of magnitude of the values $\Delta E_{\text{QM/MM}}$ discussed below. Hence, $\Delta E_{\text{QM/MM}}$ provides only a crude estimate of the force-field uncertainty compared to quantum computations. It is thus recommended to not use it to postcorrect force-field energy estimates, like ion's hydration enthalpy.

Extrapolation of single ion hydration enthalpy

We estimate the single ion hydration enthalpy ΔH_{hyd} by extrapolating ion/water droplet data as in our former studies dealing about ammonium, carboxylate, and guanidinium ions.^[13–15,17] Denoting M the number of water molecules of a droplet, we estimate the average ion/water energy $\Delta \bar{U}^{jw}(M)$ from droplet simulations where the ion distance to the droplet COM is restrained using a harmonic potential. Then we extrapolate the bulk value $\Delta \bar{U}^{jw}(\infty)$ by linearly fitting the droplet data to the power-law function:

$$\Delta \bar{U}^{jw}(M) = \Delta \bar{U}^{jw}(\infty) + a/M^{1/3}. \quad (13)$$

Here we consider only three water droplets comprising 200, 400, and 600 water molecules, respectively. By reanalyzing our former data regarding ammonium and carboxylate ions, the extrapolated values $\Delta \bar{U}^{jw}(\infty)$ computed from this droplet set equal the values extrapolated from larger droplet sets within the linear regression uncertainty, about ± 0.4 kcal mol⁻¹.

The water destabilization energy in bulk phase $\Delta \bar{U}^{ww}(\infty)$ due to the presence of an ion is computed as in our former studies.^[13,15,17] A single ion is simulated in aqueous phase and the water/water mean interaction energy $\bar{U}^{ww}(\infty)$ is computed along the bulk trajectory by ignoring the ion. The same quantity is obtained for a pure water solution and subtracted to the previous quantity to obtain $\Delta \bar{U}^{ww}(\infty)$. Summing the above two energy contributions yields the single hydration enthalpy ΔH_{hyd} of a mono atomic ion

$$\Delta H_{\text{hyd}} = \Delta \bar{U}^{jw}(\infty) + \Delta \bar{U}^{ww}(\infty) - k_{\text{B}}T. \quad (14)$$

There are three main sources of uncertainty affecting the ΔH_{hyd} estimates, namely the uncertainty δE^{lin} tied to the linear

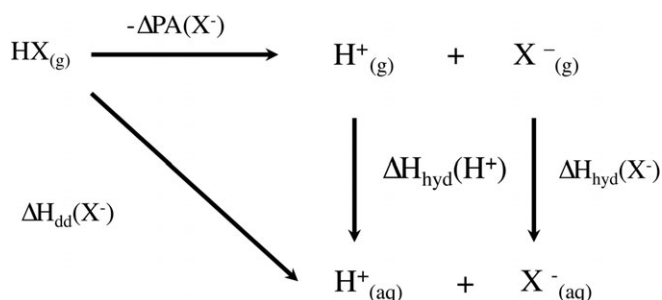


Figure 2. Thermodynamical cycle allowing to compute the proton hydration enthalpy from theoretical single anion hydration enthalpy values and well accepted experimental halide thermodynamic quantities.

fitting process corresponding to eq. (13) (at most ± 0.4 kcal mol⁻¹) and the uncertainties $\delta\bar{U}^{iw}$ and $\delta\bar{U}^{ww}$ arising from the finite size of the sampled data sets from which the energies $\Delta\bar{U}^{iw}(M)$ and $\Delta\bar{U}^{ww}(\infty)$ are computed. For all the anions, the root mean square deviations corresponding to the water/water destabilization energy and to the ion/water droplet energy are at most 6.0 and 7.4 kcal mol⁻¹, respectively. Assuming the points extracted each 1 ps from the trajectories as temporally uncorrelated, $\delta\bar{U}^{iw} + \delta\bar{U}^{ww}$ then is ± 0.15 kcal mol⁻¹. The total uncertainty affecting our computed values ΔH_{hyd} is thus ± 0.6 kcal mol⁻¹, regardless of the anion.

Single halide hydration enthalpy values allow to estimate the proton hydration enthalpy $\Delta H_{hyd}(\text{H}^+)$ according to the thermodynamic cycle shown in Figure 2, leading to the formula

$$\Delta H_{hyd}(\text{H}^+) = \Delta H_{dd} + \Delta P_{AX} - \Delta H_{hyd}(\text{X}^-). \quad (15)$$

Here ΔH_{dd} is the enthalpy cost of the two step reaction corresponding to the dissolution of a protonated acid HX from gas phase to liquid water, followed by its dissociation $\text{HX} \rightarrow \text{H}^+ + \text{X}^-$ in aqueous phase. ΔP_{AX} is the gas-phase enthalpy cost of the anion X^- protonation reaction. The experimental values of the latter quantities that we consider in the present study are provided as Supporting Information.

Results and Discussion

Quality of the original water model TCPE/2013 to model large anion first hydration shells

We discuss here the accuracy of the original model TCPE/2013 to describe water/water interactions occurring in the vicinity of an ion by considering the energy differences $\delta\bar{E}_k$ defined in Section "Definition of ion first hydration shell clusters and of their interaction energies". For chloride, the distribution of the first hydration shell clusters extracted from a 500 ps segment of a bulk phase MD trajectory *wrt* to their water size k is shown in Figure 3. The most frequent clusters comprise 8 and 9 water molecules (their weights $w_{8/9}$ are larger than 30%). However, 7 and 10 water clusters are far from being negligible, their weights w_k being larger than 10%.

