# MST Continuum Study of the Hydration Free Energies of Monovalent Ionic Species

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In this study, we revisit the protocol previously proposed within the framework of the Miertus—Scrocco—Tomasi (MST) continuum model to define the cavity between the solute and solvent for predicting hydration free energies of univalent ions [Orozco, M.; Luque, F. J. *Chem. Phys.* **1994**, *182*, 237]. The protocol relies on the use of a reduced cavity (around 10–15% smaller than the cavity used for neutral compounds) around the atom(s) bearing the formal charge. The suitability of this approach is examined here for a series of 47 univalent ions for which accurate experimental hydration free energies are available. Attention is also paid to the effect of the charge renormalization protocol used to correct uncertainties arising from the electron density located outside the solute cavity. The method presented here provides, with a minimum number of fitted parameters, reasonable estimates within the experimental error of the hydration free energy of ions (average relative error of 4.7%) and is able to reproduce solvation in water of both small and large ions.

#### Introduction

The theoretical study of chemical systems in condensed phases has experienced an extraordinary evolution in the past decades, leading to a number of computational approaches that combine quantum mechanical (QM) or classical descriptions of the solute with continuum or discrete representations of the solvent molecules.1 One of these approaches is the selfconsistent reaction field (SCRF) continuum model, where the solute resides in a cavity carved into a continuum polarizable medium that simulates the solvent.<sup>2</sup> Despite the rather crude description of the solvent, QM SCRF methods have found a widespread acceptance for several reasons: first, the availability of well-defined formalisms developed to account for the mutual coupling between the solute's charge distribution and the solvent's reaction field (see ref 3 for a recent review); second, the ease of gaining insight into the solvent-induced changes in the properties of the solute upon transfer from the gas phase to solution;<sup>2,4</sup> and third, its low computational cost, which is only slightly larger than the corresponding QM calculation in the gas phase.

Although the preceding features have made QM SCRF methods very popular for the study of molecules in solution, their *chemical* accuracy has mainly been restricted by the uncertainty in the location of the boundary between solute and solvent.<sup>2</sup> In the past decade, a large research effort has been spent to parametrize the solute cavity in different SCRF methods, such as the multipolar expansion method developed at Nancy,<sup>5</sup> the generalized Born SMx solvation models from Cramer and Truhlar,<sup>6</sup> the polarizable continuum model from

Tomasi and co-workers<sup>7</sup> and the related Miertus—Scrocco—Tomasi (MST) version developed at Barcelona,<sup>8</sup> or the conductor-like screening model from Klamt and co-workers.<sup>9</sup> As a result, the most refined QM SCRF methods predict the free energy of solvation of neutral molecules in a variety of solvents with an average error clearly below 1 kcal/mol when solute cavities adjusted to the specific electrostatic model are used.<sup>10</sup>

For ionic solutes, the uncertainty in the hydration free energies determined from QM SCRF methods is larger (around 4-5 kcal/ mol). The lower predictive accuracy for ions arises not only for the intrinsic problems in representing the strong solutesolvent interactions existing between water and ions but also to the poor quality of most experimental data. For neutral solutes, the solvation free energy can be directly obtained by measuring partition coefficients of solutes between the gas phase and dilute aqueous solutions in equilibrium. In this way, the uncertainty of the measured partition coefficient increases with increasing solvation free energy, and eventually, the concentration of solute molecules in the gas phase falls below the experimental detection limits when the solvation free energy (in absolute terms) exceeds ~12 kcal/mol.11 This makes it necessary to determine the solvation free energy of ionic species by indirect approaches based on the use of suitable thermodynamic cycles. For example, Pearson<sup>12</sup> determined the experimental solvation free energies for a number of univalent ions using the relationships given by eqs 1 and 2 for cations and anions, respectively.

$$\Delta G_{\text{sol}}(AH^{+}) = B_{g}(A) + \Delta G_{\text{sol}}(H^{+}) + \Delta G_{\text{sol}}(A) - 2.303RTpK_{a}(AH^{+})$$
(1)

$$\Delta G_{\rm sol}({\rm B}^{-}) = -B_{\rm g}({\rm B}^{-}) - \Delta G_{\rm sol}({\rm H}^{+}) + \Delta G_{\rm sol}({\rm BH}) + 2.303 RT p K_{\rm a}({\rm BH})$$
 (2)

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where  $B_{\rm g}$  is the gas-phase basicity and  $\Delta G_{\rm sol}$  denotes the free energy of solvation.

Note that according to eqs 1 and 2 the quality of the "experimental" solvation free energies of cations,  $\Delta G_{\text{sol}}(AH^+)$ , and anions,  $\Delta G_{\text{sol}}(B^-)$ , depends on the accuracy of different thermodynamic quantities, such as the gas-phase basicity, the solvation free energy of the conjugate neutral base,  $\Delta G_{\rm sol}(A)$ , or acid,  $\Delta G_{sol}(BH)$ , the p $K_a$  constant, and the solvation free energy of the proton,  $\Delta G_{\text{sol}}(H^+)$ . It is also worth noting that correction terms (not explicitly indicated in eqs 1 and 2) arising from the standard-state definition of the chemical species in the gas phase and in solution might be necessary. Thus, solvation free energies can be defined for the hypothetical process of transferring a species from a fixed position in the gas phase to a fixed position in the solution phase, which is equivalent to using the same standard states (typically 1 M concentration) for gas and solution phases. 13 However, experimental data in the gas phase is generally referred to an ideal gas at 1 atm of pressure so that a correction term of RT ln(RT) must be considered.

In his original work, Pearson used an estimated  $\Delta G_{\rm sol}({\rm H}^+)$ value of -259.5 kcal/mol, which was also adopted by Florian and Warshel in the parametrization of their Langevin dipole solvation model. <sup>14</sup> However, the values of  $\Delta G_{\text{sol}}(H^+)$  used by other authors vary considerably (from -252 to -263 kcal/ mol). 15 This range of error is similar to that determined from theoretical calculations<sup>16</sup> and introduces a noticeable range of uncertainty into the experimental hydration free energy of ions. More recently, Tissandier et al., 17 using a cluster-pair approximation and thermodynamic properties of ion-water clusters, derived a value of  $\Delta G_{\text{sol}}(H^{+}) = -264$  kcal/mol. A very similar value has recently been derived by Tuttle et al. and by Coe and co-workers. 18 Because this new  $\Delta G_{sol}(H^+)$  value is considerably more negative than the previous ones, it has a significant effect on the absolute solvation free energies of ions and the corresponding acidity/basicity constants.

