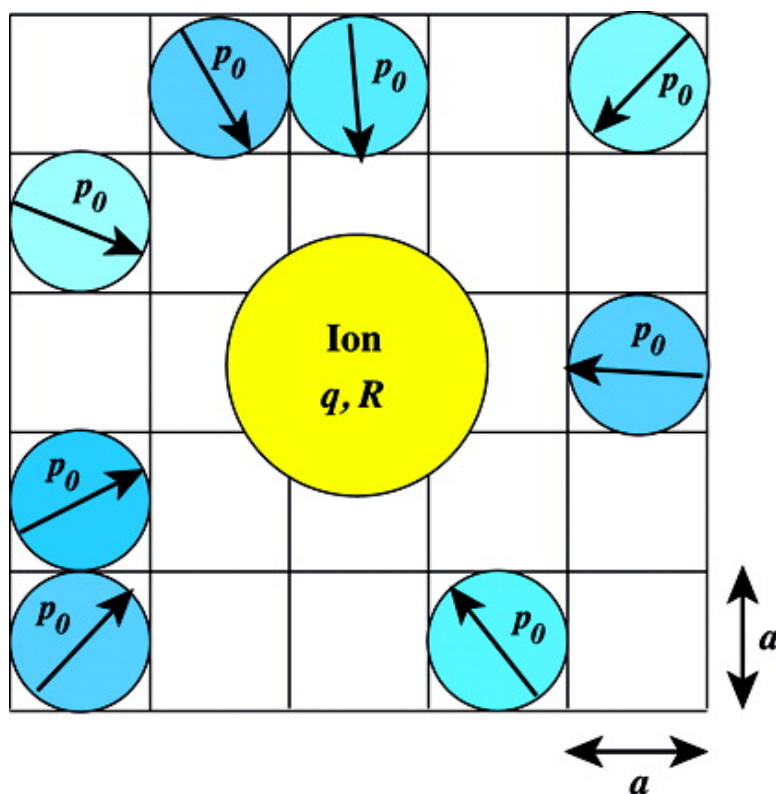


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## Computing Ion Solvation Free Energies Using the Dipolar Poisson Model

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A new continuum model is presented for computing the solvation free energies of cations in water. It combines in a single formalism based on statistical thermodynamics the Poisson model for electrostatics with the Langevin dipole model to account for nonuniform water dipole distribution around the ions. An excellent match between experimental and computed solvation free energies is obtained for 10 monovalent and divalent ions.

The chemical reactions that sustain life take place in a water environment. Water not only is the solvent that makes these reactions possible, but it also serves as reactant or product in many of these reactions. Understanding solvation is therefore central to any analysis of the chemistry of life; it has been consequently the subject of numerous experimental and theoretical studies. One of the most elemental of these studies focuses on ionic solvation, i.e., the energetics of single ions in solution and the subsequent organization of water molecule clusters around these ions. Despite the apparent simplicity of this problem compared to studying large biomolecules, it has not yet been fully solved. Many models have been proposed, either based on explicit representation of the water or based on a continuum; none of these models however can accurately and consistently predict ion solvation free energies that match with experimental values. In this Letter, a new continuum model is presented for the solvation free energy of cations in water. It combines the Poisson model for electrostatics with the Langevin dipole model to account for nonuniform water dipole distribution around the ions. Using this model, an excellent match of computed free energies with experimental values is obtained.

If a charge  $q$  is transferred from a conducting sphere of radius  $R$  in vacuo with dielectric constant  $\epsilon_0$  to the same sphere in a medium of dielectric constant  $\epsilon$ , the change in electrostatic free energy is given by the Born formula:

$$\Delta G_{\text{el}} = -\left(\frac{1}{\epsilon_0} - \frac{1}{\epsilon}\right) \frac{q^2}{2R} \quad (1)$$