The components $\delta\bar{E}_k$ and $\delta\bar{\bar{E}}_k$ are plotted *wrt* the cluster size k in Figure 3. These plots show **FF**¹⁶ to reproduce accurately

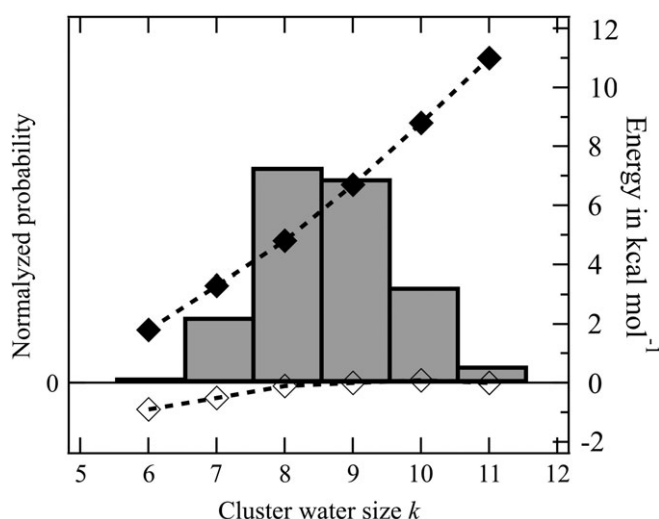


Figure 3. Mean errors $\delta\bar{E}_k$ (full diamonds) and $\delta\bar{\bar{E}}_k$ (empty diamonds) for Cl^- hydrated clusters extracted along a bulk simulation *wrt* their water size k (right axis). The distribution of the sized k clusters along that simulation is shown by the histogram plot (left axis).

the quantum results regarding the ion/water interaction energies $\delta\bar{E}_k$ within less than 1 kcal mol⁻¹ for all the cluster sizes and even within less 0.5 kcal mol⁻¹ for the most frequent ones ($k = 7 - 11$). However, a much larger difference in the values $\delta\bar{E}_k$ is observed, a difference that increases from 3.3 ($k = 7$) up to 8.8 kcal mol⁻¹ ($k = 10$). Hence, TCPE/2013 does not provide an accurate enough description of the water/water interactions in large Cl^- hydration shell clusters as compared to quantum computations.

To investigate the origin of that disagreement between our water model and quantum computations, we dissected the water/water interactions in large Cl^- hydrated clusters as a sum of water/water pairs whose interaction energies are estimated from quantum computations and compared to force-field estimates. For that purpose we selected a set of extracted halide/water first hydration shell clusters whose values $\delta\bar{E}_k$ are the largest. The analysis of the pair energies shows large $\delta\bar{E}_k$ values to arise systematically from a small set of water pairs whose structure corresponds to the **S**₃ one highlighted in Figure 1. The water pair energies of **S**₃-like structures are systematically underestimated when using TCPE/2013 compared to quantum computations, by 2–3 kcal mol⁻¹. For instance, if we consider the extracted cluster shown in Figure 1, only two of its 28 water pairs are in a **S**₃ conformation. However, they are responsible for about 65% of its $\delta\bar{E}_k$ value (6.5 kcal mol⁻¹).

The water dimer conformation **S**₃ is close to the **TS**₂ one that is shown to be a transition state of the water dimer gas-phase potential energy surface from high-end quantum computations.^[30] However, both quantum computations^[30] and TCPE/2013 predict the inter oxygen and hydrogen distances between the two OH parallel bonds to be noticeably larger in **TS**₂ than in **S**₃, by, about 0.15 and 0.75 Å, respectively. Note also that both TCPE/2013 and high end quantum computations agree within 0.1 kcal mol⁻¹ for the **TS**₂ BE (4.6 and 4.5 kcal mol⁻¹, respectively), and they predict both the

conformation **S**₃ to be unstable (it evolves toward the conformation **TS**₂ when performing a geometrical optimization, regardless of the theoretical method used).

Compared to quantum computations, the overall large error in the model interaction energy computed for large Cl⁻ first hydration shell clusters thus arises from the water model TCPE/2013 that is not able to accurately reproduce the interaction energy of the particular water pair conformation **S**₃ observed *a priori* only in large-sized halide first hydration-shell structures. The conformation **S**₃ does not correspond to an extremum of the water dimer PES in gas phase and it is characterized by short inter oxygen and hydrogen distances between its two OH parallel bonds.

The three-body correction term $U_{\text{corr}}^{3b}(X)$

To remediate the TCPE/2013 artifacts in accurately modeling water/water interactions in the first hydration shells of large-sized halide clusters, we can either reoptimize the full set of the force-field parameters or introduce an ad hoc short-range three-body term to improve the description of water interactions in the vicinity of an anion. The second option allows both faster developments and to preserve the features of the original TCPE/2013 model in describing other kinds of water systems. For instance, we may consider the following three-body function

$$U_{\text{corr}}^{3b} = \sum u^{\text{rep}}(r_{\text{OO}})f(r_{\text{XO}}^1)f(r_{\text{XO}}^2) = \sum A_w^{3b} \exp(-B_w^{3b}r_{\text{OO}})f(r_{\text{XO}}^1)f(r_{\text{XO}}^2), \quad (16)$$

here, r_{OO} and r_{XO}^n are the water inter oxygen and the anion center/water oxygen distances, respectively. u^{rep} is defined as the pair component of the repulsive term U^{rep} discussed in Section "The water and the halide/water force field". It is also smoothly zeroed for inter oxygen distances included between 4.5 and 5.0 Å and A_w^{3b} and B_w^{3b} are two adjustable parameters. To modulate the intensity of u^{rep} based on the anion/water oxygen distances, we take f as the gaussian function of the energy term U^{shb} defined in eq. (7).