Pliego and Riveros have recently derived new experimental values for the hydration free energies of 47 univalent ions using as reference the solvation free energy of the proton derived by Tissandier et al. <sup>19</sup> In light of the new reported values, the aim of this work is to revisit the original parametrization of the MST model<sup>20</sup> to predict the corrected experimental hydration free energies for ions. In turn, this makes it necessary to solve additional fundamental problems for a continuum description of solvation. First, how should solute cavities be defined for ionic compounds, which are generally characterized by a large anisotropy in the charge distribution? Second, how can errors in the solvation free energy arising from the solute charge density lying outside the cavity be corrected?

In our previous MST parametrization for ions,<sup>20</sup> the van der Waals radii used to build up the solute/solvent interface were scaled by a factor of 1.10–1.15, which is around 10% smaller than that recommended for the hydration of neutral solutes.<sup>8</sup> Moreover, the inaccuracies in the apparent surface charges due to the solute electron density lying outside the cavity were treated by means of a simple uniform correction procedure. However, owing to the small size of the ions examined in that study, the strategy of reducing the whole cavity might not be appropriate for ionic compounds having larger, more complex chemical structures, especially when there is high anisotropy in the charge distribution along the molecule. Then, we explore here the suitability of our original strategy, but limiting the reduction of the cavity to the atom(s) that bear the formal charge in the ion. Furthermore, to reduce artifacts arising from the solute

charge density penetration, different charge renormalization procedures are tested to determine their consistency in predicting the hydration free energies, particularly for anions having diffuse charge distributions

#### Methods

The MST Continuum Method. In the MST model, the free energy of solvation is determined as the sum of three contributions: electrostatic, cavitation, and van der Waals. Following the formalism of the polarizable continuum model (PCM) originally developed by Miertus, Scrocco, and Tomasi, the electrostatic term ( $\Delta G_{\rm ele}$ ) is determined by using a set of apparent charges spread over the cavity surface (eq 3), which account for the reaction field created in the solvent by the presence of the solute's charge distribution. The apparent charges are obtained by solving the Laplace equation with suitable boundary conditions (eq 4).

$$V_{\rm R} = \sum_{j=1}^{M} \frac{q_j}{|r_i - r|}$$
 (3)

where  $V_{\rm R}$  is the perturbation operator used to couple the solute's charge distribution and the solvent reaction field, M is the total number of surface elements, j, into which the solute/solvent boundary is divided, and  $q_j$  is the apparent charge at the j surface element, which is centered at  $r_j$ .

$$q_{j} = -\frac{\epsilon - 1}{4\pi\epsilon} S_{j} \left( \frac{\partial V_{T}}{\partial n} \right)_{j} \tag{4}$$

where  $V_T$  is the total electrostatic potential, which includes both solute and solvent contributions, n is the unit vector normal to the surface element j,  $S_j$  is the area of the surface element j, and  $\epsilon$  is the solvent dielectric constant.

The cavitation free energy is determined by following Pierotti's scaled particle theory<sup>21</sup> adapted to molecular-shaped cavities by using the procedure proposed by Claverie (eq 5a,b).<sup>22</sup> Thus, the cavitation free energy of atom i,  $\Delta G_{\text{C-P},i}$ , is determined by weighting the contribution of the isolated atom,  $\Delta G_{\text{P},i}$ , by the ratio between the solvent-exposed surface of such an atom,  $S_i$ , and the total surface of the molecule,  $S_T$  (eq 5a,b).

$$\Delta G_{\text{cav}} = \sum_{i=1}^{N} \frac{S_i}{S_{\text{T}}} \Delta G_{\text{P},i}$$
 (5a)

where N is the number of atoms

$$\Delta G_{P,i} = K_0 + K_1 R_{MS} + K_2 R_{MS}^2 + K_3 R_{MS}^3$$
 (5b)

where  $R_{\rm MS}$  is the sum of the radii of atom i in the solute M and the solvent molecule S, and the coefficients K's are expressed in terms of properties of the solvent and of the solution, such as the molecular radius and number density of the solvent, pressure, and temperature.<sup>21</sup>

Finally, the van der Waals term ( $\Delta G_{\rm vdw}$ ) is computed using a linear relationship to the solvent-exposed surface of each atom (eq 6). In eq 6,  $\xi_i$  denotes the atomic surface tension of atom i, and  $S_i$  stands for its solvent-exposed surface. The atomic surface tensions were derived in previous studies<sup>8</sup> by subtracting the electrostatic and cavitation components to the experimental free

energy of solvation and subsequently fitting the corresponding residual to the van der Waals term.

$$\Delta G_{\text{vdw}} = \sum_{i=1}^{N} \xi_i S_i \tag{6}$$

Molecular-shaped GEPOL cavities<sup>23</sup> are used to define the solute/solvent interface for the calculation of electrostatic and non-electrostatic (cavitation, van der Waals) terms. In the last parametrization of the MST model, a dual-cavity strategy was used<sup>24</sup> so that non-electrostatic contributions are determined by using a van der Waals surface mainly built up from Pauling's radii (in angstroms: polar hydrogen, 0.9; apolar hydrogen, 1.2; C and N, 1.5; O, 1.4; F, 1.35; S, 1.75; and Cl, 1.80), whereas the electrostatic term is determined by using a solvent-exposed surface created by scaling the atomic radii by a solventdependent factor,  $\lambda$ , which adopts values of 1.25, 1.50, 1.60, and 1.80 for the solvation of neutral compounds in water, octanol, chloroform, and carbon tetrachloride. On the basis of the comparison of the  $\Delta G_{\mathrm{ele}}$  values determined from MST and from Monte Carlo-free energy perturbation (MC-FEP) calculations for seven small ionic compounds, 20 it was found necessary to further reduce the solute cavity by around 10% to compute the hydration free energy of univalent ions. This reduction was justified by the fact that, because of strong electrostatic interactions, solvent molecules are, in general, closest to the atoms of charged molecules than to those of neutral