The free energy changes observed for the hydration of real ions however are less than those predicted by eq 1. Many have attempted to modify this equation such as to obtain a better fit between theory and experiments for ionic solvation. They all recognize that, because of polarization effects in the vicinity of charges, it is expected that the representation

of the solvent as a homogeneous dielectric medium is bound to be erroneous close to the interface. Most of their approaches use an effective Born radius for each ion instead of its crystal ionic radius, to account for the nonlinear response of the first solvation shell (see Babu and Lim<sup>1</sup> and references therein). An alternative approach is to derive the dielectric profile at the border of the solute. Noyes showed that it is possible to use the experimental data on ion solvation to derive this profile.<sup>2</sup> Conversely, a number of attempts have been made to derive the function  $\epsilon(\vec{r})$  from first principles.<sup>3–7</sup> Our approach differs in that we do not assume a dielectric profile. Instead, we consider a solvent model with built-in  $\epsilon(\vec{r})$  dependence that allows for the rapid prediction of solvent density around solutes. It is an extension from the Poisson model and is described in full detail in Azuara et al.<sup>8</sup>

Briefly, we represent the water surrounding the ion as a set of orientable dipoles of constant module  $p_0$  and bulk concentration  $c_{\text{dip}}^b$ . These water dipoles are distributed on a lattice to take into account the excluded-volume effects. The three-dimensional lattice contains  $N$  uniformly sized cuboids, of size  $a^3$ , where  $a$ , the lattice spacing, is set to the geometrical dimension of the dipole. Note that, under this assumption, the maximum water density is proportional to  $a^{-3}$ . The ion is described as a single charge  $q$  at position  $\vec{r}_0$  on the lattice, inside an empty sphere of radius  $R_{\text{ion}}$ . Following the formalism introduced by Borukhov et al.,<sup>9</sup> the grand canonical partition function  $\mathcal{Z}_1(\vec{r})$  for the lattice site at position  $\vec{r}$  is given by

$$\mathcal{Z}_1(\vec{r}) = 1 + \lambda_{\text{dip}} \frac{\sinh(u)}{u} \quad (2)$$

where  $\lambda_{\text{dip}}$  is the fugacity of the dipoles,  $u = \beta p_0 |\vec{E}(\vec{r})|$  and  $\vec{E}(\vec{r})$  is the electric field at position  $\vec{r}$ . The fugacity is derived from the bulk concentration of dipoles,

$$\lambda_{\text{dip}} = (\mathcal{N}_A c_{\text{dip}}^b a^3) / (1 - \mathcal{N}_A c_{\text{dip}}^b a^3)$$

The electrostatic potential is then found to be the solution of the modified Poisson Langevin (PL) equation:

$$\vec{\nabla} \cdot \left( \epsilon_0 \vec{\nabla} \Phi(\vec{r}) + \gamma(\vec{r}) \beta p_0 \frac{\lambda_{\text{dip}} F_1(u)}{a^3 \mathcal{Z}_1(\vec{r})} \vec{\nabla} \Phi(\vec{r}) \right) = -\rho(\vec{r}) \quad (3)$$

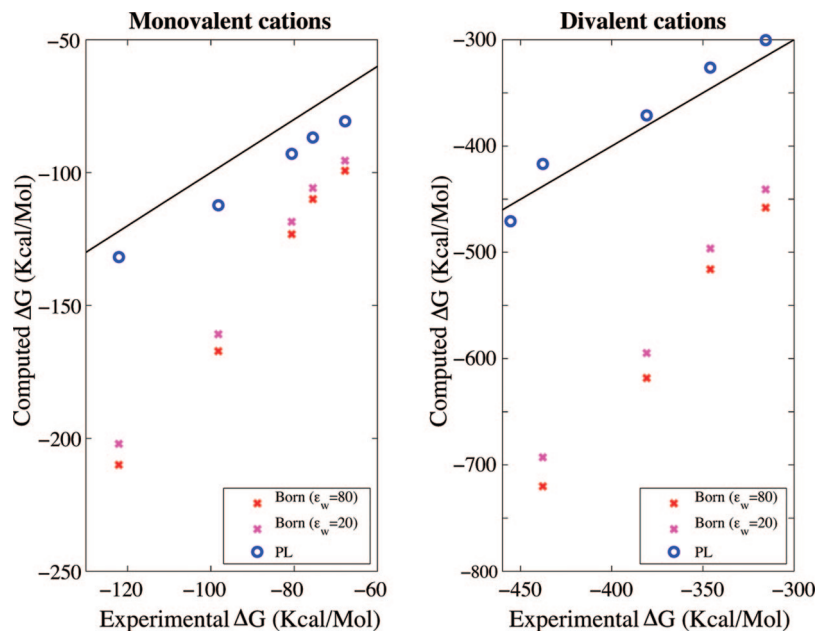
where  $\rho(\vec{r}) = q\delta(\vec{r} - \vec{r}_0)$ ,  $\gamma(\vec{r}) = 1$  if  $r > R_{\text{ion}}$  and 0 otherwise,