U_{corr}^{3b} is introduced to improve in an averaged way the description of water/water pairwise interactions in the vicinity of an anion. A priori its two parameters A_w^{3b} and B_w^{3b} have not to depend on the anion. This is the assumption that we made for the present study by considering for all the anions the set ($A_w = 2.9 \text{ \AA}^{-1}$, $B_w = 120000 \text{ kcal mol}^{-1}$) minimizing the difference $\Delta E_{\text{QM/MM}}$ for Cl⁻. We will denote hereafter **FF**¹⁶ the 2016 force field from Ref. 16, and **FF**^{corr} the new force field for which the halide/water interactions are modeled by the term $\Delta U_{\text{corr}}^{\text{iw}}$ defined as

$$\Delta U_{\text{corr}}^{\text{iw}} = \Delta U^{\text{iw}} + U_{\text{corr}}^{3b} = U^{\text{rep}} + U^{\text{qd}} + U^{\text{pol}} + U^{\text{shb}} + U_{\text{corr}}^{3b}. \quad (17)$$

Because of its analytical form, the function U_{corr}^{3b} can be computed together with U^{shb} . As both terms are short ranged, their computational complexity scales as $O(N)$ and their

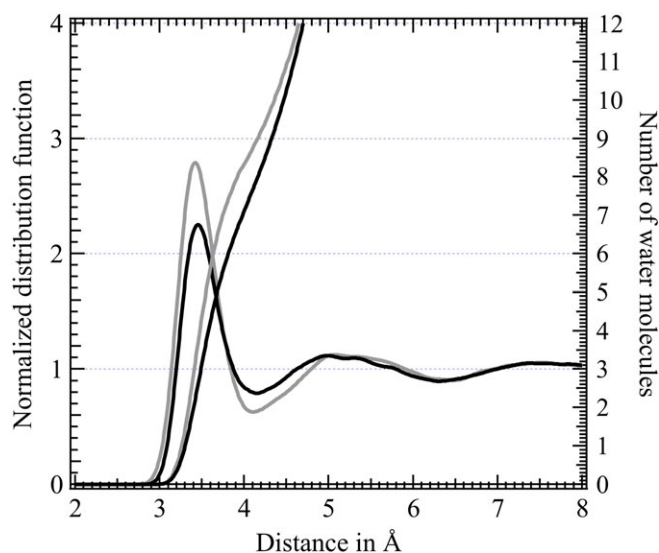


Figure 4. Cl⁻/water oxygen radial distribution function (left axis) and its integral (right axis) from MD bulk simulations. Black line: **FF**^{corr}; gray line: **FF**¹⁶. [Color figure can be viewed at wileyonlinelibrary.com]

computational cost is negligible when simulating a halide anion solvated in bulk phase.

Earlier authors already proposed to improve the description of short range repulsion-exchange effects in modeling water/water and water/ion interactions by means of three-body energy terms. We may quote among others the pioneering work of Lybrand and Kollman,^[31] the SIBFA approach developed by Gresh and coworkers^[32] and the more recent AMOEBA approach,^[33–36] for instance. At the difference of these former approaches, the three atoms that we consider to compute our U_{corr}^{3b} three-body term do not play a symmetric role. Here the ion center acts as a filter delimiting a space domain where the original water/water two body repulsion is altered. We may note that such kind of potentials was already used by one of us to improve the accuracy of a water coarse grained approach in describing ion hydration.^[37] However in that case, the many-body potential parameters were assigned to provide a reasonable ion first hydration shell structure and not to improve the description of the ion/water interaction energy.

Effect of U_{corr}^{3b} on anion hydration properties in bulk phase

In Figure 4 we plot the halide center/water oxygen radial distribution functions g_{XO} and their integrals G_{XO} computed along two MD simulations of Cl⁻ solvated in bulk water at the 10 ns scale by using the force field **FF**¹⁶ and **FF**^{corr}, respectively. The plots for the other halides are provided as Supporting Information.

For all the halides, the main features of their functions g_{XO} are close, regardless of the force field used. For instance, the positions of the first three extrema of these functions are close within at most 0.1 Å. However, compared to **FF**¹⁶, the height of the first peak of the **FF**^{corr} g_{XO} is smaller by about 25%. That yields thus smaller **FF**^{corr} coordination numbers N_c , the shift δN_c ranging from 0.5 (F⁻) to 1.7 (I⁻) water molecules. These data are in line with the expected destabilizing effect of the correction term U_{corr}^{3b} on the halide first hydration shell.

Table 1. Extrapolated anion/water energies $\Delta\bar{U}^{iw}(\infty)$, water destabilization energies $\Delta\bar{U}_{ww}$ due to the anion presence, difference in quantum versus force-field energies $\Delta E_{QM/MM}$, single anion hydration enthalpies $\Delta H_{\text{hyd}}(X^-)$, and absolute proton hydration enthalpies $\Delta H_{\text{hyd}}(\text{H}^+)$ from **FF^{corr}** and **FF¹⁶** (in parentheses and italic) All energy data in kcal mol⁻¹. N_c is the anion coordination number, in molecules. The uncertainty affecting the hydration enthalpy values is ± 0.6 kcal mol⁻¹, regardless of the anion (see Section "Molecular dynamics and potential of mean force"). The anion-based mean values $\Delta H_{\text{hyd}}(\text{H}^+)$ are provided with their root-mean-square deviations.

