New Effective Potentials Extraction Method for the Interaction between Cations and Water

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A very simple method for the extraction of effective interaction potentials from \textit{ab initio} calculations was proposed (Periole et al. \textit{J. Phys. Chem.} \textbf{1997}, \textit{101}, 5018), and simple two-body cation–water interaction potentials were derived for several cations, \catt{Li}, \catt{Na}, \catt{K}, \catt{Be}, \catt{Mg} and \catt{Ca}, using two facts: first, water molecules in the close vicinity of cations are strongly structured and present a constrained orientation towards the ion; second, at larger distances the ion-water interaction is mainly electrostatic. In the present work, an extension to \catt{Rb} and \catt{Sr} and some refinements of this method are presented. In particular, we explore the most adequate way of including the nonadditivity and polarization effects that arise from the ion-water-water and water-water interactions. The potentials obtained with the new extraction methods are compared with the empirical potentials of Åqvist (Åqvist, \textit{J. J. Phys. Chem.} \textbf{1990}, \textit{94}, 8021) that were adjusted to reproduce experimental data. Those obtained with the exploration–TIE method are also tested by performing molecular dynamics simulations of the various cation–water systems and the results are found to be in good agreement with experimental data. In particular, they yield cation hydration free energy differences (\AG values) that are, in general, in good accordance with experimental figures. This latter method is ideally suited and easy to apply to obtain effective interaction potentials for molecular systems with restricted geometric conditions that appear in numerical simulations, either Monte Carlo or molecular dynamics.

Introduction

The use of numerical simulations for the study of complex molecular systems, e.g. proteins and the chemical behavior of their active sites, is now a common application. One of the limiting factors in these studies is the availability of adequate potentials. On the one hand, they have to be of the simplest possible form, since they will be used in costly simulations in which a large number of atoms is involved and, on the other hand, they have to lead to a reasonable reproduction of the molecular interactions being considered. This has led to the construction of effective two-body potentials, originally for simple systems (for instance, well-known water potentials such as SPC/E, TIP4p, etc.) and now for complex cases where the reduced cost of such potentials can be used advantageously. Recently, a method for easily constructing an effective potential for the interaction of ions with water has been proposed.\textsuperscript{1} The important feature of this method is that the ion remains all the time inside its hydration shell with very particular orientations of the water molecules in its close vicinity. There are a few models taking advantage of the constrained orientation of waters. Cordeiro et al.\textsuperscript{2} proposed a model we shall call “breathing” and is discussed below. Bleuzen et al.\textsuperscript{3} proposed a model we shall call single-molecule detachment also discussed below, and Sanchez-Marcos and coworkers\textsuperscript{4–7} have developed a model that keeps the hydrated ion either fixed or with a restrained relaxation and construct an interaction of this cluster with water. Recently, Wasserman et al.\textsuperscript{8} took this idea further by considering the hexahydrate as a molecule and describing the interaction energy of the first shell as intramolecular energy, in this way accounting for water relaxation. Floris et al.\textsuperscript{9–11} have developed a method where nonadditivity is accounted for by a polarizable continuum environment where the solute–solvent interaction is computed, producing thus a corrected effective potential. We can say that the idea is quite successful, leading to a general agreement with experiment even on the solvation energies where earlier works had failed.\textsuperscript{2,12,13} Some of the above models are quite refined and certainly improve the system description. In our previous work,\textsuperscript{1} we used a similar idea by trying to obtain in the most inexpensive manner a very simple potential that can be used for relative comparisons, that is, a simple potential fitted to reproduce the environment and the longer range interactions adequately reproduced by the electrostatic part. In that paper the parameters for the effective potentials describing the interaction of monovalent and divalent cations with an aqueous environment were determined. They were obtained from the results of \textit{ab initio} calculations of \m{n}{M(H_2O)_n} systems where \catt{M} = \catt{Li}, \catt{Na}, \catt{K}, \catt{Be}, \catt{Mg} and \catt{Ca} and \(n = 6\), except for \catt{Be} and \(n = 4\). These potentials allow us to reproduce the water–cation interaction energy at the Hartree–Fock (HF) level through an analytical form, namely, a sum of two-body Lennard-Jones and electrostatic potentials, the water–water interactions being described using the TIP3p potential.\textsuperscript{14} In that work different forms for the effective potentials were tested and the best fits of \textit{ab initio} data were obtained with a smooth \(r^{-7}\) repulsive and a classical \(r^{-4}\) attractive term, in addition to the standard Coulombic interaction. Note that a smooth \(r^{-7}\), or \(r^{-8}\),
repulsive term has also been used by other groups, in order to
describe accurately alkaline cation-carcbylon oxygen,15 lanthanide
ions—water oxygen,16 as well as Cr³⁺—water oxygen interactions.7 The actual extraction technique used to obtain the
corresponding parameters is explained in the Methods section.

