

## Absolute Hydration Entropies of Alkali Metal Ions from Molecular Dynamics Simulations

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Received: January 28, 2009; Revised Manuscript Received: May 12, 2009

Molecular dynamics simulations in combination with the free energy perturbation technique are used in this work to calculate absolute ion hydration entropies. The hydration entropies for five alkali metal ions are estimated from van't Hoff plots using hydration free energies calculated at eight different temperatures. Considering that the ion–water potentials were parametrized only on absolute hydration free energies and ionic radii, the absolute hydration entropies agree very well with experimental data. Simulation lengths of about 3 ns at each temperature were required to achieve an uncertainty below 1 kcal/mol for the entropic contribution to the hydration free energy ( $-T\Delta S_{\text{hyd}}$ ). The uncertainties for the calculated entropies are typically four times larger than for the free energies. The possibility to use approximate approaches to calculate hydration entropies is also investigated. The entropy of creating the uncharged van der Waals spheres in water correlates well with the solvent accessible surface area of the ions. The Born continuum model and the linear response approximation cannot be used to predict the entropy of charging the van der Waals spheres in water without introducing temperature dependent empirical parameters.

## 1. Introduction

Molecular dynamics (MD) and Monte Carlo (MC) simulations can provide a detailed description of interactions between molecules and be used to calculate free energies for chemical processes such as solvation and ligand binding.<sup>1,2</sup> Calculation of thermodynamic properties from molecular simulations has become a particularly important tool for investigating the relationship between structure and function of biomolecules. Since most biomolecules interact in the aqueous phase, it is crucial that the force fields used in simulations reproduce the hydration properties of molecules. For this reason, calculation of solvation free energies for different functional groups, including amino acid side chain analogues, has become a standard means of evaluating the accuracy of force field parameters.<sup>3–9</sup> However, there are always several sets of partial charges and van der Waals parameters that can be used to obtain the correct hydration free energy, but these do not necessarily reproduce the experimental hydration enthalpy and entropy.<sup>10,11</sup> Hence, to further improve the accuracy of molecular simulations, hydration enthalpies and entropies should also be examined in evaluation and parametrization of force fields.

Free energies of solvation can be calculated efficiently using MD or MC simulations in combination with the free energy perturbation (FEP) or thermodynamic integration (TI) techniques.<sup>1,2</sup> By utilizing a thermodynamic cycle, the free energy of solvation can be calculated from annihilations of the solute in the gas and solvent environments. To enhance precision and accuracy, each transformation process is usually divided into several small steps and the total change in free energy is evaluated as the sum of these. Solvation enthalpies and entropies are considerably more challenging to calculate from simulations and can be estimated either via total potential energies or from the temperature dependence of the free energy.<sup>10–16</sup> The standard approach to calculate a solvation enthalpy is from the total

potential energies of the solute, solvent, and solute/solvent systems. The entropy can then be estimated by subtracting the calculated enthalpy from the free energy ( $-T\Delta S_{\text{sol}} = \Delta G_{\text{sol}} - \Delta H_{\text{sol}}$ ). The solvation entropy can also be calculated in a stepwise manner by utilizing the same transformation process that is used to compute the free energy of solvation.<sup>14</sup> In this case, the change in entropy for each small step is calculated from the free energy and enthalpy as described above. These simulations are typically carried out in a sphere or box with  $\sim 10^2$ – $10^3$  water molecules, which results in a large number of solvent–solvent interaction terms in the potential function describing the system. For this reason, total potential energies are dominated by large fluctuations in solvent–solvent energies, which lead to considerable uncertainties in the calculated solvation enthalpies and entropies. An alternative approach is to estimate the solvation enthalpy and entropy from the temperature dependence of the free energy. For example, the entropy and enthalpy can be obtained from free energies calculated at different temperatures by using a van't Hoff plot. In this case, the relation between  $\Delta G_{\text{sol}}/T$  and  $1/T$  is used to calculate enthalpies and entropies

$$\frac{\Delta G_{\text{sol}}}{T} = \frac{1}{T}\Delta H_{\text{sol}} - \Delta S_{\text{sol}} \quad (1)$$

If  $\Delta H_{\text{sol}}$  and  $\Delta S_{\text{sol}}$  are assumed to be independent of temperature over a temperature range, the solvation enthalpy and entropy can be calculated from the slope and intercept ( $T^{-1} \rightarrow 0$ ), respectively, of eq 1. While the van't Hoff approach avoids all problems associated with calculating total potential energies, the method involves calculation of solvation free energies with high precision at several temperatures. Which of the two techniques that is most efficient is not completely clear, and in order to make a fair comparison of the two alternatives, the simulation protocol used to calculate the entropies must be carefully optimized to yield maximal precision for each method.