Charge Normalization. Owing to the solute charge density that lies outside the cavity, and to the numerical errors due to tessellation of the cavity surface (eq 4), the sum of the apparent surface charges,  $Q_{\sigma} = \sum_{j} q_{j}$ , in the MST (PCM) model do not satisfy the relationship given by eq 7, where  $Q_{\rm M}$  denotes the total charge of the solute (denoted by M), and the error in the charges is given by  $\Delta_{\sigma} = Q_{\rm theor} - Q_{\sigma}$ , where  $Q_{\rm theor} = -(\epsilon - 1/\epsilon)Q_{\rm M}$ .

$$Q_{\sigma} = -\frac{\epsilon - 1}{\epsilon} Q_{\rm M} \tag{7}$$

The MST model<sup>8</sup> takes into account the charge normalization by using the expressions given in the original formalism<sup>7a</sup> (denoted in the following as the *standard correction*, or SC, approach), as noted in eq 8a,b, where  $Q_{\sigma}^{+}$  and  $Q_{\sigma}^{-}$  denote the sum of positive and negative apparent charges, respectively.

$$q'_{j} = q_{j} \left[ 1 + \Delta_{\sigma} / (2Q_{\sigma}^{+}) \right]$$
 for  $q_{j} \ge 0$  (8a)

$$q_i' = q \left[ 1 + \Delta_{\sigma}/(2Q_{\sigma}^-) \right]$$
 for  $q_i < 0$  (8b)

More elaborate treatments of the charge compensation have been developed by the Pisa group.  $^{26}$  The most accurate procedure (denoted *density-corrected*, or DC, approach hereafter) relies on two main features: first, the introduction of separate factors to correct the apparent charges induced by nuclei ( $f^{\rm Z}$ ) and electrons ( $f^{\rm e}$ ), which makes it possible to correct the numerical errors on the nuclear charges, which are only affected by the discretization of the cavity (eq 9); and second, the explicit calculation of the charge density outside the cavity ( $Q_{\rm out}$ ), which is determined from the flux of the solute electric field through the cavity surface (eq 10). By using this new approach, the solvent response induced by the electron charge density inside

the cavity  $(Q_{in})$  is then only affected by the numerical errors due to tessellation of the cavity (eq 11).

$$f^{Z} \sum_{i} q_{i}^{Z} = -\frac{\epsilon - 1}{\epsilon} Q_{M}^{Z} \tag{9}$$

$$Q_{\text{out}} = -(Q_{\text{M}}^{\text{e}} - Q_{\text{in}}) = -\left(Q_{\text{M}}^{\text{e}} + \frac{1}{4\pi} \int_{S} E_{\text{M}}(s) \cdot n_{s} \cdot ds\right)$$
 (10)

where  $E_{\rm M}(s)$  is the electric field created at each tessera of the cavity.

$$f^{e} \sum_{j} q_{j}^{e} = -\frac{\epsilon - 1}{\epsilon} Q_{\text{in,M}}^{e}$$
 (11)

For the sake of completeness, let us note that an alternative procedure is used by other groups to alleviate the effects due to the charge density that lies outside the cavity, where the continuous charge distribution obtained from quantum mechanical or density functional calculations is replaced by a set of atomic point charges, often supplemented by point dipoles, which are then used to evaluate the solvent reaction field by means of finite-difference Poisson—Boltzmann or boundary element techniques.<sup>27</sup> This approach, nevertheless, demands that the set of point charges accurately reproduces the charge distribution of the solute, which then raises the question about the best procedure to derive the atomic charges.<sup>28</sup>

**Computational Details.** The set of compounds compiled by Pliego and Riveros<sup>19</sup> has been used to examine the suitability of our previous parametrization of the MST model to predict the hydration free energy of univalent ions. To be consistent with our previous work, <sup>20</sup> all calculations have been performed at the HF/6-31+G(d) level. In accordance with the standard MST protocol, 8,20 the gas-phase geometry of the charged molecules was fully optimized and subsequently used for calculations in solution. The MST hydration free energies were determined by using a locally modified version of Monstergauss.<sup>29</sup> For the sake of comparison, computations were also performed by using the integral equation formalism<sup>30</sup> of the polarizable continuum model (IEF-PCM), which has been claimed to be less sensitive to the inaccuracies arising in the calculation of the electrostatic term. IEF-PCM calculations were performed by using the code implemented in Gaussian 03.31

# **Results and Discussion**

Cavity Definition for Ionic Species. Although the choice of the solute/solvent boundary is a crucial parameter in the development of any QM SCRF method, the definition of the solute cavity is even more delicate for ionic compounds, whose electrostatic field strongly perturbs the solvent, thus making the solvent molecules in the first hydration shells exhibit properties clearly different from those of the bulk solvent. In turn, hydration also changes the electron density distribution of ions,<sup>32</sup> leading to differential trends in the electron rearrangement that takes place for cations and anions. Therefore, it can be questioned whether the hydration of ions can be described in an effective way by means of a suitable refinement of the solute cavity in continuum models, and whether such a refinement is well-suited to reproduce the solvent-induced change in different molecular properties of the solute.<sup>33</sup>

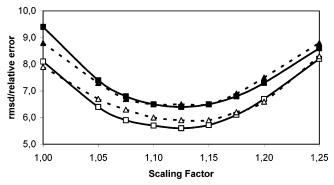
An attempt often considered to describe the solvation of ions consists of the addition of an arbitrary number of solvent molecules to the solute, while the rest of the solvent is treated as a continuum dielectric.<sup>34</sup> This approach, however, raises some

problems, such as the increase in the computational task, the need to obtain appropriate averages of the thermally accessible configurations, or the treatment of the librational motions originated from the weak interactions between solute and solvent molecules. Moreover, by adding few solvent molecules, the conceptual problem of the solvation of the solute alone is transformed into the solvation of the solute—solvent cluster. Finally, the analysis of solute—solvent clusters for medium- and large-sized molecules becomes even more problematic and computationally more expensive. Because of these considerations, we prefer here to limit the QM discrete description exclusively to the solute. This choice, nevertheless, raises the delicate question about the suitability of transferring the cavity definition optimized for the solvation of neutral solutes to ionic compounds.