Using this effective potential and its associated parameters for
molecular dynamics (MD) simulations of Na⁺ and K⁺ in
water lead to structural and thermodynamic properties in good
accordance with known experimental data.1 However, the
results obtained from MD simulations of Be²⁺, Mg²⁺, Ca²⁺, and Li⁺ in
water were not of the same quality. As a matter of
fact, good results were obtained for the cases where the M–H₂O
*ab initio* interaction energy is low, namely, about 26 and 18
kcal/mol for Na⁺ and K⁺, respectively. The corresponding
interaction energies for Be²⁺, Mg²⁺, Ca²⁺, and Li⁺ are about
141, 81, 55, and 37 kcal/mol, respectively. Thus, the method
proposed previously may work very well only for cations having
a low interaction energy with the aqueous environment.

The first goal of the present work was to study the Sr²⁺—
and the Rb⁺—water systems in order to verify the trends
observed previously. Since the description of the cation—water
systems first used to obtain the effective potentials proved
insufficient to account for large cation—water interactions, we
decided it necessary to take into account not just one but two
hydration shells in the model systems from which the effective
potential was to be extracted. The basic idea was that such
models would reflect in a more realistic way the situation for
stronger interacting cation—water systems. We have thus
studied Ca²⁺ and Mg²⁺ with their first two hydration shells.
This, of course, led us to consider new ways to extract the
important information from these model systems and to recover
the simple two-body effective potential we are looking for.
These new methods will be referred to as “exploration” and
“breathing” techniques and will be described in the following
section. We shall also present there the quantum chemical
method used as well as the basis sets and computational details.
In the next section we present the results regarding the effective
potentials, the MD simulations, and free energy difference
calculations that were performed in order to verify their
good behavior and the general discussion of these results. We also
discuss in that section the problem of whether or not the effective
potentials are dependent on the molecular model used to extract
them and, if so, to what extent this is important. Various MD
calculations are performed using these potentials but with
different size of the system in order to check the size dependency
of the results. Finally, in the last section, we give our
conclusions.

Methods

1. Quantum Chemical Calculations. For the calculation of
molecular interactions between ionic species, the crucial
aspect is the correct evaluation of the electrostatic contributions,
which are the dominant parts of the interaction. Since most of
these contributions are readily included at the HF level, we
decided to use this level for the bulk of our calculations. As a
matter of fact, in this specific case, the basis set superposition
(BSSE) correction (which decreases the interaction energy) is
largely compensated by the neglect of post-HF contributions.
This is illustrated in ref 1 where we compared our results with
more refined calculations in which both BSSE and electronic
correlation effects are taken into account. As a matter of fact,
in a recent work, Pavlov et al.17 have shown that proper
description of the dipole moment of water, a crucial character-
istic in the ion—water interaction, is attained when the ghost
basis set is considered. The overall precision obtained is likely
to be sufficient for our purpose which implies a not very detailed
analysis of the potential energy surface. On the other hand,
maintaining an inexpensive level of theory is in line with the
main idea of the present work, which is to test an easy-to-apply
method that can be extended to larger systems where refinements
such as the inclusion of electronic correlation effects and BSSE
corrections are out of the question.

The atomic basis sets come from the TURBOMOLE library,18
except for Ca²⁺, for which an effective core potential of 10
electrons (ecp-10) and the corresponding basis set was derived in
previous works.19 Since polarization effects are mostly
important for the oxygen atom, we chose a TZP (triple-ζ +
polarization) basis including two d functions. We use an
effective core potential of 36 electrons (ecp-36) and the
 corresponding basis for the Sr²⁺ and the Rb⁺.20 Thus, basis
set sizes are as follows:

\[
\begin{align*}
\text{Sr}^{2+} & : (3s3p)[2s2p] + ecp-36 \\
\text{Ca}^{2+} & : (6s8p5d)[4s6p2d] + ecp-10 \\
\text{Mg}^{2+} & : (11s7p1d)[6s3p1d] \\
\text{Be}^{2+} & : (9s2p)[5s2p] \\
\text{Rb}^{+} & : (3s3p)[2s2p] + ecp-36 \\
\text{K}^{+} & : (14s9p1d)[9s5p1d] \\
\text{Na}^{+} & : (11s7p2d)[6s3p2d] \\
\text{Li}^{+} & : (9s2p)[4s2p] \\
\text{O} & : (9s5p2d)[5s3p2d] \\
\text{H} & : (4s2p)[2s2p]
\end{align*}
\]

For all the quantum chemical calculations we used the parallel
version of GAUSSIAN-94 on the Facultad de Ciencias-UAEM
4-processor SGI-Power Challenge L computer. Quantum
chemistry calculations performed previously within the frame
of this work were found to be in very good agreement with
previous works on these kind of systems,1 as are our new
calculations on the Sr²⁺— and Rb⁺—water systems. Such
calculations are now done following well-established standards,
with standard program packages. Moreover, numerous works
on cation—water systems have already been performed at the
HF and post-HF levels, allowing for an accurate check of the
results obtained.