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**Figure 1.** Comparing experimental and computed ion solvation free energies. The experimental values are taken from Burgess,<sup>10</sup> and the ionic radii are taken from Cotton and Wilkinson.<sup>11</sup> The Born solvation energies are computed using 1 with  $\epsilon = 80$  and  $\epsilon = 20$ . The PL solvation energies are computed by solving eq 3 with  $a = 3 \text{ \AA}$  and  $p_0 = 2.35 \text{ D}$ . The solid line shows the first diagonal (i.e., perfect match).

**TABLE 1: Computed versus Experimental Solvation Free Energies of Ions**

ion	radius <sup>a</sup> (Å)	$\Delta G_{\text{exp}}^b$ (kcal/mol)	$\Delta G_{\text{PL}}^c$ (kcal/mol)	$\Delta G_{\text{Born}80}^d$ (kcal/mol)	$\Delta G_{\text{Born}20}^e$ (kcal/mol)	$\Delta G_{\text{W}}^f$ (kcal/mol)	$\Delta G_{\text{MSA}}^g$ (kcal/mol)	$\Delta G_{\text{qLD}}^h$ (kcal/mol)
Li <sup>+</sup>	0.78	-122.1	-132.7	-210.0	-202.1	-223.1	-122.0	-142.5
Na <sup>+</sup>	0.98	-98.2	-114.1	-167.2	-160.8	-210.8	-106.0	-121.5
K <sup>+</sup>	1.33	-80.6	-94.8	-123.2	-118.5	-177.3	-86.5	-98.2
Rb <sup>+</sup>	1.49	-75.5	-88.5	-110.0	-105.0	-162.3	-79.8	-90.6
Cs <sup>+</sup>	1.65	-67.8	-82.4	-99.3	-95.5	-149.4	-74.0	-84.1
Mg <sup>2+</sup>	0.78	-455.5	-474.5	-840.2	-808.3	-555.5	-487.9	-517.2
Mn <sup>2+</sup>	0.91	-437.8	-422.4	-720.2	-692.9	-552.5	-444.8	-462.0
Ca <sup>2+</sup>	1.06	-380.8	-377.3	-618.3	-594.8	-537.5	-403.8	-414.3
Sr <sup>2+</sup>	1.27	-345.9	-333.0	-516.0	-496.5	-517.3	-357.5	-365.1
Ba <sup>2+</sup>	1.43	-315.5	-307.5	-458.0	-440.9	-493.0	-328.8	-336.4
RMS <sup>i</sup> (kcal/mol)			14	187	169	124	15	28

<sup>a</sup> Goldschmidt ionic radius from Cotton and Wilkinson.<sup>11</sup> <sup>b</sup> Experimental values from Burgess.<sup>10</sup> <sup>c</sup> This work (see text for details). <sup>d</sup> Born solvation energy computed using eq 1 with  $\epsilon = 80$ . <sup>e</sup> Born solvation energy computed using eq 1 with  $\epsilon = 20$ . <sup>f</sup> Solvation free energies using Warshel's Langevin dipole model, computed using ChemSol.<sup>12</sup> <sup>g</sup> Computed using the MSA approximation.<sup>13</sup> <sup>h</sup> Computed using the charge-dependent Langevin-Debye model.<sup>14</sup> <sup>i</sup> Root mean square deviation between computed and experimental solvation free energies, averaged over all 10 ions.

$F_1(u) = [\sinh(u/u^2)]\mathcal{L}(u)$  and  $\mathcal{L}(u) = 1/\tanh(u) - 1/u$  is the Langevin function.