	$-\Delta\bar{U}^{iw}(\infty)$	$\Delta\bar{U}_{ww}$	$\Delta E_{QM/MM}$	$-\Delta H_{\text{hyd}}(X^-)$	$-\Delta H_{\text{hyd}}(\text{H}^+)$	N_c
F ⁻	154.7 (164.0)	44.2 (47.4)	4.5 (8.8)	100.5 (116.8)	275.9 (269.8)	5.9 (6.4)
Cl ⁻	129.3 (137.3)	47.4 (54.1)	2.2 (4.8)	81.9 (83.2)	269.4 (268.1)	7.5 (8.8)
Br ⁻	121.1 (128.7)	48.1 (53.1)	3.9 (6.4)	73.0 (75.6)	270.9 (268.3)	7.9 (9.1)
I ⁻	104.4 (113.0)	45.4 (51.8)	1.2 (6.4)	59.0 (61.2)	275.2 (273.1)	6.8 (9.1)
At ⁻	102.4 (110.6)	43.3 (50.4)	5.2 (6.0)	59.1 (60.2)	na	6.5 (9.1)
CH ₃ COO ⁻	126.0 (143.5)	38.9 (47.4)	4.4 (8.8)	85.7 (98.5)	275.6 (262.8)	
Average					273.4 \pm 3.0 (268.4 \pm 3.7)	

We computed the halide center/water hydrogen radial distribution functions g_{XH} and the mean water molecular dipole moment functions $\bar{\mu}$ as a function of the anion/water oxygen distance from the above MD simulations (their plots are provided as Supporting Information). The g_{XH} features are fully in line with the g_{XO} ones. Regarding water dipoles, the use of U_{corr}^{3b} yields slightly larger $\bar{\mu}$ values at short range from the halide center, at most by 0.1 Debye and regardless of the halide.

Regarding the water destabilization energy $\Delta\bar{U}^{ww}(\infty)$ in bulk phase due to the ion presence, we got close values for all the halides, see Table 1. They range from 47 to 54 kcal mol⁻¹ for **FF¹⁶** and from 43 to 48 kcal mol⁻¹ for **FF^{corr}**. The use of the correction term U_{corr}^{3b} leads to less hydrated halide structures in bulk phase (by about 1.2 water molecules on average). In turn, that weakens the magnitude of the water bulk destabilization due to the halide presence and that favors the halide hydration in aqueous phase by about 5 kcal mol⁻¹ on average.

We also computed the halide diffusion coefficient D_{sim} from the autocorrelation functions of their velocities sampled each 5 fs along a 9 ns MD segments of the halide bulk simulation according to the methodology described in Ref. 16. The **FF^{corr}** D_{sim} values are close (and included within the error bars) to the **FF¹⁶** ones for F⁻ to Br⁻ (i.e. 1.79, 1.84 and 1.84 \pm 0.1 10^{-5} cm² s⁻¹, respectively), whereas they are noticeably smaller for I⁻ and At⁻, 1.58 and 1.54 10^{-5} cm² s⁻¹ (the **FF¹⁶** values are about 1.85 10^{-5} cm² s⁻¹). It is not obvious to explain the stronger effect of the term U_{corr}^{3b} on the diffusion properties of I⁻/At⁻ compared to the lighter halides. However, both our **FF¹⁶** and **FF^{corr}** estimates of D_{sim} values for the latter two heavier halides are in line with the experimental data recently reported by Guo et al.,^[38] within the experimental error bars.

Our results for the carboxylate anion CH₃COO⁻ are in line with the halide ones. However, the shift δN_c for the carboxylate oxygen is slightly smaller, only 0.3 water molecules. See the results summarized in Table 1 and the plots provided as Supporting Information.

Effect of U_{corr}^{3b} on single anion hydration enthalpies

The Cl⁻ **FF¹⁶** and **FF^{corr}** PMFs are plotted as a function of the anion/droplet COM distance R in Figure 5. The U_{corr}^{3b} effect on these PMFs is weak. For all droplets, the Cl⁻ PMFs present a shallow minimum close to the droplet surface that is shifted to larger distances R when using **FF^{corr}** compared to **FF¹⁶**. The