In the original MST parametrization,<sup>20</sup> the optimum cavity for the hydration of ions was defined by scaling the atomic radii by a factor of 1.10-1.15, which implies a reduction with regard to the scaling factor of 1.25 (i.e., the value optimized for the hydration of neutral solutes).8 A similar correction was also adopted in the united atom for Hartree-Fock (UAHF) parametrization of the PCM model,7c where the atomic radii are reduced depending on the formal charge carried by atoms, although different correction factors are used for cations and anions. Others authors have also proposed to exploit alternative relationships between the atomic charge and the effective atomic radius<sup>35</sup> or to use a modified set of atomic radii.<sup>36</sup> An alternative approach for cavity size comes from the use of isodensity contours of the electron density, which can be adjusted during the SCRF calculation as the charge distribution of the solute is polarized by the solvent reaction field.<sup>37</sup> Here, the electron density contour that leads to better agreement with the experimental solvation free energy for ions is larger than that required for neutral compounds.38

For our purposes here, we have decided to retain the original idea of reducing the scaling factor ( $\lambda$ ) that multiplies the atomic radii in order to build up the solute cavity used to calculate the  $\Delta G_{\rm ele}$  component. However, instead of reducing the whole cavity of the solute, which might be appropriate for small-sized ions, the scaling down is limited here to the heavy atom (and the hydrogen atoms attached to it) that bears the formal charge. Thus, for alcohol cations and anions, the reduction in the cavity only affected the  $-OH_2^+$  and  $-O^-$  groups. In the case of ionized carboxylic acids, such a reduction only affected the two oxygen atoms in the -COO<sup>-</sup> group. This approach resembles the procedure adopted by Barone et al. in the definition of the cavity for ionic solutes, 7c because it assumes a formal description of the electronic structure of the solute in the sense that it is based exclusively on the chemical formula. Clearly, more elaborate treatments that exploit a functional relationship between the radii and the net charge of the atoms<sup>35</sup> take into account a more real description of the electronic structure of the solute. Nevertheless, the procedure used to derive the net atomic charges and their dependence on the basis set are factors that must be considered for the practical generalization of those functional relationships. Besides retaining the simplicity of the original approach,<sup>20</sup> the strategy adopted here allows us to exploit the same set of scaling factors that modulate the cavity definition for the calculation of the electrostatic component of the solvation free energy (see Methods section), while introducing a minimum number of parameters to describe the hydration of ionic species.

Refinement of the MST Model for Ions. The adjustment of the scaling factor  $\lambda$  used to determine  $\Delta G_{\rm ele}$  was performed with the aim of minimizing the deviation of the calculated



**Figure 1.** Representation of the changes in the root-mean-square deviation (rmsd; solid line) and the relative error (in percentage; dashed line) between the experimental hydration free energies and the MST values obtained by varying the scaling factor used to correct the atomic radii of charged atoms in the calculation of the electrostatic component of the hydration free energy (see text for details). The electrostatic free energy of solvation was determined by using both SC (black) and DC (white) charge renormalization schemes (see text for details). The rmsd values are in kcal/mol.

hydration free energy,  $\Delta G_{\rm hyd}$ , from the experimental value for the series of monovalent ions. In accordance with our previous study,<sup>20</sup> MST-HF/6-31+G(d) calculations were performed by progressively reducing the scaling factor from  $\lambda = 1.25$  to  $\lambda =$ 1.00. The  $\Delta G_{\rm ele}$  values were calculated by using both SC (eqs 8a,b) and DC (eqs 10 and 11) charge renormalization schemes. The cavity used to compute the  $\Delta G_{\rm ele}$  term was built up by using the set of atomic radii typically used in MST calculations (see Methods section). Finally, the non-electrostatic (cavitation and van der Waals) component, which was estimated by using the standard atomic surface tensions determined for neutral molecules, was added to the  $\Delta G_{\rm ele}$  term to calculate  $\Delta G_{\rm hyd}$ . This computational strategy benefits from the fact that the  $\Delta G_{
m ele}$  term is the dominant contribution to the hydration of ionic solutes and from the partial cancellation between cavitation and van der Waals components.

Figure 1 shows the profiles of the root-mean-square deviation (rmsd) and relative error (in percentage) between experimental and calculated  $\Delta G_{\rm hyd}$  values determined for different scaling factors. The smallest deviation is found for a scaling factor  $\lambda$  ranging between 1.10 and 1.15. It is also worth noting that such a range of values is in agreement with the results found previously by comparing the  $\Delta G_{\rm ele}$  values determined from MST and MC-FEP calculations for a subset of small ions.<sup>20</sup> The results in Figure 1 also point out that both the rmsd and the relative error are further reduced by nearly 1 kcal/mol when the DC charge renormalization scheme is considered. This finding can be attributed to the larger efficiency of this method to account for the anisotropies in the charge distribution of the ions

Table 1 reports the electrostatic component of the hydration free energy determined from MST calculations by using a scaling factor of 1.15 and the two charge compensation schemes. For the sake of comparison, it also reports the values determined by using the IEF-PCM formalism and the same cavity definition for the univalent ions. Comparison of the MST and IEF results is shown in Figure 2. The regression equations indicate that there is close agreement between MST and IEF results. Thus, the MST-SC  $\Delta G_{\rm ele}$  values (eq 12) are around 3% larger than the IEF ones, and such a difference is reduced to only 2% when the MST-DC results are considered (eq 13). The most notable difference between the two charge normalization schemes, nevertheless, is reflected in the correlation coefficient of the regression equations, which is significantly larger when the

TABLE 1: Electrostatic Component of the Free Energy of Hydration (kcal/mol) Determined at the HF/6-31+G(d) Level from MST Calculations Using Both SC and DC Charge normalization Procedures<sup>a</sup> and from IEF Calculations