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Both methods have successfully been used to calculate hydration free entropies for small neutral molecules in cases where the system size is kept small.<sup>10,11,15,16</sup> For larger or more complex systems, it is extremely difficult to obtain reliable total potential energies, and in such cases, the van't Hoff approach appears preferable.<sup>14,17</sup>

Modeling of ionic interactions is one of the most challenging problems in computational chemistry, and development of force field parameters for metal ions has been an active field of research for more than 20 years.<sup>5,18–24</sup> In particular, accurate representation of metal ions in molecular simulations is necessary to be able to study important biomolecules such as ion channels, nucleic acids, and many enzymes. Åqvist derived the first van der Waals parameters for metal ions that were based on reproducing experimental absolute free energies of hydration.<sup>5</sup> Recently, we presented calculations of the difference in hydration entropy between Na<sup>+</sup> and Cs<sup>+</sup>.<sup>16</sup> In this paper, we evaluate absolute hydration free energies and entropies for five alkali metal ions (Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup>) using van't Hoff plots in combination with MD simulations and the FEP technique. The accuracy of the Born continuum model and the linear response approximation for predicting hydration entropies is also investigated.

## 2. Methods

The absolute free energy of hydration for an ion (I = Li, Na, K, Rb, or Cs) is calculated here from the expression

$$\Delta G_{\text{hyd}}^{\text{FEP}} = \Delta G_{0 \rightarrow \text{Na}^0}^{\text{FEP}} + \Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}} + \Delta G_{\text{Na}^+ \rightarrow \text{I}^+}^{\text{FEP}} + \Delta G_{\text{Born}} \quad (2)$$

The first and second terms correspond to creating an uncharged sphere in water with van der Waals parameters of Na<sup>+</sup> and charging this sphere, respectively. Na<sup>+</sup> thus serves as our reference ion, and to obtain the hydration energies for other ionic species, the free energy difference between Na<sup>+</sup> and ion I<sup>+</sup>,  $\Delta G_{\text{Na}^+ \rightarrow \text{I}^+}^{\text{FEP}}$ , is calculated. Due to the long-range nature of electrostatic interactions, the treatment of the system boundaries becomes very important in calculations involving the creation of charges.<sup>25–30</sup> For such simulations, the use of spherical boundary conditions (SBC) is a particularly suitable choice.<sup>31–34</sup> With SBC, restraints are applied to reproduce the correct density and polarization of water molecules at the sphere boundary to model the effect of a surrounding bulk system of infinite size. The electrostatic contribution from outside the simulation sphere can then easily be taken into account using a continuum correction term. This term can be calculated from the Born equation, which (in kcal/mol and Å) yields

$$\Delta G_{\text{Born}} = -166 \left( 1 - \frac{1}{\epsilon(T)} \right) \frac{Q^2}{R_{\text{Born}}} \quad (3)$$

where  $\epsilon(T)$  is the temperature dependent dielectric constant,  $Q$  is the charge of the ion, and  $R_{\text{Born}}$  is the radius of the simulation sphere. The dielectric constant at each temperature can be obtained from an empirical relationship derived for liquid water in ref 35,  $\epsilon(T) = 311.17e^{-T/216}$ . The hydration entropy for an ion,  $\Delta S_{\text{hyd}}^{\text{FEP}}$ , is calculated from the intercept ( $T^{-1} \rightarrow 0$ ) of a van't Hoff plot based on free energies calculated at eight different temperatures (278, 288, 298, 308, 318, 328, 338, and 348 K). While the difference between Gibbs and Helmholtz free energies is very small for hydration of small molecules, Kubo et al.

showed that there is an ensemble dependence of the enthalpies and entropies that sometimes cannot be neglected.<sup>10</sup> The difference between solvation enthalpy at constant pressure and internal energy at constant volume at 298 K can be estimated from the radii of the ions. In our case, the hydration enthalpy would be approximately 0.0, 0.1, 0.2, 0.3, and 0.5 kcal/mol larger than the internal energy for Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup>, respectively, and the Gibbs hydration entropy ( $-T\Delta S$ ) would be reduced by the same amount in each case. Spherical boundary models are usually parametrized so as to maintain a correct average density of the system. If the density, or volume, is kept close to its target value by means of radial restraints as in several SBC models,<sup>31,33,34</sup> the resulting simulation system does not strictly correspond to a constant volume situation, since the volume is allowed to fluctuate subject to the internal forces and external restraints. Depending on the actual implementation of surface restraints, the model can be made similar to either the *NVT* or *NPT* ensembles. Hence, the ensemble corrections for the enthalpies given above provide upper bounds to the true corrections, and since these are within the errors of the experimental values anyway, we will not apply them to our calculations.