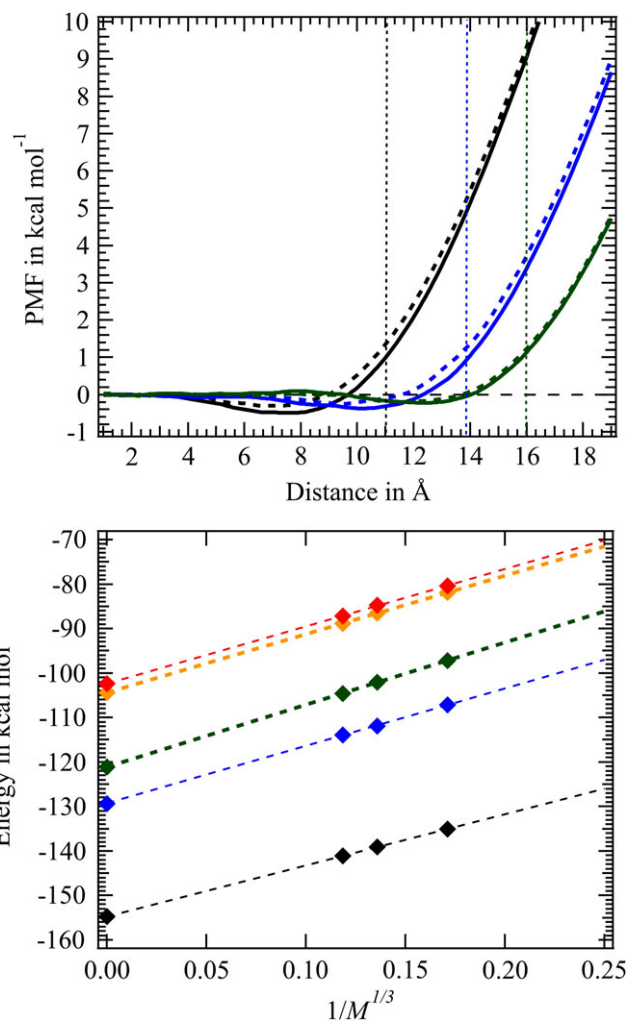


Figure 5. Cl⁻/droplet PMFs computed from the **FF¹⁶** and **FF^{corr}** (up) and mean halide/water droplet interaction energies $\Delta\bar{U}^{iw}(M)$ (down). For the PMFs (full line, **FF^{corr}** and dashed line, **FF¹⁶**), the vertical lines are located at the droplet radius^[14] and the 200, 400, and 600 droplet PMFs are shown in black, blue, and green, respectively. For the mean interaction energies, black, blue, green, orange, and red symbols correspond to the series F⁻-At⁻. The linear regression fit corresponding to these energies, see eq. (13), are plotted in dashed lines. The corresponding linear regression coefficients are all larger than 0.999. The mean interaction energies corresponding to $M = \infty$ are plotted at the origin of the bottom axis. [Color figure can be viewed at wileyonlinelibrary.com]

propensity of Cl^- for the droplet surface is thus slightly reinforced when using $\mathbf{FF}^{\text{corr}}$. That seems to be in line with the overall destabilizing character of U_{corr}^{3b} on anion/water interactions. We reported as Supporting Information the $\mathbf{FF}^{\text{corr}}$ PMFs for all the halides. The halide propensity for the droplet surfaces increases along the series. This is in agreement with earlier simulation studies, see among others Refs. 39–41. In particular the depth of the PMF minimum close to the 600-droplet surface for Γ^-/At^- is predicted by our approach to be particularly large, -3.6 and -5.0 kcal mol $^{-1}$, while it is only -0.2 and -0.7 kcal mol $^{-1}$ for Cl^- and Br^- , respectively. Regarding Γ^- , that PMF min value is about twice as large as the one usually reported for that halide at the water bulk interface (see the above mentioned studies). However, we showed for alkylated carboxylates that the PMF minimum value close to the water surface is still far to be converged in droplets comprising 600 and less water molecules.

The anion/droplet interaction energy $\Delta U^{iw}(M)$ values computed from $\mathbf{FF}^{\text{corr}}$ are plotted wrt $M^{1/3}$ in Figure 5 and the extrapolated \mathbf{FF}^{16} and $\mathbf{FF}^{\text{corr}}$ anion/water interaction energies $\Delta \bar{U}^{iw}(\infty)$ are reported in Table 1. Adding to $\Delta \bar{U}^{iw}(\infty)$ the bulk water destabilization energy $\Delta \bar{U}^{ww}$ yields the single anion hydration enthalpy $\Delta H_{\text{hyd}}(X^-)$ from which we estimate the proton hydration enthalpy $\Delta H_{\text{hyd}}(\text{H}^+)$ (according to the thermodynamical cycle shown in Fig. 2). These values for the two force fields are also summarized in Table 1.

As expected from the repulsive nature of the term U_{corr}^{3b} , the extrapolated bulk halide/water interaction energies $\Delta \bar{U}^{iw}(\infty)$ are all smaller by about 9 kcal mol $^{-1}$ for halides and by 17 kcal mol $^{-1}$ for CH_3COO^- when using $\mathbf{FF}^{\text{corr}}$ as compared to \mathbf{FF}^{16} . The bulk water destabilization energies $\Delta \bar{U}^{ww}(\infty)$ are also smaller when using $\mathbf{FF}^{\text{corr}}$ than \mathbf{FF}^{16} , however by a smaller amount of energy, i.e., from 4 to 5 kcal mol $^{-1}$. This yields the $\mathbf{FF}^{\text{corr}}$ single halide bulk hydration enthalpy to be smaller by about 2 kcal mol $^{-1}$ for halides and by 13 kcal mol $^{-1}$ for CH_3COO^- as compared to \mathbf{FF}^{16} data.

The halide hydration enthalpies yield the proton hydration enthalpy estimate to vary from 263 (CH_3COO^-) to 273 (Γ^-) kcal mol $^{-1}$ and from 269 (Cl^-) to 276 (F^-) as using \mathbf{FF}^{16} and $\mathbf{FF}^{\text{corr}}$, respectively. Note that for \mathbf{FF}^{16} we consider the CH_3COO^- value^[17] computed accordingly to the protocol detailed in the present study. By averaging the values computed for all the anions here considered, we get $\Delta H_{\text{hyd}}(\text{H}^+) = 274.0 \pm 3.0$ kcal mol $^{-1}$ for $\mathbf{FF}^{\text{corr}}$ and 269.0 ± 3.7 kcal mol $^{-1}$ for \mathbf{FF}^{16} . The $\mathbf{FF}^{\text{corr}}$ mean value agrees remarkably with the most current experimental-based value, 274.9 kcal mol $^{-1}$.^[42] Moreover our $\mathbf{FF}^{\text{corr}}$ anion-based estimate is fully in line with our former ammonium-based proton hydration estimate, 272.5 kcal mol $^{-1}$.^[13]