The PL equation includes three parameters: the bulk dipole concentration,  $c_{\text{dip}}^b$ , the dipole strength,  $p_0$ , and the lattice size,  $a$ . We set  $c_{\text{dip}}^b$  to 55 M,  $p_0$  to its value in solution, i.e., 2.35 D, and  $a$  to approximately the diameter of a water molecule, i.e., 3.0 Å. Using these values, we compute the electrostatics contribution to the solvation free energies of five monovalent (Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, Cs<sup>+</sup>) and five divalent (Mg<sup>2+</sup>, Mn<sup>2+</sup>, Ca<sup>2+</sup>, Sr<sup>2+</sup>, Ba<sup>2+</sup>) cations. Equation 3 is solved numerically on a cubic grid with 257<sup>3</sup> vertices, with two adjacent vertices distant by 0.08 Å. Comparisons of the resulting values with those computed using the Born equation and the corresponding experimental values are shown in Figure 1 and Table 1. We also provide in the latter the solvation free energies of the same ions computed with three other implicit solvent models that modify the dielectric profile in the neighborhood of the ions, namely, the Langevin dipole model of Warshel and co-workers,<sup>12,15</sup> the mean sphere approximation model (MSA) of Wertheim<sup>16</sup> and Chan et al.,<sup>13</sup> and the charge-dependent Langevin-Debye model (qLD) of Jha and Freed.<sup>14</sup>

As previously observed,<sup>1,17</sup> the Born equation systematically overestimates the ion solvation free energy. The agreement between the experimental solvation free energy and the Born energy computed with eq 1 can be improved by considering the radius of the ion as a parameter, thereby defining an effective Born radius. Using this approach, Babu and Lim obtained a much better fit, with an rms between the computed solvation free energies and the corresponding experimental values of 3 kcal/mol.<sup>1</sup> In this approach, however, the Born radius is adjusted differently for each ion type, leading to a large number of parameters, which casts doubt on its potential extension to larger systems. Another option is to increase the contribution of the solvent by reducing its dielectric constant. We tested  $\epsilon = 20$  instead of 80 and only observed a marginal improvement.

The Langevin dipole model, as developed by Warshel and co-workers,<sup>12,15,18</sup> treats the solvent molecules as polarizable point dipoles; the position of these dipoles is kept fixed (usually defined by a 3D grid around the solute), while their strength and orientation are optimized simultaneously, accounting for the solute and interactions between the dipoles. The solvation free energy is then computed as the sum of the contribution of

each individual dipole. The Langevin dipole model has been implemented in the program ChemSol, freely available from their authors.<sup>12</sup> We used ChemSol with its standard parameters to compute the solvation free energies of the 10 ions considered in this study; results are shown in Table 1. While the Langevin dipole model gives better results than a simple application of the Born model, the agreement is still poor, with an rms of 169 kcal/mol.

The MSA model considers the solute as being represented by a hard sphere of radius  $R$  submerged in a solvent whose molecules are represented by point dipoles centered in hard spheres of diameter  $d$ . The MSA is an extension of the Debye–Hückel or Poisson–Boltzmann theory that account for the finite sizes of the solute and solvent. It can be cast as the solution of the Ornstein–Zernike integral equation for the ion–ion, ion–dipole, and dipole–dipole correlation functions.<sup>13,16</sup> The solvation free energy of an ion in the MSA model is given by

$$\Delta G_{\text{MSA}} = -\frac{q^2}{2(R + R_s)} \left( \frac{1}{\epsilon_0} - \frac{1}{\epsilon} \right) \quad (4)$$

where

$$R_s = \left( \frac{1}{2} - \frac{3\zeta}{1 + 4\zeta} \right) d \quad (5)$$

Here, the constant  $\zeta$  is related to the dipole number density, the dipole moment, and the dielectric constant  $\epsilon$  of pure liquid (for water,  $\zeta = 0.178$ ). It is interesting to note that, phenomenologically, the MSA modifies the Born equation by adjusting the size of the ion to account for the dielectric properties of the water. Note that, in the limit of a large ion, eq 4 reduces to the Born energy given by eq 1. We have computed the solvation free energy of the five monovalent and five divalent ions considered here using eq 4; results are given in Table 1. The MSA model performs well, with an rms between the computed and experimental solvation energies of 15 kcal/mol.