Each FEP calculation was carried out in  $n$  discrete steps, which represent intermediates between the initial and final states of the transformations in eq 2. The intermediate states are defined by the mixed potential  $U_m = \lambda_m U_A + (1 - \lambda_m) U_B$ , where  $U_A$  and  $U_B$  are the potential energy functions of the initial and final states, respectively, and  $\lambda_m$  is a mapping parameter that varies from 0 to 1. The free energy difference between states  $A$  and  $B$  can be calculated by summing up the free energy differences of the  $n$  intermediate states using<sup>1,2</sup>

$$\Delta G_{A \rightarrow B}^{\text{FEP}} = -kT \sum_{m=1}^{n-1} \ln \langle e^{-(U_{m+1} - U_m)/kT} \rangle_m \quad (4)$$

where  $\langle \dots \rangle_m$  represents an ensemble average on the potential  $U_m$ , which is calculated from MD simulations. Each FEP calculation was carried out here with 200  $\lambda$ -steps. At each step the system was simulated for 40–50 ps and potential energies were saved every 0.005 or 0.01 ps. In the calculation of energy ensemble averages, the first 10% of each trajectory was discarded as equilibration. The free energy of transforming each ion to Na<sup>+</sup> was estimated as the average of an FEP calculation in both the forward and backward directions. The free energy of creating Na<sup>0</sup> in water ( $\Delta G_{0 \rightarrow \text{Na}^0}^{\text{FEP}}$ ) was calculated from two annihilation calculations, which were carried out starting from different equilibration schemes. The free energy of charging Na<sup>0</sup> ( $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}}$ ) was estimated from four independent transformations. Uncertainties for the values of  $\Delta G_{0 \rightarrow \text{Na}^0}^{\text{FEP}}$ ,  $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}}$ , and  $\Delta G_{\text{Na}^+ \rightarrow \text{I}^+}^{\text{FEP}}$  were estimated as the standard error of the mean of the calculations carried out for each transformation. The uncertainty for the total hydration free energy was estimated as the square root of the sum of the squared standard errors of the mean. The hydration entropy,  $\Delta S_{\text{hyd}}^{\text{FEP}}$ , and its associated uncertainty was then calculated using linear regression by minimizing

$$\sum_i [(\Delta G_{\text{hyd},i}^{\text{FEP}}/T_i - (\Delta H_{\text{hyd}}^{\text{FEP}}/T_i - \Delta S_{\text{hyd}}^{\text{FEP}}))/\sigma_i]^2 \quad (5)$$

where the sum is over all temperatures and  $\sigma_i$  is the estimated uncertainty for  $\Delta G_{\text{hyd},i}^{\text{FEP}}/T_i$ .<sup>36</sup>

**TABLE 1: Calculated ( $\Delta G_{\text{hyd}}^{\text{FEP}}$ ) Hydration Free Energies (kcal/mol) for Five Alkali Metal Ions at Eight Different Temperatures<sup>a</sup>**

<i>T</i> (K)	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
278	−124.79 ± 0.04	−99.72 ± 0.02	−82.18 ± 0.02	−76.76 ± 0.03	−69.26 ± 0.02
288	−124.46 ± 0.05	−99.43 ± 0.05	−81.97 ± 0.05	−76.52 ± 0.05	−69.01 ± 0.05
<b>298</b>	<b>−124.40 ± 0.04</b>	<b>−99.38 ± 0.03</b>	<b>−82.00 ± 0.04</b>	<b>−76.60 ± 0.03</b>	<b>−69.05 ± 0.04</b>
308	−124.12 ± 0.04	−99.17 ± 0.03	−81.85 ± 0.03	−76.50 ± 0.03	−68.99 ± 0.05
318	−123.81 ± 0.06	−98.90 ± 0.03	−81.66 ± 0.03	−76.28 ± 0.03	−68.82 ± 0.03
328	−123.56 ± 0.05	−98.71 ± 0.05	−81.53 ± 0.05	−76.17 ± 0.05	−68.62 ± 0.05
338	−123.31 ± 0.05	−98.47 ± 0.02	−81.37 ± 0.02	−76.01 ± 0.03	−68.50 ± 0.03
348	−123.02 ± 0.06	−98.26 ± 0.03	−81.24 ± 0.03	−75.89 ± 0.04	−68.35 ± 0.03
<b>298</b>	<b>−124.0</b>	<b>−100.1</b>	<b>−82.5</b>	<b>−77.4</b>	<b>−69.7</b>