The form of our effective two-body potential is the following:1

\[
E_{\text{int}} = E_{\text{elec}} + E_{\text{LJ}} = \sum_{ij} \left( \frac{q_i q_j}{r_{ij}} \right) + \sum_{(M,O)} \left( \frac{A}{r_{MO}^{12}} - \frac{B}{r_{MO}^{6}} \right) + \sum_{(O,O)} \left( \frac{A_{OO}}{r_{OO}^{12}} - \frac{B_{OO}}{r_{OO}^{6}} \right)
\]

(1)

where \( A_{OO} \) and \( B_{OO} \) are the Lennard-Jones parameters of the
TIP3p water model, and where the electrostatic term is
calculated with standard charges, namely, \( q_M = +1 \) or +2, \( q_O = -0.834 \) and \( q_H = +0.417 \).

2. Techniques Used To Extract the M–H₂O Effective
Potential. In this section we shall describe the three techniques
used to obtain the A and B parameters of the effective cation—
water interaction. The first technique, called single molecule
detachment (SMD), was the one used in our previous work,1
or in a recent study for extending the original frozen hydrated
ion model of Sanchez-Marcos et al.21 to produce a fully flexible
hydrated ion model for the intermolecular interaction, in order
to determine the intracluster interaction potential of Cr³⁺
(H₂O)₆. As mentioned previously, it produced excellent
effective Na⁺—water and K⁺—water potentials. The molecular
system consists of the cation and its first hydration shell with
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4 (in D_{3h} symmetry for Be^{2+} and Li^{+}) or 6 (in T_{d} symmetry for all other cations) water molecules. The overall geometry of this M(H_{2}O)_{n} (n = 4, 6) system is first optimized at the HF level. Then a single water molecule is moved along the corresponding M–O axis. Thus we obtain the interaction energy of a water molecule and a system composed of the n − 1 remaining water molecules plus the cation, as a function of their distance. We systematically used 12−15 points to construct a reliable curve. These are actually very few points for a potential surface, but we were also interested in reducing the cost of the parameter extraction to a minimum. Note that, as the M–O distance increases, one may go too quickly into the region where the nonadditive effects arising from both subsystems become negligible, henceforth not fully including this information into the effective potential.

The second technique, which we called exploration, allows for obtaining the interaction energy of a cation and one or two hydration shells. This can be represented in a compact notation as M−(H_{2}O)_{n}−(H_{2}O)_{m} = (M)_{mn}, where n water molecules are in the first hydration shell and m water molecules in the second shell of the cation. In order to obtain the effective interaction energy for different cation–oxygen distances, the position of the cation is changed from its equilibrium geometry obtained at the HF level. These displacements of the cation are the following: ±0.2 and ±0.4 Å along the x, y, z axes and along the four (±1, ±1, ±1)−(1, 1, 1)−(1, 1)−(1) lines which are equidistant from the x, y, and z axes. This produces 28 different positions lying in two spheres with radii 0.2 and 0.4 Å whose centers are at the equilibrium position of the cation. Of course for symmetric arrangements the potential surface reduces to fewer different values depending on the symmetry. Note that all the water molecules are kept frozen at their optimized geometries. This technique has advantages with respect to the SMD technique, since it can be applied directly to complex biological systems where no reoptimizations can be made as the cation moves inside its first neighbor’s sphere. It can also be applied to nonsymmetrical solvation environments such as those coming from MD simulations. As it turns out, it also allows for the introduction, in a better manner than in the previous technique, of the polarization effects on the water molecules due to the presence of the cation as well as of the water–water nonadditive effects. Note that all M–O distances are modified at each new position of the cation.

The third technique, called breathing, resembles the first one except that in this case all the water molecules of the first hydration shell are displaced in a symmetrical manner from their equilibrium positions (as if inflating a balloon). This idea was used by Cordeiro et al. to produce an effective pair potential. Unfortunately, in their case the interaction between the first hydration shell and the external waters lead to a wrong expansion of the cluster and to an incorrect coordination number. This may be due to the fact that the nonadditivity of the water–water interaction was not included at the same level of approximation and therefore produced some imbalance in the treatment. Here we found that the technique works fine but care has to be taken with the water–water description. This technique has the added advantage that the high symmetry of the initial model system (T_{d}) is kept and thus important CPU time savings are possible. Like the SMD technique, it allows for the introduction of the cation–water polarization effects not only as function of the effective cation–water distances but also as a function of water–water distances.

It is possible to define three different types of interaction energy for these cation–water systems. We called the first one “single molecule detachment–interaction energy” (SMD-IE) because of its link to the first technique. This quantity is obtained by subtracting from the total energy of the system (cation plus n water molecules) the energy of an isolated water molecule and the overall energy of the cation plus (n − 1) water molecules at their initial equilibrium geometry. This was the advantage used in our previous work. It corresponds to the interaction of a semihydrated ion with a single water molecule. For the exploration and breathing techniques we defined two new types of interaction energy: (a) the “total interaction energy” (TIE) which is obtained by subtracting the total energy of the system, the isolated cation energy, and n times the energy of an isolated water molecule in its equilibrium geometry and (b) the “partial interaction energy” (PIE) where we subtract from the overall energy the isolated cation energy and the total energy of the water molecules at the geometry of the hydration shell(s) without the cation inside. This latter definition was expected to counterbalance the inaccuracies that could come from the description of water–water interaction energies with the TIP3p potential.