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ion	MST-SC <sup>b</sup>	MST-DC <sup>c</sup>	IEF
$F^-$	-101.7	-101.7	-98.4
Cl-	-75.4	-75.4	-72.5
OCl-	-74.6	-76.1	-73.5
$OH^-$	-106.4	-104.1	-98.7
$\mathrm{HO_2}^-$	-92.6	-92.5	-89.4
$\mathrm{NH_2}^-$	-102.5	-96.8	-90.3
CN-	-74.8	-75.0	-71.6
HCC-	-81.7	-81.9	-75.8
$CH_3O^-$	-90.3	-88.8	-84.7
$CH_3CH_2O^-$	-89.8	-86.1	-81.4
$C_6H_5O^-$	-77.0	-70.9	-66.1
$HCOCH_2^-$	-76.5	-73.5	-69.4
CH <sub>3</sub> COCH <sub>2</sub> <sup>-</sup>	-77.3	-73.0	-68.9
HCOO-	-80.3	-79.8	-76.6
$CH_3COO^-$	-82.8	-80.7	-76.9
CH <sub>2</sub> COOEt <sup>-</sup>	-74.0	-70.0	-66.7
CH <sub>3</sub> CONH <sup>-</sup>	-79.3	-76.4	-72.7
$N_3^-$	-72.6	-71.9	-68.9
$CH_2CN^-$	-70.3	-69.6	-65.8
CH <sub>3</sub> CHCN <sup>−</sup>	-69.2	-67.1	-64.1
$\mathrm{CH_2NO_2}^-$	-76.5	-73.5	-70.7
$HS^-$	-80.3	-76.5	-71.8
$CH_3S^-$	-78.4	-76.2	-71.4
$C_6H_5S^-$	-74.9	-67.4	-63.2
CH <sub>3</sub> SO <sub>3</sub> <sup>-</sup>	-77.8	-76.4	-72.9
$H_3O^+$	-105.2	-106.3	-107.6
$CH_3OH_2^+$	-83.8	-84.7	-86.3
$CH_3CH_2OH_2^+$	-77.3	-79.1	-80.3
$(CH_3)_2OH^+$	-68.5	-68.9	-69.6
$(Et)_2OH^+$	-59.2	-60.1	-61.4
$\mathrm{NH_4}^+$	-93.5	-93.7	-94.9
$CH_3NH_3^+$	-81.2	-81.3	-82.9
$(CH_3)_2NH_2^+$	-70.7	-70.6	-72.4
$(CH_3)_3NH^+$	-60.9	-60.7	-62.3
$CH_3CH_2NH_3^+$	-76.1	-77.2	-78.9
$(Et)_3NH^+$	-52.4	-53.1	-54.1
$n$ -PrNH $_3$ <sup>+</sup>	-73.1	-75.6	-77.5
$n$ -BuNH $_3$ <sup>+</sup>	-71.2	-75.2	-76.7
$C_6H_5NH_3^+$	-69.1	-76.1	-77.8
$(CH_3COCH_3)H^+$	-66.5	-67.6	-68.4
$(PhCOCH_3)H^+$	-53.6	-56.8	-58.6
(CH <sub>3</sub> COOEt)H <sup>+</sup>	-61.2	-63.1	-63.4
$HCONH_3^+$	-78.4	-79.4	-80.4
CH <sub>3</sub> CONH <sub>3</sub> <sup>+</sup>	-74.2	-74.7	-75.7
$C_5H_5NH^+$	-59.5	-60.5	-61.8
$(CH_3)_2SH^+$	-63.7	-63.5	-64.7
(CH3SOCH3)H+	-63.3	-64.9	-65.7

<sup>a</sup> See Charge Normalization in Methods section. <sup>b</sup> Eq 8a,b. <sup>c</sup> Eqs 9 and 11.

MST-DC results are considered. This finding points out not only the superiority of the DC charge normalization scheme but also the lower sensitivity of the IEF formalism to the errors arising from the penetration of the charge density outside the solute cavity. Moreover, these results suggest that the MST-DC optimized cavities can be considered to be transferable to the IEF-PCM framework.

$$\Delta G_{\text{ele}}(\text{IEF}) = 0.970(\pm 0.009) \Delta G_{\text{ele}}(\text{MST-SC})r = 0.90F = 191.2 (12)$$

$$\Delta G_{\text{ele}}(\text{IEF}) = 0.979(\pm 0.005) \Delta G_{\text{ele}}(\text{MST-DC})r = 0.97F = 748.8$$
 (13)

where r is the Pearson's correlation coefficient and F stands for the Snedeckor's distribution parameter.

If one considers the MST-DC results shown in Table 1, the rmsd between calculated and experimental hydration free

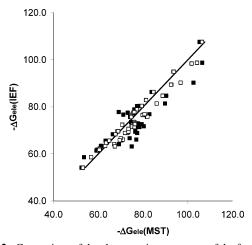


Figure 2. Comparison of the electrostatic component of the free energy of hydration (kcal/mol) determined from MST calculations by using a scaling factor of 1.15 and both SC (black) and DC (white) charge renormalization schemes and IEF calculations at the HF/6-31+G(d) level. The plot displays the ideal regression line y = cx with slope c equal to unity.

energies amounts to 5.8 kcal/mol (relative error of 5.9%). For the subset of 25 anions, the rmsd is 4.7 kcal/mol, but it amounts to 6.9 kcal/mol for the 22 cations. On the basis of this finding, one might be tempted to use different scaling factors to build up the solute cavity for anions and cations. However, the larger rmsd found for cations mainly arises from deviations in protonated R-O-R' (methanol, ethanol, dimethyl ether, diethyl ether) and R-CO-R' (acetone, methyl phenyl ketone, methyl ethyl ester) groups, which have relative errors of  $\geq 10\%$ . When these compounds are excluded, the rmsd for the subset of cations (3.6 kcal/mol) is similar to that found for anions. It is not clear whether the notable deviation found for these compounds might stem from short-range interactions with hydrating water molecules not properly accounted for in the continuum model. If we keep in mind the limited availability of accurate  $\Delta G_{\text{hyd}}$  values for ionic compounds and the assumptions intrinsic to the continuum method, it seems to us not justified, at least on the basis of the present results, to use different scaling factors for anions and cations, a procedure already used in the context of solvation calculations of ion hydration carried out by using the Born equation.<sup>39</sup> Likewise, attempts to reduce these errors by distinct reshaping of solute cavities does not seem justified and might even yield to nonphysical overtrained models.