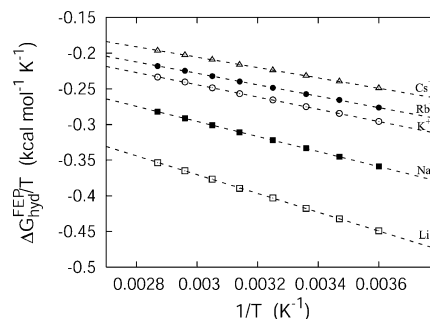
<sup>a</sup> The experimentally observed ( $\Delta G_{\text{hyd}}^{\text{obs}}$ ) hydration free energies at 298 K are also given.<sup>41</sup>

All MD simulations and FEP calculations were performed with the program Q.<sup>34</sup> The MD simulations of the solvated ions were carried out in a spherical water droplet filled with SPC<sup>37</sup> water molecules and, unless stated otherwise, the radius of the system was 18 Å. The time step in the simulations was set to 2 fs except for the annihilation of Na<sup>0</sup>, where 1 fs was used. The temperature was controlled using the algorithm of Berendsen et al.<sup>38</sup> A nonbonded cutoff of 10 Å was used and electrostatic interactions beyond this cutoff were treated with the local reaction field (LRF) method.<sup>39</sup> No cutoffs were applied to the interactions of the ion. To reproduce the experimental density and polarization of water molecules close to the sphere boundary, radial and polarization restraints according to our version of the SCAAS algorithm were used.<sup>31,34</sup> The SHAKE<sup>40</sup> procedure was applied to all solvent molecules, and nonbonded pair lists were updated every 25 steps. A weak harmonic restraint of 0.5 kcal/(mol Å<sup>2</sup>) was applied to the ion in the simulations to keep it close to the center of the sphere.

### 3. Results and Discussion

The calculated hydration free energies for the five alkali metal ions are summarized in Table 1. The absolute free energies of hydration are slightly more negative than those originally calculated by Åqvist using a smaller system radius (15 Å).<sup>5</sup> These minor differences may be due both to our revised version of the SCAAS model, that has a somewhat different implementation of the radial and polarization restraints,<sup>34</sup> and to the fact that our present system size is larger. A calculation of the absolute free energy for Na<sup>+</sup> in the smaller 15 Å sphere gave  $\Delta G_{\text{hyd}}^{\text{FEP}} = -98.5$  kcal/mol, which is essentially identical to the older value,<sup>5</sup> and the small difference between the 15 and 18 Å spheres results is similar to that obtained by Sham and Warshel.<sup>27</sup> The experimental absolute hydration free energies from Burgess<sup>41</sup> are also given in Table 1 and have been corrected for changing the standard state in the gas phase from 1 atm to 1 M ( $-RT \ln 24.45$ ). While more recent compilations based on a revised value for the proton hydration energy may be closer to the true single ion hydration free energies,<sup>42</sup> we will still use the scale of ref 41 here since it corresponds to that of the original ion parametrization.<sup>5</sup> The absolute hydration free energies are found to be well-reproduced ( $\text{error} = 0.6$  kcal/mol at 298 K), which is not surprising considering that they were explicitly parametrized on this property.

The van't Hoff plots are shown in Figure 1 and reveal close to perfect linear relationships between  $\Delta G_{\text{hyd}}^{\text{FEP}}/T$  versus  $1/T$  for all ions. The experimental absolute hydration entropies ( $-T\Delta S_{\text{hyd}}^{\text{obs}}$ ) are reproduced with an average unsigned error of about 0.6 kcal/mol at 298 K, as judged by comparison to the average hydration entropies from two different experimental

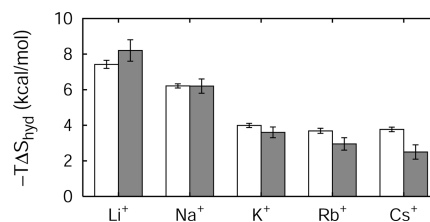


**Figure 1.** Van't Hoff plots for five alkali metal ions (Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup>) based on free energies of hydration ( $\Delta G_{\text{hyd}}^{\text{FEP}}$ ) calculated at eight different temperatures (278, 288, 298, 308, 318, 328, 338, and 348 K).