We recall here that Åqvist optimized his parameters for the classical $r^{-12}−r^{-6}$ Lennard-Jones potential in such a way to reproduce, as best as possible, experimentally obtained quantities via molecular dynamics simulations making use of his empirically optimized pair potentials. Note that during these MD simulations he used the SPC potential to account for the water–water interactions and showed that using the TIP3p model allows to obtain the same results. In fact, the SPC and TIP3p models are very similar. Since we want to compare our effective potential with those obtained by Åqvist, it is natural to use the same TIP3p (or SPC) potential to account for the water–water interactions.

3. Molecular Dynamics and Free Energy Difference Calculations. All the MD simulations were performed at 300 K with a modified version of the CHARMM-24 program package. Simulation parameters are standard ones. In particular, bond lengths were constrained with the SHAKE algorithm, a 2 fs integration time step was used, and nonbonded interactions were calculated with a 14 Å cutoff and a SHIFT truncation procedure for electrostatics. All Lennard-Jones interactions between the cation and water molecules were taken into account.

The computational model for solvation is as follows: the cation is held fixed at the center of a 15 Å sphere containing 460 TIP3p water molecules. Water molecules lying more than 11 Å away from the cation are also held fixed, as well as water oxygens lying more than 9 Å away. Thus, water molecules in the three first hydration shells of the cation are free to move within a 9 Å radius sphere surrounded by a 2 Å soft boundary, in which water molecules are only free to rotate. This simplified model was designed in order to perform, in a cost-effective manner, free energy perturbation calculations both in water and in a protein environment. Since it is different from the standard fully relaxed model used by Åqvist, it was checked that results obtained with both models are similar. To do so, MD and free energy difference calculations were performed with our water solution model and the parameters and potential energy functions used by Åqvist in his study, both with the SPC and the TIP3p water models, and we found that the results do agree. Differences of hydration free energies were computed with the thermodynamic perturbation method. The underlying principle of such calculations is as follows: first, several MD simulations are performed during which a cation in a water solution (state “a” of the system) is transformed into another
TABLE 1: Main Characteristics of the Interaction Energy Curve between a Cation and a Single Water Molecule, As Obtained Using Åqvist’s Empirical Potential[22] or Using the Effective Interaction Potential Obtained with the SMD-IE Methoda

<table>
<thead>
<tr>
<th>Cation</th>
<th>Åqvist</th>
<th>SMD-IE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_{eq}$</td>
<td>$R_{eq}$</td>
</tr>
<tr>
<td>Be$^{2+}$</td>
<td>-97.93</td>
<td>1.47</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>-57.40</td>
<td>1.92</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>-42.30</td>
<td>2.34</td>
</tr>
<tr>
<td>Sr$^{2+}$</td>
<td>-38.55</td>
<td>2.48</td>
</tr>
<tr>
<td>Li$^+$</td>
<td>-33.33</td>
<td>1.76</td>
</tr>
<tr>
<td>Na$^+$</td>
<td>-23.46</td>
<td>2.23</td>
</tr>
<tr>
<td>K$^+$</td>
<td>-16.89</td>
<td>2.66</td>
</tr>
<tr>
<td>Rb$^+$</td>
<td>-17.11</td>
<td>2.69</td>
</tr>
</tbody>
</table>

a Except for Sr$^{2+}$ and Rb$, the latter results are taken from ref 1. $E_{eq}$ is the interaction energy at the equilibrium position, $R_{eq}$ is the corresponding cation–oxygen distance, and msd is the mean-square difference obtained during our fit of the $ab$ initio data. The energies are in kcal/mol and the distances in Å. Åqvist did not consider the Be case.

Results and Discussion

The most adequate way to compare the parameters obtained for the interaction potentials with the different approaches considered in the present work would have been to test each of them through molecular dynamics and free energy calculations, and to retain those leading to values close to experimental data, for quantities such as radial distribution functions, solvation free energy differences, etc. Since such calculations, and the corresponding analysis, are heavy ones, our choice was to perform them only in the case of a selected set of parameters. To select such a set, in the first part of this work, we use two main quantities that describe, in an approximate manner, the interaction potentials for different cations with a water molecule in $C_{2v}$ symmetry, namely, the well depth ($E_{eq}$), and the cation–oxygen equilibrium distance ($R_{eq}$), and we compare them to the corresponding values obtained by Åqvist with his empirical approach.[22] Such a comparison is shown in Table 1 for the parameters obtained in our previous study,1 or in the present one, in the case of the Sr$^{2+}$ and the Rb$^+$–water systems. Though Åqvist’s parameters were determined for a standard 12-6 Lennard-Jones interaction potential, and ours are for a 7-4 one (see the Methods section), the comparison between the corresponding well depth and cation–oxygen equilibrium distances proved to be useful since the closest values observed in the present work happen to be with parameters leading to calculated quantities closer to experimental data than with the parameter set determined in our previous study (see below).