An alternative strategy to reduce the difference between computed and experimental data involves the adjustment of the atomic surface tensions,  $\xi_i$  (see eq 6), which in the MST model are typically determined by fitting the experimental free energies of solvation. Because steric terms are used in continuum models to account implicitly for effects other than pure bulk electrostatic effects, the fitted parameters for neutral and charged molecules might not be equal. Accordingly, one can expect that restricting the refinement of the surface tensions only to the atom(s) bearing the formal charge would suffice to improve the agreement between calculated and experimental  $\Delta G_{\text{hyd}}$  values. From a practical point of view, caution is required owing to the limited availability of data for certain atom types, which can lead to overtraining of the method. Thus, the only statistically significant improvement was obtained when the surface tension of the OH+ group was adjusted to -0.51 kcal mol<sup>-1</sup> Å<sup>-2</sup>, which is nearly 4× more negative than the corresponding value for neutral molecules ( $-0.14 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ ). 8d With only the correction of this surface tension, the rmsd between calculated and experimental  $\Delta G_{\text{hyd}}$  values is 4.6 kcal/mol.

TABLE 2: Electrostatic and Non-Electrostatic Contributions (kcal/mol) to the Free Energy of Hydration Determined from MST-HF/6-31+G\* Calculations for the Series of Univalent Ions Used in the Parametrization $^a$ 

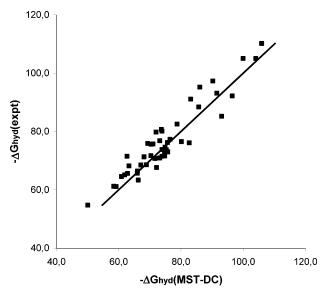
ion	$\Delta G_{ m ele}$	$\Delta G_{ m n-ele}$	$\Delta G_{\rm hyd}$ (MST-DC)	exptl <sup>b</sup>
F-	-101.7	1.7	-99.9	-105.0
Cl-	-75.4	0.5	-74.8	-74.6
OCl-	-76.1	2.4	-73.7	-80.7
$OH^-$	-104.1	0.1	-104.0	-105.0
$\mathrm{HO_2}^-$	-92.5	2.3	-90.2	-97.3
$\mathrm{NH_2}^-$	-96.8	0.3	-96.5	-92.2
CN-	-75.0	2.9	-72.1	-67.6
HCC-	-81.9	-0.8	-82.7	-76.1
$\mathrm{CH_{3}O^{-}}$	-88.8	2.7	-86.0	-95.2
CH <sub>3</sub> CH <sub>2</sub> O <sup>-</sup>	-86.1	3.0	-83.1	-91.1
$C_6H_5O^-$	-70.9	2.8	-68.1	-71.3
$HCOCH_2^-$	-73.5	2.5	-71.0	-75.7
CH <sub>3</sub> COCH <sub>2</sub> <sup>-</sup>	-73.0	2.6	-70.4	-75.6
HCOO-	-79.8	4.1	-75.7	-76.2
CH <sub>3</sub> COO <sup>-</sup>	-80.7	4.2	-76.5	-77.3
CH <sub>2</sub> COOEt-	-70.0	4.0	-66.0	-66.4
CH <sub>3</sub> CONH <sup>-</sup>	-76.4	2.5	-73.9	-80.1
$N_3^-$	-71.9	0.3	-71.6	-70.7
CH <sub>2</sub> CN <sup>-</sup>	-69.6	3.6	-66.0	-65.7
CH <sub>3</sub> CHCN <sup>-</sup>	-67.1	4.3	-62.8	-65.6
CH <sub>2</sub> NO <sub>2</sub> <sup>-</sup>	-73.5	4.2	-69.3	-75.9
HS <sup>-</sup>	-76.5	1.8	-74.8	-71.6
$CH_3S^-$	-76.2	0.9	-75.3	-73.7
$C_6H_5S^-$	-67.4	1.1	-66.3	-63.3
$CH_3SO_3^-$	-76.4	6.1	-70.3	-71.7
$H_3O^+$	-106.3	0.4	-105.9	-110.2
$CH_3OH_2^+$	-84.7	-6.9	-91.5	-93.1
$CH_3CH_2OH_2^+$	-79.1	-6.6	-85.7	-88.4
$(CH_3)_2OH^+$	-68.9	-3.2	-72.0	-79.8
$(Et)_2OH^+$	-60.1	-2.6	-62.6	-71.5
$NH_4^+$	-93.7	0.6	-93.1	-85.2
$CH_3NH_3^+$	-81.3	1.2	-80.2	-76.5
$(CH_3)_2NH_2^+$	-70.6	1.7	-68.9	-68.6
$(CH_3)_3NH^+$	-60.7	2.3	-58.4	-61.2
CH <sub>3</sub> CH <sub>2</sub> NH <sub>3</sub> <sup>+</sup>	-77.2	1.5	-75.8	-73.0
$(Et)_3NH^+$	-53.1	3.1	-50.0	-54.7
n-PrNH <sub>3</sub> <sup>+</sup>	-75.2	2.0	-73.2	-70.9
n-BuNH <sub>3</sub> +	-75.6	1.7	-73.9	-71.5
$C_6H_5NH_3^+$	-76.1	1.4	-74.7	-72.8
(CH <sub>3</sub> COCH <sub>3</sub> )H <sup>+</sup>	-67.6	-5.6	-73.2	-76.8
(PhCOCH <sub>3</sub> )H <sup>+</sup>	-56.8	-5.2	-61.9	-65.1
(CH <sub>3</sub> COOEt)H <sup>+</sup>	-63.1	-4.0	-67.1	-68.5
HCONH <sub>3</sub> <sup>+</sup>	-79.4	0.6	-78.7	-82.5
CH <sub>3</sub> CONH <sub>3</sub> <sup>+</sup>	-74.7	0.8	-73.9	-73.8
$C_5H_5NH^+$	-60.5	1.3	-59.2	-61.1
$(CH_3)_2SH^+$	-63.5	2.6	-60.9	-64.5
(CH <sub>3</sub> SOCH <sub>3</sub> )H <sup>+</sup>	-64.9	1.6	-63.3	-68.2

<sup>a</sup> The electrostatic term was determined by using a scaling factor of 1.15 and the DC charge renormalization scheme. The experimental hydration free energies are also given. <sup>b</sup> Data taken from ref 19.