**TABLE 2: Experimentally Observed<sup>43</sup> ( $-T\Delta S_{\text{hyd}}^{\text{obs}}$ ) and Calculated ( $-T\Delta S_{\text{hyd}}^{\text{FEP}}$ ) Hydration Entropies (kcal/mol) for Five Alkali Metal Ions at 298 K<sup>a</sup>**

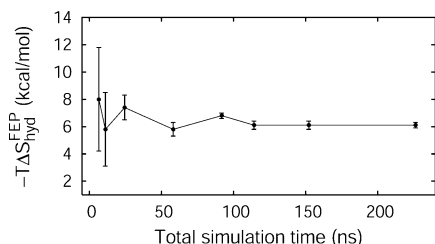
	$-T\Delta S_{\text{hyd}}^{\text{FEP}}$	$-T\Delta S_{\text{hyd}}^{\text{LD}}$	$-T\Delta S_{\text{hyd}}^{\text{obs}}$
Li <sup>+</sup>	7.4 ± 0.2	6.7	7.6, 8.8
Na <sup>+</sup>	6.2 ± 0.1	5.9	5.8, 6.6
K <sup>+</sup>	4.0 ± 0.1	5.1	3.3, 3.9
Rb <sup>+</sup>	3.7 ± 0.1	4.8	2.6, 3.3
Cs <sup>+</sup>	3.8 ± 0.1	4.3	2.1, 2.9

<sup>a</sup> The hydration entropies obtained by Florian and Warshel using the Langevin-dipole method are also given ( $-T\Delta S_{\text{hyd}}^{\text{LD}}$ ).<sup>43</sup>



**Figure 2.** FEP calculated (unfilled bars) and experimentally observed<sup>43</sup> (filled bars) absolute hydration entropies ( $-T\Delta S_{\text{hyd}}$ , kcal/mol) for five alkali metal ions at 298 K. The uncertainties for the calculated and observed values are shown as error bars. Uncertainties for the experimentally observed hydration entropies were estimated as half the difference between the two values for each ion that are shown in Table 2.

sources (Table 2).<sup>43</sup> However, as the absolute scale for hydration free energies is still subject to some uncertainty, it may be more relevant to compare to relative experimental hydration entropies in this case. As can be seen from Figure 2, the relative hydration free energies are also quite accurate considering that the van der Waals parameters were only adjusted to reproduce hydration free energies. The convergence of the hydration entropy calculations was investigated by reducing the number of steps



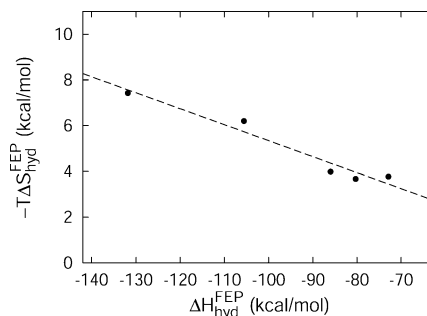
**Figure 3.** Calculated hydration entropies ( $-T\Delta S_{\text{hyd}}^{\text{FEP}}$  at 298 K, kcal/mol) for  $\text{Na}^+$  using a series of different simulation lengths. The uncertainties for the calculated values are shown using error bars.

in the FEP calculations. The hydration entropy of  $\text{Na}^+$  was estimated based on FEP calculations consisting of 2, 4, 10, 25, 40, 50, 67, and 100 steps, which yield total simulation times between 7 and 226 ns. The results from these calculations are shown in Figure 3. A total simulation time of 7 ns is clearly not sufficient to obtain precise or accurate hydration entropies and more than 25 ns of simulation time is required to push the uncertainty for  $-T\Delta S_{\text{hyd}}^{\text{FEP}}$  values below 1 kcal/mol. On average, the uncertainty for  $-T\Delta S_{\text{hyd}}^{\text{FEP}}$  is about four times larger than for the hydration free energies used in the van't Hoff plots.