As shown in Table 1, as far as this criterion is concerned, results close to Åqvist’s are obtained for Rb$^+$ and Sr$^{2+}$ cations, which confirm our initial guess, namely, that the SMD-IE method produces good interaction potentials for cases where the cation–water interaction energy is low, i.e., less than 35–40 kcal/mol. In order to explain why this is not the case when the interaction energy becomes larger, two hypotheses were put forward:

1. The poor results obtained for the divalent cations reflect the need for using more realistic models to represent the physical system. In this case it comes down to include the second hydration shell in the model system. The molecules of the second shell should have an influence on those of the first shell and this may allow for reproducing Åqvist’s results. In the line of this hypothesis, the agreement with Åqvist’s results for the monocations would be due to the fact that for such water–cation systems the nonadditive and polarization effects produced by water on water are much smaller compared to those of dications.

2. With the SMD technique, it may not be possible to properly reproduce the nonadditivity and polarization effects arising from the water–water and cation–water interactions.

In order to test the first hypothesis, the second hydration shell was included in two models. The geometries of these systems, (Mg$^{2+}$)$_6$, and (Ca$^{2+}$)$_8$, were directly picked from molecular dynamics simulations. Since the SMD technique cannot be applied directly in such a case, as a result of the presence of the second water shell, the exploration method was used, and the difference between the parameters obtained with the two methods was assessed by studying the same $ab$ initio geometries as in our previous work, with six water molecules in the first hydration shell of the cations. As shown in Table 2, for both ions, the effect of including the second hydration shell is rather small, leading to increases of 1.3 and 1.0 kcal/mol of the well depths of Ca$^{2+}$ and Mg$^{2+}$, respectively. Hence, the important information that can be obtained with our method, about polarization and nonadditivity effects, is likely to be already included in the first hydration shell. In other words, the effective potentials derived using a single hydration shell seem to be able to reproduce the nonadditivity appearing in the second hydration shell, despite the fact that the latter is certainly important.[28] In a recent article, Pavlov et al.[17] have stressed the role of the interaction between the first and second shell of waters. However, in their study they force very symmetric arrangements for both shells which do not happen in the liquid structure.

TABLE 2: $M(H_2O)_n$ Systems: Comparison of the Parameters Obtained with the Exploration–PIE and with the Breathing–PIE Method, Applied on $ab$ Initio Geometries with One Hydration Shell, or with Configurations Including One or Two Hydration Shells, Picked from Molecular Dynamics Simulations (MD)

<table>
<thead>
<tr>
<th>System</th>
<th>Configuration</th>
<th>Method</th>
<th>$E_{eq}$</th>
<th>$R_{eq}$</th>
<th>msd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca$^{2+}$(H$_2$O)$_6$,16</td>
<td>MD</td>
<td>Expl-PIE</td>
<td>-42.64</td>
<td>2.34</td>
<td>2.21</td>
</tr>
<tr>
<td>Ca$^{2+}$(H$_2$O)$_8$,0</td>
<td>MD</td>
<td>Expl-PIE</td>
<td>-41.32</td>
<td>2.35</td>
<td>0.39</td>
</tr>
<tr>
<td>Ca$^{2+}$(H$_2$O)$_6$,0</td>
<td>ab initio</td>
<td>Expl-PIE</td>
<td>-46.01</td>
<td>2.33</td>
<td>0.0005</td>
</tr>
<tr>
<td>Ca$^{2+}$(H$_2$O)$_6$,0</td>
<td>ab initio</td>
<td>Br-PIE</td>
<td>-45.85</td>
<td>2.35</td>
<td>11.49</td>
</tr>
<tr>
<td>Mg$^{2+}$(H$_2$O)$_8$,18</td>
<td>MD</td>
<td>Expl-PIE</td>
<td>-62.51</td>
<td>1.91</td>
<td>2.11</td>
</tr>
<tr>
<td>Mg$^{2+}$(H$_2$O)$_6$,0</td>
<td>MD</td>
<td>Expl-PIE</td>
<td>-61.50</td>
<td>1.91</td>
<td>1.78</td>
</tr>
<tr>
<td>Mg$^{2+}$(H$_2$O)$_6$,0</td>
<td>ab initio</td>
<td>Expl-PIE</td>
<td>-64.29</td>
<td>1.92</td>
<td>0.18</td>
</tr>
<tr>
<td>Mg$^{2+}$(H$_2$O)$_6$,0</td>
<td>ab initio</td>
<td>Br-PIE</td>
<td>-63.15</td>
<td>1.95</td>
<td>140.01</td>
</tr>
</tbody>
</table>

$n$ is the number of water molecules in the first shell, $m$ is the number of water molecules in the second shell.
TABLE 3: M(H₂O)ₙ Systems: Parameters Obtained Using the Exploration–TIE Method Applied on ab Initio Geometries