The calculated  $\Delta G_{\rm hyd}$  and its electrostatic and non-electrostatic components determined for the univalent anions are given in Table 2. With the exception of the protonated R-O-R' and R-CO-R' groups (see preceding discussion), the non-electrostatic term is generally positive and only amounts, on the average, to 3.9% of the hydration free energy. Overall, there is satisfactory agreement between experimental and calculated  $\Delta G_{\rm hyd}$  values, as noted in a relative error of 4.7%, and in the comparison of the regression equation given in eq 14 (see Figure 3), especially keeping in mind the variety of functional groups and sizes of the ionic compounds.

$$\Delta G_{\text{hyd}}(\text{exp}) = 1.019(\pm 0.008) \Delta G_{\text{hyd}}(\text{MST-DC})r = 0.94F = 351.0 (14)$$

**Prediction of pK**<sub>a</sub> Values. Because the acidity/basicity of molecules is crucial to understanding chemical reactivity and



**Figure 3.** Comparison of the experimental and calculated hydration free energies (kcal/mol) for the series of univalent ions. Theoretical estimates were obtained from MST-HF/6-31+G(d) calculations carried out by using a scaling factor of 1.15 and the DC charge renormalization schemes. The plot displays the ideal regression line y = cx with slope c equal to unity.

intermolecular interactions, an intense research effort has been devoted to checking the reliability of theoretical methods, particularly QM SCRF continuum methods, to accurately predict the p $K_a$ . Thus, Chen et al. were able to predict the p $K_a$  values for several molecules by using a model where the reaction potential was solved via finite-difference solutions to the Poisson—Boltzmann equation. 25c For a small series of imidazole derivatives, Topol et al. predicted  $pK_a$  values with an average absolute deviation of 0.8 units from experimental data by combining results obtained from Gaussian-2 (G2) or density functional calculations with SCRF estimates of the hydration free energies.<sup>25d</sup> Schüürmann et al. estimated the acidities of carboxylic acids by using the PCM-UAHF model at the SCF and MP2 levels, obtaining good correlations for relative  $pK_a$ values but not for the absolute ones, arguing that the major sources of error stem from gas-phase calculations.<sup>40</sup> Recently, Shields and co-workers predicted accurate absolute  $pK_a$ 's for carboxylic acids<sup>41</sup> and phenols<sup>42</sup> using the C-PCM model along with state-of-the-art gas-phase ab initio calculations. Chen and MacKerell compared  $pK_a$  differences in substituted pyridines by using semiempirical and ab initio gas-phase free energies along with IPCM, SCIPCM, and SM2 solvation calculations, and relevant differences between the  $pK_a$  values obtained at different levels of theory were found.<sup>43</sup> By using the SSC(V)-PE model, Chipman checked different isodensity thresholds to build up cavities in order to predict the  $pK_a$ 's for alcohols, acids, and amines.<sup>38b</sup> This study showed that no single isodensity contour can be applied to neutral compounds, anions, and cations and that good correlations can be obtained only for compounds sharing the same acidic functional group. Other studies also have pointed out the difficulty of predicting absolute  $pK_a$  values, which demand highly accurate estimates of both the gas-phase free energy difference between acid and base partners and the corresponding solvation free energies.<sup>44</sup>

To assess the performance of the MST parametrization for ionic compounds, we have determined the  $pK_a$  values for a series of carboxylic acids and substituted pyridines by using the thermodynamic cycle shown in Figure 4 and eq 15. These compounds were chosen because of the availability of experimental data for the gas-phase basicities.  $^{45,46}$  For consistency with

Figure 4. Thermodynamic cycle used for the calculation of the  $pK_a$ values for the series of substituted pyridines and carboxylic acids.

the MST parametrization, the experimental  $\Delta G_{\text{sol}}(H^+)$  value determined by Tissandier<sup>17</sup> was used. The hydration free energies of the neutral species were calculated by using the HF/ 6-31G(d) version of the MST model.8d Finally, to further compare the effect of the charge normalization scheme, both MST-SC and MST-DC calculations were performed for ionic compounds.

$$pK_a = -\log K_a = \Delta G_{aq}/2.303RT$$
 (15)

Table 3 shows the results obtained for the two series of compounds, which encompasses a range of  $pK_a$  values larger than 5 units. Comparison of the results obtained by using the two charge renormalization schemes supports the better performance of the DC procedure. Thus, whereas both MST-SC and MST-DC methods give rise to similar relative  $pK_a$  variations within the series of compounds (the rmsd between calculated and experimental  $pK_a$  differences varies between 0.4 and 1.2  $pK_a$  units), the absolute  $pK_a$  values determined from MST-DC computations are in better agreement (in absolute terms) with the experimental values, as noted in rmsd's (in  $pK_a$  units) of 1.0 (MST-DC) and 2.4 (MST-SC) for carboxylic acids and of 1.9 (MST-DC) and 3.2 (MST-SC) for substituted pyridines.

If the two series of compounds are taken together, the rmsd of the  $pK_a$  values predicted from MST-DC calculations amount to 1.6 p $K_a$  units. This uncertainty can be mainly ascribed to the error in the hydration free energy of the ionic species, because the difference between calculated and experimental hydration free energies for neutral compounds (experimental  $\Delta G_{
m hyd}$ available for acetic acid is -6.8 kcal/mol; pyridine, -4.7 kcal/ mol; and 4-methylpyridine, -4.9 kcal/mol) is less than 0.5 kcal/ mol. Chen and McKerell reported rmsd values ranging from 1.22 to 4.14 p $K_a$  units depending on the method used to compute the solvation free energy (see preceding text). For carboxylic acids alone, standard deviations of 0.4 pKa units have been reported by using complete basis set models in conjunction with C-PCM calculations.<sup>41</sup> However, accurate estimates of  $pK_a$ values (i.e., with an error of one-half  $pK_a$  unit) are typically obtained by means of an empirical fitting of the experimental  $pK_a$  values. 44b-d In the absence of those empirical adjustaments, the  $pK_a$  values determined from MST-DC calculations compare satisfactorily with the experimental ones, thus giving support to the computational strategy used here to refine the MST method for the hydration of ionic compounds.