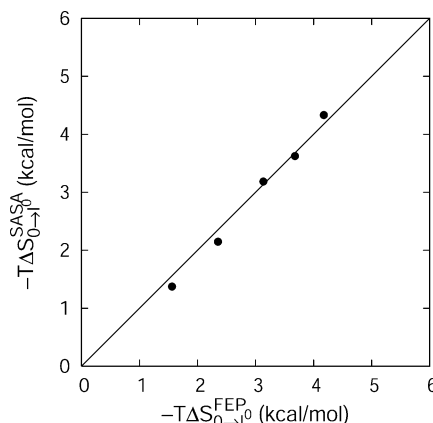
To further investigate the origin of the entropy and enthalpy terms, we now focus only on the two transformation processes used to compute the free energy of hydration for  $\text{Na}^+$ . Although the hydration entropy for the creation or charging of a sphere in solution cannot be compared to experimental data, it is enlightening to compare the magnitudes of the calculated energies for these two steps. First, the free energy of creating the uncharged van der Waals sphere in water was calculated ( $\Delta G_{0 \rightarrow \text{Na}^0}^{\text{FEP}}$ ), which yielded a free energy equal to 2.9 kcal/mol at 298 K. In the second step, the free energy of charging the “neutral” ion in water ( $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}}$ ) was calculated. This yielded  $-102.3$  kcal/mol, which includes a Born term equal to  $-9.2$  kcal/mol. The total calculated free energy of transfer is  $-99.4$  kcal/mol, which is in good agreement with the experimental value of  $-100.1$  kcal/mol. The calculated entropy,  $-T\Delta S_{\text{hyd}}^{\text{FEP}} = 6.2$  kcal/mol, is also close to experimental values. Although the individual  $\Delta G_{0 \rightarrow \text{Na}^0}^{\text{FEP}}$  and  $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}}$  values cannot be compared to experiment, it is also interesting to calculate the balance between entropy and enthalpy in these two steps. Cavity formation is mainly an entropic term, and our calculated value is  $-T\Delta S_{0 \rightarrow \text{Na}^0}^{\text{FEP}} = 2.5$  kcal/mol, while  $\Delta H_{0 \rightarrow \text{Na}^0}^{\text{FEP}} = 0.4$  kcal/mol. However, the entropic contribution for charging  $\text{Na}^0$  is more than 50% larger,  $-T\Delta S_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}} = 3.8$  kcal/mol. This term mainly reflects that the solvent molecules in the inner solvation shells become restricted by the strong interactions with the ion, which leads to a decrease in the total entropy of the system. However, this penalizing term is overshadowed by the favorable electrostatic interactions between the ion and the solvent dipoles ( $\Delta H_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}} = -106.1$  kcal/mol). In this context, it is also interesting to note that the calculated results, as often observed experimentally, display a linearly anticorrelated relation between hydration enthalpy and entropy (Figure 4). The smaller ions can interact stronger with the solvent dipoles, but this always leads to a more negative change in entropy because the orientations of the water molecules become more restricted.

It is also interesting to ask whether simpler approximate methods can be used to reliably predict hydration entropies. To investigate this issue, the hydration entropy is again decomposed into two terms:

$$\Delta S_{\text{hyd}} = \Delta S_{0 \rightarrow \text{I}^0} + \Delta S_{\text{I}^0 \rightarrow \text{I}^+} \quad (6)$$



**Figure 4.** Relation between the FEP calculated ion hydration enthalpies ( $\Delta H_{\text{hyd}}^{\text{FEP}}$ ) and entropies ( $-T\Delta S_{\text{hyd}}^{\text{FEP}}$ ) for five alkali metal ions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$ , and  $\text{Cs}^+$ ) at 298 K.



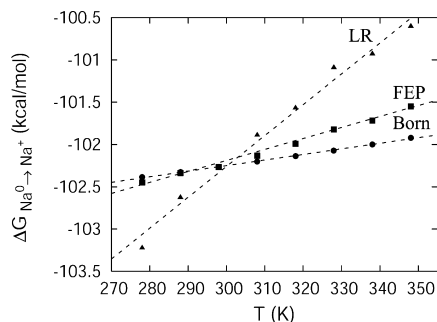
**Figure 5.** FEP calculated entropies ( $-T\Delta S_{0 \rightarrow \text{I}^0}^{\text{FEP}}$ ) of creating a series of uncharged van der Waals spheres in water vs an approximation based on the solvent accessible surface area ( $-T\Delta S_{0 \rightarrow \text{I}^0}^{\text{SASA}}$ , eq 7).

where  $\Delta S_{0 \rightarrow \text{I}^0}$  represents the entropy change for creating the uncharged sphere in water ( $\text{I}^0$ ) and  $\Delta S_{\text{I}^0 \rightarrow \text{I}^+}$  is the entropy contribution for charging this sphere. Experimental hydration free energies and entropies often correlate well with solute size and empirical models relating these thermodynamic properties to solvent accessible surface area (SASA) can perform rather well.<sup>43–46</sup> This suggests that  $\Delta S_{0 \rightarrow \text{I}^0}$  can be approximated by