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sr²⁺</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
<th>Be²⁺</th>
<th>Rb⁺</th>
<th>K⁺</th>
<th>Na⁺</th>
<th>Li⁺</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>12195.05</td>
<td>8716.88</td>
<td>2978.22</td>
<td>769.30</td>
<td>9379.13</td>
<td>10168.35</td>
<td>3141.81</td>
<td>954.25</td>
</tr>
<tr>
<td>B</td>
<td>510.43</td>
<td>510.12</td>
<td>303.76</td>
<td>236.62</td>
<td>276.41</td>
<td>334.67</td>
<td>165.58</td>
<td>70.13</td>
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<tr>
<td>msd</td>
<td>0.260</td>
<td>0.0006</td>
<td>0.250</td>
<td>7.34</td>
<td>0.003</td>
<td>0.0004</td>
<td>0.00005</td>
<td>0.020</td>
</tr>
<tr>
<td>Eeq</td>
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<td>-69.23</td>
<td>-125.33</td>
<td>-16.89</td>
<td>-17.24</td>
<td>-24.76</td>
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<td>Req</td>
<td>2.49</td>
<td>2.31</td>
<td>1.89</td>
<td>1.42</td>
<td>2.73</td>
<td>2.74</td>
<td>2.22</td>
<td>1.81</td>
</tr>
</tbody>
</table>

*The energies are in kcal/mol and the distances in Å.*
TABLE 4: M(H₂O)₈ Systems: Comparison of the Parameters Obtained Using the Exploration–TIE Method Applied on Systems with One or Two Hydration Shells Picked from MD Simulations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ca²⁺(H₂O)₁₆</th>
<th>Ca²⁺(H₂O)₁₆</th>
<th>Mg²⁺(H₂O)₁₀</th>
<th>Mg²⁺(H₂O)₁₈</th>
<th>Ca²⁺(H₂O)₁₈</th>
</tr>
</thead>
<tbody>
<tr>
<td>msd</td>
<td>0.393</td>
<td>2.233</td>
<td>2.062</td>
<td>2.315</td>
<td></td>
</tr>
<tr>
<td>Eeq</td>
<td>−45.69</td>
<td>−41.77</td>
<td>−67.39</td>
<td>−59.89</td>
<td></td>
</tr>
<tr>
<td>Req</td>
<td>2.31</td>
<td>2.35</td>
<td>1.87</td>
<td>1.92</td>
<td></td>
</tr>
</tbody>
</table>

Note: Effective potentials close to Åqvist’s and that a minimum number of water molecules have to be included in most cations in a water solution. Note also that for Ca²⁺ of water molecules close to the number of molecules surrounding most cations in a water solution. Note that for Ca²⁺ and Sr²⁺ the evolution of the Eeq value as a function of n is quite smooth (those are known to have a larger number of water molecules in their first hydration shell).

Molecular Dynamics Simulations

All potentials of Table 3 were tested in molecular dynamics simulations using a modified version of the CHARMM-24 program package in which the 7-4 Lennard-Jones form had been implemented. The Rₖ and Nₖ values, corresponding respectively to the first maximum of the cation–oxygen radial distribution function and to the coordination number of the cation, are given in Table 6. They were computed from the last 100 ps of 120 ps simulations. As in our previous work, they are found to be consistent with experimental data, although calculated Rₖ values are found to be slightly shorter than experimental ones for the smallest alkaline and alkaline-earth cations (there is up to a 0.09 Å difference in the case of Be²⁺).

Free Energy Difference Calculations

As in our previous work, Na⁺ and Mg²⁺ were used as starting points of perturbation simulations of alkaline and alkaline-earth cations, respectively. All protocols used are summarized in Table 7 and the main results obtained are given in Table 8.

For each alkaline cation, the protocol used is the one described in the Methods section and the given value is an average between a forward and a backward ΔG calculation, the accuracy of the calculation being estimated with the hysteresis of the Na⁺ → Na⁺ calculation. For the three transformations studied, it is found to be nearly 0.2 kcal/mol. The results for alkaline cations are all in better agreement with experimental data than those obtained previously, with the set of parameters determined with the SMD-IE method. Notably, both Li⁺ → Na⁺ and Na⁺ → K⁺ cases have been improved. Nevertheless, most of our results are still underestimated with respect to experimental data, especially as far as the Li⁺ → Na⁺ case is concerned. Since Li⁺ is the alkaline cation with the largest interaction energy with water, it is naturally expected to be a difficult case.
A protocol yielded a much better hysteresis value: set of initial conditions, another calculation performed with the protocol A, they are still not satisfactory. With a different protocol (D), the corresponding hysteresis values with protocols B, C, and D are smaller than with our previous method, named A hereafter, is 119.7 ± 15 kcal/mol; that is, the average calculated value is now very close to the experimental data. However, the hysteresis value for this calculation is quite large. Three other simulations were done in order to improve its accuracy. First, in order to allow the system to equilibrate better, the length of the simulation at each step of the transformation was increased, up to 20 ps (10 + 20), in the “B” protocol, and to 50 ps (20 + 30), in the “C” protocol. The ΔG values thus obtained are 124 ± 9 and 124 ± 9.5 kcal/mol, respectively. Second, instead of the 10 steps of protocol A, a 20-step transformation was performed (protocol D), the corresponding ΔG value being 122 ± 5 kcal/mol. Though hysteresis values with protocols B–D are smaller than with protocol A, they are still not satisfactory. With a different set of initial conditions, another calculation performed with the A protocol yielded a much better hysteresis value: ΔG = 119.4 ± 0.3 kcal/mol (protocol “E”). Note that all these results are quite good in spite of the large msd value found during the extraction of the Be2+ interaction potential.