To assess the improvement in the anion/water energy description arising from the use of $\mathbf{FF}^{\text{corr}}$ compared to \mathbf{FF}^{16} , we may also consider the $\Delta E_{\text{QM/MM}}$ values summarized in Table 1 that are twice as weak on average for all the anions when using $\mathbf{FF}^{\text{corr}}$. Note that we computed the difference in energy $\Delta E_{\text{QM/MM}}$ for NH_4^+ as for the anions. It is almost negligible as it amounts to 0.1 kcal mol $^{-1}$. A priori that demonstrates the ability of our TCPE/2013 model to accurately describe water interactions

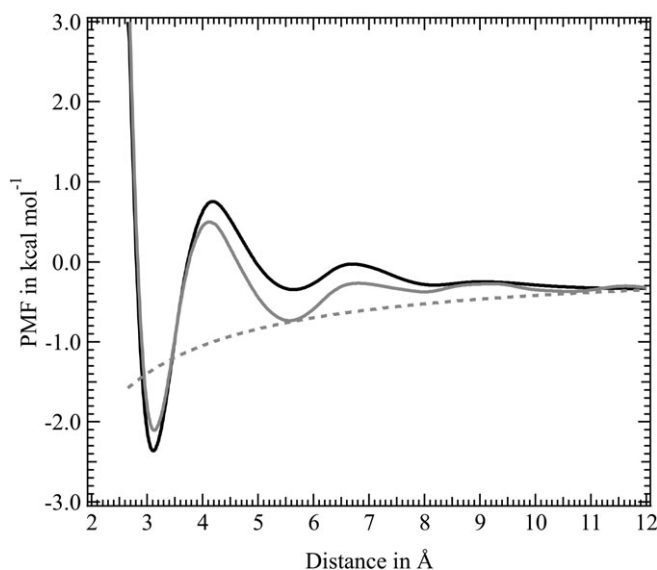


Figure 6. Potential of mean force of a single ion pair $\text{NH}_4^+/\text{Cl}^-$ dissolved in bulk water. Black line: PMF($\mathbf{FF}^{\text{corr}}$); gray line: PMF(\mathbf{FF}^{16}); dashed gray line: effective Coulomb potential of two opposite point charges dissolved in bulk water. The force-field PMF profiles are shifted to meet the coulomb potential value at a nitrogen/chloride distance of 12 Å.

within the small first hydration shells of a cation like NH_4^+ (our approach predicts the ammonium coordination number N_c to be small compared to halides, i.e., 4.5 molecules^[13]).

Effect of U_{corr}^{3b} on the potential of mean force of the $\text{NH}_4^+/\text{Cl}^-$ ion pair in aqueous phase

Our aim here is to investigate the effect of our three-body term U_{corr}^{3b} on the $\text{NH}_4^+/\text{Cl}^-$ ion pair interaction in a diluted salt solution to check the transferability of U_{corr}^{3b} to study nonhomogeneous hydrated anion microscopic systems. For that purpose, we built a reasonable *ab initio*-based model to investigate aqueous $\text{NH}_4^+/\text{Cl}^-$ salt solutions using the same protocol as for carboxylate/ammonium salts.^[43] The details are provided as Supplementary Information. The potentials of mean force, PMFs, corresponding to a single $\text{NH}_4^+/\text{Cl}^-$ pair dissolved in aqueous phase from \mathbf{FF}^{16} and $\mathbf{FF}^{\text{corr}}$ MD bulk phase simulations are plotted in Figure 6. Both the PMF(\mathbf{FF}^{16}) and PMF($\mathbf{FF}^{\text{corr}}$) profiles exhibit two minima at about 3.1 and 5.6 Å separated by a maximum at about 4.1 Å, in agreement with the contact ion pair/separated ion pair picture of ion pairing in aqueous phase.^[44,45] However the depth and the height of the first PMF minimum and maximum are larger for $\mathbf{FF}^{\text{corr}}$ compared to \mathbf{FF}^{16} , by about 0.3 kcal mol $^{-1}$. This is interpreted as resulting from the smaller hydration shell of Cl^- when using $\mathbf{FF}^{\text{corr}}$ that facilitates the accommodation of the cation in the halide first hydration sphere compared to \mathbf{FF}^{16} .

We estimate the number of water molecules released Δn_{IP} upon the formation of the $\text{NH}_4^+/\text{Cl}^-$ ion pair as in our former study.^[43] From the constrained simulation corresponding to an inter ionic target distance r_{target} that is the closest from the location of the PMF first minimum, we compute the mean number of water molecules $\bar{n}_{\text{N,Cl}}$ that lie at a distance smaller than the first hydration shell radius r_{min} of the NH_4^+ nitrogen or of the chloride center. Δn_{IP} is then the difference between the

sum of the coordination numbers N_c of NH_4^+ and Cl^- solvated alone in bulk water and $\bar{n}_{\text{N,Cl}}$. We get $\bar{n}_{\text{N,Cl}} = 10$ (**FF**¹⁶) and 9 (**FF**^{corr}) molecules and thus $\Delta n_{\text{IP}} = 3$ molecules for both force fields, a value that matches those reported experimentally for alkali/chloride ion pairs in methanol.^[44]