$$-T\Delta S_{0 \rightarrow \text{I}^0} \approx cA_{\text{I}^0} \quad (7)$$

where  $c$  is an empirical constant and  $A_{\text{I}^0}$  corresponds to the SASA of the “uncharged” ion. To test this approximation,  $-T\Delta S_{0 \rightarrow \text{I}^0}^{\text{FEP}}$  values for the ions were estimated from van't Hoff plots, which were based on MD simulations in a spherical system of 15 Å radius. Estimating the SASA in eq 7 from the minimum energy distance of the ion–water oxygen van der Waals potential ( $R_{\text{Li}^0 \rightarrow \text{O}} \approx 2.91$  Å,  $R_{\text{Na}^0 \rightarrow \text{O}} \approx 3.64$  Å,  $R_{\text{K}^0 \rightarrow \text{O}} \approx 4.44$  Å,  $R_{\text{Rb}^0 \rightarrow \text{O}} \approx 4.74$  Å,  $R_{\text{Cs}^0 \rightarrow \text{O}} \approx 5.18$  Å) was found to give good correlation with the calculated hydration entropies. Optimization of eq 7 yielded  $c = 0.013$  kcal/(mol Å<sup>2</sup>) with an average unsigned error of 0.1 kcal/mol. Hence,  $-T\Delta S_{0 \rightarrow \text{I}^0}$  could be very accurately reproduced using the SASA, and these results are shown in Figure 5. It should be noted that the use of surface area descriptors to predict thermodynamic properties is becoming increasingly questioned and the strong correlation obtained using eq 7, to some extent, reflects that only small spherical cavities were considered. For more challenging cases, Levy et al. have found that a simple surface area description is not sufficiently accurate for predicting solvation and binding free energies.<sup>47</sup>





**Figure 6.** Temperature dependence for the free energy of charging a sphere with the van der Waals parameters of  $\text{Na}^+$  in ref 5 ( $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{FEP}}$ ) using FEP (squares), the LR approximation (triangles) and the Born equation (circles).

For the electrostatic contribution,  $\Delta S_{\text{I}^0 \rightarrow \text{I}^+}$ , two different approximations were investigated here and we again focus only on the charging of  $\text{Na}^0$ . As a representative of continuum models, the Born equation can be used to predict hydration entropies from the temperature dependence of the dielectric constant. Parametrizing the radius in eq 3 to reproduce the charging free energy of  $\text{Na}^0$  at 298 K yields  $R_{\text{Born}}^{\text{Na}^+} = 1.602 \text{ \AA}$ . A van't Hoff plot using the empirical<sup>35</sup>  $\epsilon(T)$  gives  $-T\Delta S_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{Born}} = 2.0 \text{ kcal/mol}$  at 298 K. Thus, although the Born equation was parametrized to yield the correct absolute free energy at 298 K, it does not reproduce the balance between hydration entropy and enthalpy found in the FEP calculations. The Born model is found to underestimate the derivative (slope) of the free energy with respect to temperature compared to the FEP calculations (Figure 6). From previous studies, it is also clear that to reproduce the experimental temperature dependence of hydration free energies, continuum models have to be extensively parametrized. For example, Elcock and McCammon found that the Poisson–Boltzmann continuum model could only be used to reproduce the temperature dependence of hydration free energies if both the atomic radii and the dielectric constant were made temperature dependent.<sup>48</sup> There are also examples of Generalized-Born and Langevin-dipole (LD) methods that combined with surface-area descriptors have been explicitly parametrized to reproduce the experimental temperature dependence of the free energy.<sup>43,49,50</sup> For comparison, the hydration entropies calculated by Florian and Warshel using an empirically parametrized version of the LD method are also given in Table 2.<sup>43</sup> The LD model has an average unsigned error of about 1.4 kcal/mol compared to experiment, which appears somewhat less accurate than the hydration entropies calculated here.

As an alternative to continuum models, we investigated if the linear response (LR) approximation could predict the temperature dependence of the free energy. According to the LR approximation, the free energy of charging a van der Waals sphere can be estimated from

$$\Delta G_{\text{I}^0 \rightarrow \text{I}^+}^{\text{LR}} = \beta \langle U_{\text{I}^+ - \text{s}}^{\text{el}} \rangle_{\text{I}^+} + \langle U_{\text{I}^+ - \text{s}}^{\text{el}} \rangle_{\text{I}^0} \quad (8)$$

where  $\langle U_{\text{I}^+ - \text{s}}^{\text{el}} \rangle_{\text{I}^+}$  is the average ion–solvent ( $\text{I}^+ - \text{s}$ ) electrostatic interaction energy obtained from a simulation of the ion in explicit solvent.<sup>51</sup> The second term is calculated from a simulation where the charge of the ion is turned off, but in the evaluation of  $\langle U_{\text{I}^+ - \text{s}}^{\text{el}} \rangle_{\text{I}^0}$ , the interaction energy is calculated as if the charge on the ion was present. For neutral solutes the latter term is close to zero, but for ions it contributes significantly to the hydration free energy.<sup>51</sup>  $\beta$  is equal to 1/2 according to the