Figure 1, a and b shows, for the “forward” and “backward” calculations, respectively, the ΔG as a function of for each of the A–E simulations. For the D one, each value is the sum of ΔG and ΔG. Along the forward paths, there is a regular increase of ΔG up to 1 = 0.95, where a sudden jump is observed. The preliminary increase corresponds to the contraction of the first hydration shell of the cation; that is, average cation–oxygen distances are decreasing, while the free energy jump corresponds to a transition between a state in which there are six water molecules in the first hydration shell of the cation, as in the case of Mg2+, to a state in which there are four such water molecules, as in the case of Be2+ (data not shown). In the A calculation only, the “fifth” and “sixth” water molecules leave the first hydration shell of the cation during the production period of the 1 = 0.9 simulation, while in other calculations they leave it during the corresponding equilibration period (data not shown). However, in all cases, these two water molecules behave in an apparently cooperative manner. In other words, the configurations with five water molecules in the first hydration shell of the cation seem unstable. Along the backward paths, things happen in a quite different way. Indeed, in only one of our backward simulations, namely, the E one, the fifth and sixth water molecules enter the first hydration shell at the same 1 value they leave it in the forward simulation. This explains why the hysteresis value was found to be so good in this case (0.3 kcal/mol)—such a link between larger hysteresis values and the variation of the water environment in forward and backward calculations at a given 1 value was already observed in detailed analysis of Mg2→Ca2+ transformations. During three other backward calculations, i.e., the A–C ones, both water molecules enter the first hydration shell of the cation at different 1 values, ranging from 0.6 to 0.8. This suggests that it is more difficult to add two water molecules in the first hydration shell of a beryllium-like cation, as in our backward calculations, than to remove them, as in our forward calculations. In other words, in the former case, special initial conditions are likely to be required (for instance, an “expanded” geometry of the four other molecules), that is, the entropic component of the free energy barrier is expected to be large. This will be checked in future works. During the D backward calculation, the two water molecules enter the first shell at 1 = 0.85; in this case Δλ = 0.05 (there are 20 steps in this simulation instead of 10 in the other ones).

To test whether a similar phenomenon is important in the cases of our two other dication transformations, simulations of

### Table 8

<table>
<thead>
<tr>
<th>Transformation</th>
<th>( \Delta G_{\text{calc}} ) (kcal/mol)</th>
<th>( \Delta G_{\text{exp}} ) (kcal/mol)</th>
<th>( \Delta G_{\text{old}} ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Li}^+ \rightarrow \text{Na}^+ )</td>
<td>19.0 ± 0.2</td>
<td>26.3–27.5</td>
<td>13.4</td>
</tr>
<tr>
<td>( \text{Na}^+ \rightarrow \text{K}^+ )</td>
<td>15.0 ± 0.2</td>
<td>16.7–17.5</td>
<td>20.1</td>
</tr>
<tr>
<td>( \text{Na}^+ \rightarrow \text{Rb}^+ )</td>
<td>21.6 ± 0.2</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>( \text{Be}^{2+} \rightarrow \text{Mg}^{2+} )</td>
<td>121.7 ± 5.0</td>
<td>120.8–135.0</td>
<td>98.5</td>
</tr>
<tr>
<td>( \text{Mg}^{2+} \rightarrow \text{Ca}^{2+} )</td>
<td>66.3 ± 1.4</td>
<td>77.7–80.3</td>
<td>45.7</td>
</tr>
<tr>
<td>( \text{Mg}^{2+} \rightarrow \text{Sr}^{2+} )</td>
<td>108.4 ± 0.8</td>
<td>107.6–113.2</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Comparison with experimental data\(^{37,38} \) and with results obtained with our previous method, \( \Delta G_{\text{old}} \). \( ^b \) Hysteresis value. \( ^c \) Rms value on several simulations (see text).
TABLE 9: Differences of Hydration Free Energies of Mg$^{2+}$ and Ca$^{2+}$, Na$^+$ and K$,^+$, Obtained with the Parameters of Table 3, Protocol A, and Systems with Different Numbers of Free Water Molecules around the Cations$^a$

<table>
<thead>
<tr>
<th>Transformation</th>
<th>M$_1$ → M$_2$</th>
<th>R$_i$ (Å)</th>
<th>R$_o$ (Å)</th>
<th>ΔG$_{M_1,M_2}$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$ → K$^+$</td>
<td>9</td>
<td>11</td>
<td>15</td>
<td>15.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>13</td>
<td>15</td>
<td>15.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>15</td>
<td>19</td>
<td>13.5 ± 0.1</td>
</tr>
<tr>
<td>Mg$^{2+}$ → Ca$^{2+}$</td>
<td>9</td>
<td>11</td>
<td>15</td>
<td>66.3 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>13</td>
<td>15</td>
<td>67.1 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>15</td>
<td>19</td>
<td>65.3 ± 0.3</td>
</tr>
</tbody>
</table>

$^a$R$_i$ is the radius of the system studied, centered on the cation. R$_o$ is the radius of the sphere in which the water molecules are free to move. Water molecules are fixed outside a sphere of radius R$_o$. Otherwise, only their hydrogen atoms are free to move.