In all, the above results show the weak effect of U_{corr}^{3b} on the properties of $\text{NH}_4^+/\text{Cl}^-$ diluted salt solutions. This suggests that the term U_{corr}^{3b} may be used to investigate the properties of complex salt solutions without introducing a major source of drawback. However, it has to be noted that force-fields providing weak differences in ion pair PMFs may lead to predict large differences in solution macroscopic properties like the osmotic pressure, for instance.^[46]

Conclusion

We propose an approach to improve the force-field description of water/water interactions in the vicinity of an anion that prevents to reassign the full set of water force-field parameters. That approach is based on introducing an *ad hoc* short-range three-body energy term centered on the anion center and whose parameters are taken constant regardless of the anion. Here we apply that approach (and its correction three-body energy term) to improve the description of halide (from F^- to At^-) hydration when using the water model TCPE/2013. Our results show that it is able to noticeably improve the energetic description of anion hydration with a negligible impact on the computational time. Interestingly the correction three-body energy term has a weak effect on the $\text{NH}_4^+/\text{Cl}^-$ ion pairing in aqueous phase, suggesting that term will not be a source of drawbacks when modeling complex system involving different anion/cation species in solvent mixture, for instance. We also assess the transferability of that approach by using the three-body energy term (and its halide-based parameter set) to investigate the hydration properties of the carboxylate CH_3COO^- . Even for that organic anion, we note noticeable improvements in particular to predict the proton hydration enthalpy from simulated $\text{CH}_3\text{COO}^-/\text{water}$ droplet data that is in very good agreement with the most well accepted experimental based value.

The correction scheme used here to specifically remediate a drawback of the water model TCPE/2013 can be used to improve the quality of any kind of force fields to model the interactions of solvent or ligand molecules in the vicinity of any kind of chemical species, from ions to neutral molecules. The quality of the improvements tied to such a scheme obviously depends on the quality of the analysis performed to identify the origin of the original force field drawback in order to propose a reliable and physically founded three-body correction energy term. Moreover, we recommend to use it when the force-field deficiency regarding the description of solvent interactions yields errors amounting to about 10 $k_B T$. The correction scheme will then correspond to a smooth transition between the solvent core phase and the solute vicinity.


Acknowledgments

The authors thank Pr Michael Mautner (Meot-Ner) for fruitful discussions and support. The members of the PhLAM laboratory

acknowledge support from the CaPPA project (Chemical and Physical Properties of the Atmosphere) that is funded by the French National Research Agency (ANR) through the PIA (Programme d'Investissement d'Avenir) under contract "ANR-11-LABX-0005-0" and by the Regional Council "Hauts de France" and the "European Funds for Regional Economic Development" (FEDER) through the Contrat de Projets Etat-Région (CPER) CLIMIBIO (Changement climatique, dynamique de l'atmosphère, impacts sur la biodiversité et la santé humaine). Furthermore, this work was granted access to the HPC resources of [CINES/IDRIS/TGCC] under the allocation 2016-2019 [x2016081859, A0010801859 and A0050307078] made by GENCI.

Keywords: force field · anion hydration · salt solution

How to cite this article: F. Réal, V. Vallet, M. Masella. *J. Comput. Chem.* **2019**, *40*, 1209–1218. DOI: 10.1002/jcc.25779

 Additional Supporting Information may be found in the online version of this article.

- [1] F. Réal, M. Trumm, B. Schimmelpfennig, M. Masella, V. Vallet, *J. Comput. Chem.*, **2012**, *34*, 707.
- [2] B. Temelso, K. A. Archer, G. C. Shields, *Chem. Eur. J.* **2011**, *115*, 12034.
- [3] H. J. C. Berendsen, J. R. Grigera, T. P. Straatsma, *J. Phys. Chem.* **1987**, *91*, 6269.
- [4] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, M. L. Klein, *J. Chem. Phys.* **1983**, *79*, 926.
- [5] J. L. F. Abascal, C. Vega, *J. Chem. Phys.* **2005**, *123*, 234505.
- [6] V. Babin, G. R. Medders, F. Paesani, *J. Phys. Chem. Lett.* **2012**, *3*, 3765.
- [7] G. Lamoureux, A. D. Mackerell, B. Roux, *J. Chem. Phys.* **2003**, *119*, 5185.
- [8] L. X. Dang, T.-M. Chang, *J. Phys. Chem. B* **2002**, *106*, 235.
- [9] A. Grossfield, P. Ren, J. W. Ponder, *J. Am. Chem. Soc.* **2003**, *125*, 15671.
- [10] G. Lamoureux, B. Roux, *J. Phys. Chem. B* **2006**, *110*, 3308.
- [11] H. Yu, T. W. Whitfield, E. Harder, G. Lamoureux, I. Vorobyov, V. M. Anisimov, A. D. Mackerell, B. Roux, *J. Chem. Theor. Comp.* **2010**, *6*, 774.
- [12] F. Réal, V. Vallet, J.-P. Flament, M. Masella, *J. Chem. Phys.* **2013**, *139*, 114502.
- [13] C. Houriez, M. Meot-Ner (Mautner), M. Masella, *J. Phys. Chem. B* **2014**, *118*, 6222.
- [14] J. P. Coles, C. Houriez, M. Meot-Ner (Mautner), M. Masella, *J. Phys. Chem. B* **2016**, *120*, 9402.
- [15] C. Houriez, M. Meot-Ner (Mautner), M. Masella, *J. Phys. Chem. B* **2017**, *121*, 11219.
- [16] F. Réal, A. Severo Pereira Gomes, Y. O. Guerrero Martinez, T. Ayed, N. Galland, M. Masella, V. Vallet, *J. Chem. Phys.* **2016**, *144*, 124513.
- [17] C. Houriez, M. Meot-Ner (Mautner), M. Masella, *J. Phys. Chem. B* **2015**, *119*, 12094.
- [18] J. Rheinecker, J. M. Bowman, *J. Chem. Phys.* **2006**, *125*, 133206.
- [19] E. Kamarchik, J. M. Bowman, *J. Phys. Chem. Lett.* **2013**, *4*, 2964.
- [20] P. Bajaj, A. W. Götz, F. Paesani, *J. Chem. Theory Comput.* **2016**, *12*, 2698.
- [21] M. Riera, N. Mardirossian, P. Bajaj, A. W. Götz, F. Paesani, *J. Chem. Phys.* **2017**, *147*, 161715.
- [22] P. Bajaj, X.-G. Wang, T. Carrington, F. Paesani, *J. Chem. Phys.* **2018**, *148*, 102321.
- [23] M. Trumm, Y. O. Guerrero Martinez, F. Réal, B. Schimmelpfennig, M. Masella, V. Vallet, *J. Chem. Phys.* **2012**, *136*, 044509.
- [24] T. H. Dunning, Jr., *J. Chem. Phys.* **1989**, *90*, 1007.
- [25] K. A. Peterson, D. Figgen, E. Goll, H. Stoll, M. Dolg, *J. Chem. Phys.* **2003**, *119*, 11113.
- [26] R. Polly, H.-J. Werner, F. R. Manby, P. J. Knowles, *Mol. Phys.* **2004**, *102*, 2311.
- [27] H.-J. Werner, F. R. Manby, P. J. Knowles, *J. Chem. Phys.* **2003**, *118*, 8149.