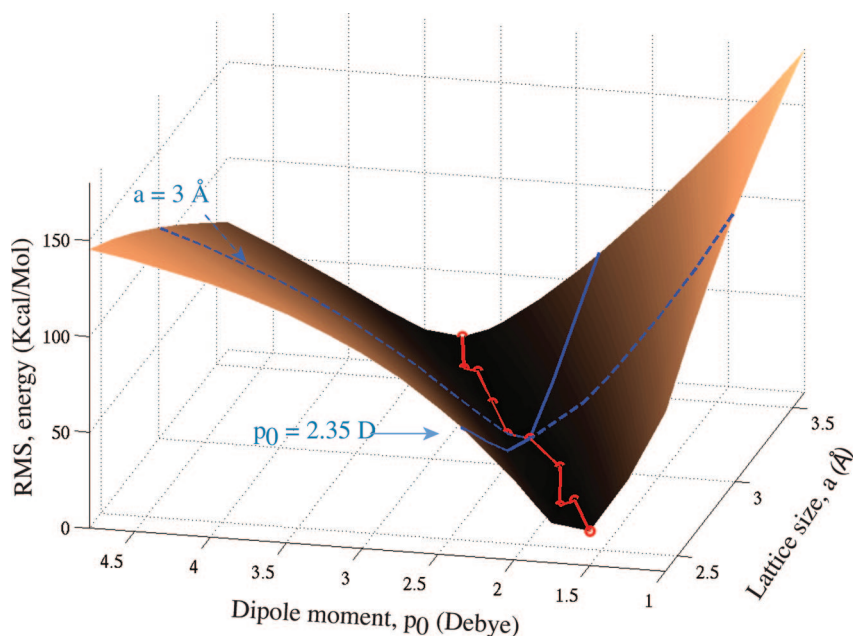
The Poisson–Boltzmann model that leads to the Born equation for a single ion in water assumes a linear response of

the solvent dipoles to the electric field generated by the charges of the solute. In the direct proximity of the solute, however, this electric field is intense; the solvent polarization saturates, and the solvent dipoles no longer respond linearly. This nonlinear effect is well described by the Langevin–Debye model<sup>3</sup> which introduces the concept of dielectric saturation with a sigmoidal dependence of the dielectric constant. Many models have been proposed to mimic this sigmoidal behavior.<sup>6,14,19</sup> Among those, the charge-dependent Langevin dipole formalism of Jha and Freed<sup>14</sup> leads to a generalized Born equation for solvation:

$$\Delta G_{\text{qDL}} = -\frac{q^2}{2R} \left( \frac{1}{\epsilon_0} - \frac{1}{\epsilon} \right) - \frac{sq^2}{2\epsilon} \int_{sR}^{\infty} \left( \frac{1}{1 - \gamma(x^2 + 2x + 2)e^{-x}} - 1 \right) \frac{dx}{x^2} \quad (6)$$

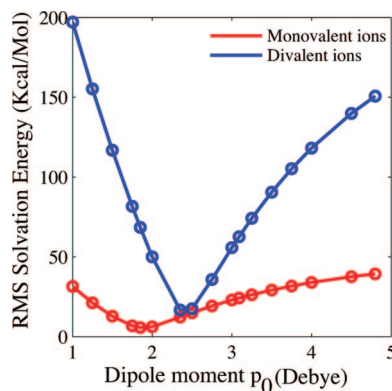
where  $\gamma = (\epsilon - \epsilon_0)/2\epsilon$  and  $s$  is a parameter for the model describing the sigmoidal behavior of  $\epsilon$ , set to be charge-dependent ( $s = 0.274$  for  $q = 1$  and  $s = 0.0685$  for  $q = 2$ ).<sup>14</sup> We used the qDL model to compute the solvation free energies of the ions surveyed in this paper; results are given in Table 1. The qDL model performs well, with an overall rms of 28 kcal/mol.