TABLE 10: Differences of Hydration Free Energies (kcal/mol) of Mg$^{2+}$ and Ca$^{2+}$ Computed with Two Cutoff Values (3.5 and 14 Å)$^a$

<table>
<thead>
<tr>
<th>Cutoff (Å)</th>
<th>ΔG$_{\text{Avqvist}}$</th>
<th>ΔG$_{\text{this work}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>78.4 ± 1.6</td>
<td>65.6 ± 0.1</td>
</tr>
<tr>
<td>3.5</td>
<td>79.0 ± 1.6</td>
<td>79.9 ± 0.1</td>
</tr>
</tbody>
</table>

$^a$Two MD free energy difference calculations were performed, with protocol D, one with the parameters of Table 3 and one with Åqvist’s.

B and D kinds were performed in both cases. For the Mg$^{2+}$ → Ca$^{2+}$ transformation, they yield ΔG values of 65.9 ± 3.2 and 65.6 ± 0.1 kcal/mol, respectively. As in Mg$^{2+}$ → Be$^{2+}$ B and D calculations, the hysteresis of the D calculation happens to be the smaller one. This suggests that splitting such calculations in a larger number of steps is more efficient than increasing the time span of each step. However, the ΔG values obtained through A, B, and D calculations are all at variance with experimental data by a significant amount (more than 10 kcal/mol). Such a discrepancy is observed in spite of the fact that Mg$^{2+}$ → or Ca$^{2+}$ → oxygen potential energy functions used in the present calculations look similar to those proposed by Åqvist, as judged from the location of their minimum (see Tables 1 and 3). In order to understand this point, we first checked that our results do not depend upon the size of the system we considered in our free energy difference calculations, which is different from Åqvist’s (see Table 9).

Then, starting from D simulations performed either with our parameters or with Åqvist’s, the Mg$^{2+}$ → Ca$^{2+}$ free energy difference was recomputed, taking only into account water molecules within 3.5Å of the cation, that is, only those of the first hydration shell. As expected, in this case, there is no significant difference between the results obtained with both kind of parameters (see Table 10), and they are both in good agreement with experimental data. This means that Åqvist’s parameters were obtained in such a way that the contributions to the free energy difference of water molecules outside the first hydration shell cancel out each other, which is not the case with our potential energy functions. Indeed, our attractive term is a longer range one. Åqvist’s van der Waals-like interactions may have some significant consequences. Also, we have to bear in mind that with the exploration–TIE method the potentials are extracted by adjusting points around the equilibrium distance, whereas in a solution the potential along all M–O distances is important. It could be that in these two cases more points of the potential energy surface should be taken into account during the extraction of the parameters. Moreover, the fact that the orientations of the water molecules around the ion are kept highly symmetrical, the cation at its equilibrium position and the atoms of a water molecule being coplanar, may also have some consequences. Obviously for ions where this approximation is less valid, that is, when the first hydration shell waters are more likely to go away from this orientation, the model may miss some important information. As a matter of fact, even theoretical studies show the lack of rigidity of the molecules in the first hydration shell of Ca$^{2+}$ as compared to Mg$^{2+}$. For Li$^+$ the difficulty is even clearer; it is known that water orientations in its first hydration shell exhibit a strong departure (tilt angle of ≈50°) from our assumption. All these facts may explain the difficulty of our method to reproduce accurately Ca$^{2+}$ and Li$^+$ properties in solution. In other words, in these cases, the failure of our method may come from not considering the most physically relevant geometrical environment of the cations.

**Conclusion**

A new and improved version of an extraction technique proposed previously for determining effective cation–water potentials was developed and tested in molecular dynamics simulations, leading to very good structural and energetic results for many of the studied systems. The improvement of the extraction technique was done in two ways: the introduction of a new approach for the exploration of the potential energy surface from which the effective potential is to be extracted and the definition of a modified interaction energy to be adjusted. It was found that this technique produces effective potentials that converge as the number of water molecules considered in the model system approaches the hydration number.

Molecular dynamics simulations using the presently derived potentials were done to test their ability to describe the hydration of the monovalent and divalent cations. In all cases the first maximum of the cation–oxygen radial distribution function and the coordination number of the cation are found to be in good agreement with experimental data. Free energy difference calculations for the cation–water systems were done using the perturbation method. The results for the previously studied Li$^+$ → Na$^+$ and Na$^+$ → K$^+$ transformations have been noticeably improved with the new effective potentials. Even if our free energy differences are still underestimated with respect to experimental data, they yield a very good approximation, given the simplicity of the potential used. Large discrepancies were only found for Li$^+$ → Na$^+$ and Ca$^{2+}$ → Mg$^{2+}$ cases where, as discussed, the environmental conditions of the Li$^+$ and Ca$^{2+}$ ions in solution were probably not properly accounted for.

We think that one of the most important advantages of this new method of extraction is that it can be easily applied to very complex molecular systems and environments such as those found in the metallic or catalytic sites of proteins where geometric and steric conditions are imposed on the moieties surrounding the cations.

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References and Notes

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