- [28] Werner, H.-J.; Knowles, P. J.; Knizia, G.; Manby, F. R.; Schütz, M.; Celani, P.; Györfy, W.; Kats, D.; Korona, T.; Lindh, R.; Mitrushenkov, A.; Rauhut, G.; Shamasundar, K. R.; Adler, T. B.; Amos, R. D.; Bernhardsson, A.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert, F.; Goll, E.; Hampel, C.; Hesselmann, A.; Hetzer, G.; Hrenar, T.; Jasen, G.; Köppl, C.; Liu, Y.; Lloyd, A. W.; Mata, R. A.; May, A. J.; McNicholas, S. J.; Meyer, W.; Mura, M. E.; Nicklass, A.; O'Neill, D. P.; Palmieri, P.; Peng, D.; Pflüger, K.; Pitzer, R.; Reiher, M.; Shiozaki, T.; Stoll, H.; Stone, A. J.; Tarroni, R.; Thorsteinsson, T.; Wang, M. MOL-PRO, Version 2015.1, A Package Of *Ab Initio* Programs. **2015**; see <http://www.molpro.net>.
- [29] J. Kästner, W. Thiel, *J. Chem. Phys.* **2005**, *123*, 144104.
- [30] G. S. Tschumper, M. L. Leininger, B. C. Hoffman, E. F. Valeev, H. F. Schaefer III, M. Quack, *J. Chem. Phys.* **2002**, *116*, 690.
- [31] T. P. Lybrand, P. A. Kollman, *J. Chem. Phys.* **1985**, *83*, 2923.
- [32] R. Chaudret, N. Gresh, O. Parisel, J.-P. Piquemal, *J. Comput. Chem.* **2011**, *32*, 2949.
- [33] P. Ren, J. W. Ponder, *J. Phys. Chem. B* **2003**, *107*, 5933.
- [34] J.-P. Piquemal, L. Perera, G. A. Cisneros, P. Ren, L. G. Pedersen, T. A. Darden, *J. Chem. Phys.* **2006**, *125*, 054511.
- [35] J. C. Wu, J.-P. Piquemal, R. Chaudret, P. Reinhardt, P. Ren, *J. Chem. Theory Comput.* **2010**, *6*, 2059.
- [36] J. Y. Xiang, J. W. Ponder, *J. Comput. Chem.* **2012**, *34*, 739.
- [37] M. Masella, D. Borgis, P. Cuniassé, *J. Comput. Chem.* **2013**, *34*, 1112.
- [38] N. Guo, F. Pottier, J. Aupiais, C. Alliot, G. Montavon, J. Champion, *Inorg. Chem.* **2018**, *57*, 4926.
- [39] C. D. Wick, *J. Chem. Phys.* **2009**, *131*, 084715.
- [40] Y. Zhao, H. Li, X. C. Zeng, *J. Am. Chem. Soc.* **2013**, *135*, 15549.
- [41] A. C. Stern, M. D. Baer, C. J. Mundy, D. J. Tobias, *J. Chem. Phys.* **2013**, *138*, 114709.
- [42] T. R. Tuttle, S. Malaxos, J. V. Coe, *J. Phys. Chem. A* **2002**, *106*, 925.
- [43] C. Houriez, V. Vallet, F. Réal, M. Meot-Ner (Mautner), M. Masella, *J. Chem. Phys.* **2017**, *147*, 161720.
- [44] Y. Marcus, G. Hefter, *Chem. Rev.* **2006**, *106*, 4585.
- [45] N. F. A. van der Vegt, K. Haldrup, S. Roke, J. Zheng, M. Lund, H. J. Bakker, *Chem. Rev.* **2016**, *116*, 7626.
- [46] Y. Luo, W. Jiang, H. Yu, A. D. MacKerell, B. Roux, *Faraday Discuss.* **2013**, *160*, 135.

Received: 2 October 2018

Revised: 19 December 2018

Accepted: 22 December 2018

Published online on 31 January 2019