The PL model is by construction very simple, yet it reproduces the experimental solvation free energy of isolated ions with remarkable precision (rms = 14 kcal/mol; see Table 1 and Figure 1). In opposition to the Born and MSA models, it does not modify the physical radii of the ions, nor does it assume a mathematical form for the behavior of  $\epsilon$  in the proximity of the ion, such as the one used by the qDL model. Instead, the dielectric behavior of the water is an output of a PL calculation, derived from the dipole density in the domain surrounding the solute. It bears similarity to the Langevin dipole model of Warshel and co-workers, with the key additional feature that the dipoles are allowed to have variable density. In addition, the PL equation is a continuous limit of the discrete lattice gas model; as such, it is insensitive to the problem of positioning the solute with respect to the grid of dipoles.



**Figure 2.** Finding the right parameters for the PL model. We computed the solvation energies of the 10 ions (see text) for each pair  $(a, p_0)$  and recorded the rms difference from the corresponding experimental values. The red line shows the position of the trough of the corresponding 2D surface.





**Figure 3.** Different ion types lead to different dipole strengths. The rms difference between experimental and computed solvation free energies is plotted versus the dipole strength  $p_0$  for monovalent (red) and divalent (blue) ions. The lattice size is fixed at 3 Å. The optimal value for  $p_0$  leads to a minimum for the rms difference; this value is different for monovalent and for divalent ions.

Figure 1 shows that a good agreement is reached between the experimental and computed solvation free energies for diverse cations using a small set of parameters (i.e., the lattice size,  $a$ , and the water dipole intensity,  $p_0$ ) that are physically sound. We did check if a better agreement could be reached with different sets of parameters. We kept the bulk concentration of water dipole at 55 M but repeated the calculations presented above for different pairs of values for  $a$  and  $p_0$ . Each pair is subsequently characterized by the rms difference between the computed and experimental solvation free energies for the 10 cations considered. Results are shown in Figure 2. There is a whole range of values for  $(a, p_0)$  that provides a good fit. Interestingly, the best value for  $a$  when  $p_0$  is set to 2.35 D is 3 Å and, reversely, the best value for  $p_0$  when  $a$  is set to 3 Å is 2.35 D.

It is conceivable that the optimal values for the parameters  $a$  and  $p_0$  are not universal, and depend on the system studied. Figure 1, for example, shows that a better fit is observed for divalent cations than for monovalent cations, for  $(a, p_0) = (3, 2.35)$ . We optimized  $p_0$  separately for the two types of ions (monovalent and divalent), keeping  $a$  constant, set to 3 Å. Results are shown in Figure 3. Clearly, the optimal values for  $p_0$  differ for monovalent and divalent ions: a value of 1.85 D (close to the estimated value for water in the gas phase) is best for the former, while a value of 2.35 D (the estimated value for liquid water) is best for the latter. This difference is not unexpected. Different charges will induce different polarization of the solvent, which is reflected in our calculation through the strength of the dipole moment.

Water plays a central role in biological chemistry, as it defines the structures and properties of biomolecules. As such, it is the focus of much theoretical and computational modeling. Recent models describe fine-scale properties with increased structural details, at heavy computational costs.<sup>20,21</sup> The formalism presented here aims at characterizing the water surrounding

molecules at an intermediate level of detail. It generalizes the standard Poisson formalism to include a water model based on discrete nonoverlapping dipoles. The resulting formalism is simple, and its equation can be solved numerically with little computational cost; as such, it represents an attractive alternative to the computationally demanding explicit solvent models. It is general enough however to give a realistic picture of the dielectric response of water to the presence of a charged molecule. We have shown that it is accurate enough to predict the solvation free energy of ions with high accuracy. This formalism is not deprived of limitations. The dipole strength  $p_0$  is assumed constant and independent of the solutes; this may be incorrect in the presence of strong polarization. In addition, we assume a symmetric model for the dipoles that cannot account for the specific packing observed in water. As such, it would predict the same solvation free energy for an anion and a cation of the same size. In reality, however, positive ions are hydrated differently from negative ions in water. This has long been recognized, and in a simple explanation dating from 1939, Latimer et al. attributed it to the asymmetric structure of water.<sup>22</sup> We are currently working on including this asymmetry in our model.

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