LR approximation, and the value of this scaling factor has been studied extensively by our group.<sup>51,52</sup> Depending on the chemical nature of the solute, the value of the coefficient varies between 0.37 and 0.52. Equation 8 has also been used in calculations of hydration free energies of small molecules with excellent results.<sup>52,53</sup> In this case, we tested the possibility to parametrize the  $\beta$  coefficient on the hydration free energy at 298 K and then use the LR approximation to predict the temperature dependence of this free energy. A  $\beta$  coefficient close to 0.5 was obtained ( $\beta = 0.472$ ) for  $\text{Na}^+$  from two 1 ns simulations. While the Born equation was found to underestimate the temperature derivative of  $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}$ , the LR approximation instead overestimates the slope ( $-T\Delta S_{\text{Na}^0 \rightarrow \text{Na}^+}^{\text{LR}} = 10.6 \text{ kcal/mol}$ ). In the LR approximation, the  $-T\Delta S$  term resulting from solvent reorganization upon charging of the ion is embedded in the  $\beta$  coefficient.<sup>16</sup> This implies that the value of  $\beta$  should be temperature dependent. A closer look at the charging free energies at different temperatures (data not shown) revealed that there is a strong linear relationship between the  $\beta$  coefficient and temperature ( $\beta \approx 0.00012T + 0.4358$ ,  $278 \leq T \leq 348$ ,  $R^2 = 0.96$ ). Since the van't Hoff plot relies on accurate estimates of very small changes in free energy, these differences affect the calculated entropies significantly. The temperature dependence of  $\Delta G_{\text{Na}^0 \rightarrow \text{Na}^+}$  for the FEP, LR, and the Born equations is shown in Figure 6. Hence, the Born and LR approximations cannot predict the  $\Delta S_{\text{I}^0 \rightarrow \text{I}^+}$  obtained from FEP simulations without introducing temperature dependence of the atomic radii or the  $\beta$  value, respectively.

Considering that the van der Waals parameters investigated here were not fitted to absolute hydration entropies, the agreement with experiment is very good. A possible explanation for this result is that the additional constraint to reproduce the location of the first peak of the radial distribution function, which obviously is connected to the entropy, is sufficient to obtain accurate parameters also for hydration entropies. It should also be noted that the SPC water model was used in all calculations presented here. For ionic molecules, the properties of the water model, e.g. the dipole moment, will significantly affect calculated hydration free energies,<sup>54</sup> and hydration enthalpies and entropies can be even more sensitive to this choice.<sup>11</sup> For this reason, one cannot in general expect ion parameters to be transferable between different water models. The possibility to use the FEP method together with van't Hoff plots to calculate entropies for more complex biochemical problems seems quite promising. Recently, Bjelic et al. have applied this approach to investigate differences between thermo- and psychrophilic enzymes.<sup>17</sup> The balance between entropy and enthalpy is believed to play an important role in these enzymes and with extensive sampling it seems that quantitative results can be obtained even in such challenging cases.

#### 4. Conclusions

In this work, hydration entropies for a series of alkali metal ions were calculated from molecular dynamics simulations. The calculations show that it is now possible to obtain quantitative results for both solvation free energies and entropies even in the challenging case of ion hydration. The hydration entropies were calculated from the temperature dependence of the free energy, and the results are in good agreement with experimental values. However, the highly accurate free energies required to estimate entropies from van't Hoff plots appear to limit the possibility to use more approximate techniques, e.g. continuum models and LR theory, to estimate solvation entropies. The methodology presented here can also be used to calculate relative

binding free energies, enthalpies, and entropies for host–guest systems and protein–ligand complexes.

**Abbreviations.** MD, molecular dynamics; MC, Monte Carlo; FEP, free energy perturbation; TI, thermodynamic integration; SBC, spherical boundary conditions; SASA, solvent accessible surface area; LD, Langevin-dipole; LR, linear response.

**Acknowledgment.** Support from the Swedish Foundation for Strategic Research (SSF/Rapid) and the Swedish Research Council (VR) is gratefully acknowledged. Computational resources were provided by SNIC and UPPMAX.

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JP900818Z