Zwitterion-Neutral Equilibria. Because of the high anisotropy in the charge distribution of zwitterions, the equilibrium between neutral and charge-separated forms is particularly wellsuited to examining the effect of the charge renormalization scheme within the framework of the MST model. To this end, we have examined the equilibrium between neutral and zwitterionic forms of nicotinic and isonicotinic acids (see Figure 5), a system that was previously studied by Nagy et al.<sup>47</sup> In their study, the free energy of tautomerization in water was

Figure 5. Representation of the neutral and zwitterionic species of nicotinic (top) and isonicotinic (bottom) acids.

determined by adding the relative free energies of hydration to the gas-phase free energy difference between neutral and zwitterionic species. This latter quantity was estimated from calculations carried out at the MP2/6-311++G(d,p) level and subsequently corrected from zero-point energy, thermal, and entropy corrections determined at the MP2/6-31G(d). At this level, the neutral forms are predicted to be favored by 33-35 kcal/mol in the gas phase. To determine the relative stability of tautomers in water, we adopted the relative gas-phase stabilities determined by Nagy et al., while the hydration free energies of the neutral species were determined from MST/HF6-31G(d) calculations<sup>8d</sup> and those of the zwitterionic compounds were obtained from both MST-SC and MST-DC calculations.

Table 4 reports the hydration free energies of the neutral and zwitterionic species as well as the predicted tautomerization free energy ( $\Delta G_t$ ) in water. As was found for the calculated p $K_a$ values, the results obtained from MST-DC computations are in better agreement with the experimental data than those determined from MST-SC calculations. Thus, whereas both neutral and zwitterionic forms of nicotinic acid are predicted to have similar stability in water from MST-SC calculations, the neutral form is predicted to be destabilized by around 2.8 kcal/mol according to MST-DC results, which agrees with the observed preference of the zwitterion in aqueous solution by around 2.0 kcal/mol. With regard to the isonicotinic acid, the MST-SC method again predicts the neutral form to be preferred in water, whereas the opposite trend is found from MST-DC calculations, which predict the zwitterion to be more stable by 1.7 kcal/mol, in agreement also with the experimental data.

**Solvent Reaction Field in SC and DC Schemes.** The whole of the preceding results support the better performance of the DC charge renormalization scheme for predicting the hydration free energy of ionic compounds. This finding agrees with the results obtained from the analysis of the fractional contributions of specific groups to the hydration free energy within a series of congeneric alkane derivatives, 48 because the DC scheme was found to consistently yield more transferable group contributions than the SC scheme.

To gain further insight into the origin of the differences noticed between both SC and DC charge renormalization schemes, we have compared a series of electrostatic properties determined by using the wave function of the fully hydrated solute for a small subset of charged monosubstituted alkane derivatives (CH<sub>3</sub>X and CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>X, with X being NH<sub>3</sub><sup>+</sup>, OH<sub>2</sub><sup>+</sup>, NH<sup>-</sup>, and O<sup>-</sup>). This series of compounds is well-suited to our purposes, because (i) the enlargement of the side chain is expected to play a relatively small perturbing effect on the hydration of the X unit, and (ii) this allows us to concentrate on the differences in the solvent reaction field around the X group. To this end, we have computed the rmsd between the electrostatic potential at selected points in four layers around

TABLE 3: Calculated and Experimental  $pK_a$  Values for a Series of Substituted Pyridines and Carboxylic Acids<sup>a</sup>

compound	$\Delta G_{ m gas}$ $^b$	$\Delta G_{ m sol}({ m A})$	$\Delta G_{\rm sol}({\rm AH^+})~({\rm SC})$	$pK_a$ (SC) <sup>c</sup>	$\Delta G_{\rm sol}({\rm AH^+})~({\rm DC})$	$pK_a$ (DC) <sup>c</sup>	$pK_a (exptl)^d$
			Pyridin	e Derivatives			
Н	213.7	-4.9	-58.2	2.2	-59.2	2.9	5.2
	2100		<b>7</b> 40	0.0		0.0	0.0
p-CH <sub>3</sub>	218.0	-5.3	-54.9	2.6	-56.2	3.6 0.7	6.0
m-CH <sub>3</sub>	216.6	-5.2	-55.1	0.4 1.8	-56.7	3.0	0.8 5.7
m-C113	210.0	3.2	33.1	-0.4	30.7	0.1	0.5
m-F	206.7	-3.5	-61.2	0.3	-62.3	1.1	3.0
				-1.9		-1.8	-2.2
p-Cl	210.4	-3.9	-59.4	1.4	-60.8	2.4	3.8
				-0.9		-0.5	-1.4
m-Cl	207.5	-4.0	-60.0	-0.3	-61.4	0.7	2.8
o-OCH <sub>3</sub>	220.9	-4.9	-52.9	-2.5 3.6	-54.5	-2.3 $4.8$	-2.4
0-ОСП3	220.9	-4.9	-32.9	1.4	-34.3	4.8 -1.9	6.6 1.4
m-OCH <sub>3</sub>	216.7	-4.6	-54.2	1.7	-55.9	2.9	4.8
00115	210.7		5 <u>2</u>	-0.5	00.7	0.0	-0.4
p-CN	202.5	-5.5	-64.4	-1.9	-67.8	0.6	1.9
				-4.1		-2.3	-3.4
m-CN	201.7	-6.1	-65.5	-2.2	-69.0	0.4	1.4
NO	200.2	5.4	66.4	-4.4	<b>60.0</b>	-2.5	-3.9
m-NO <sub>2</sub>	200.2	-5.4	-66.4	-2.1 -4.3	-69.8	$0.4 \\ -2.5$	-4.0
$mse^e$				-3.2		-1.8	4.0
11130				-0.2		0.5	
rmsd				3.2		1.9	
				0.4		0.8	
			Carbo	oxylic Acids			
formic	336.5	-7.1	-76.2	2.5	-75.7	2.9	3.8
				0.0		0.0	0.0
acetic	339.5	-6.8	-78.6	2.7	-76.5	4.3	4.8
	221.0	0.4	67.1	0.2	((1	1.4	1.0
cyanoacetic	321.8	-9.4	-67.1	$0.1 \\ -2.4$	-66.1	0.9 -2.0	2.5 -1.3
chloroacetic	327.0	-8.3	-68.7	1.9	-69.0	1.7	2.9
emoroacette	327.0	0.5	00.7	-0.6	07.0	-1.2	-0.9
pivalic	335.9	-4.7	-75.5	0.8	-69.8	5.0	5.0
1				-1.7		2.1	1.2
mse				-2.2		-0.8	
				-0.2		-0.3	
rmsd				2.4		1.0	
				1.2		0.6	
			All C	Compounds		1 7	
mse				-2.9		-1.5	
rmsd				-0.2 3.0		0.3 1.6	
				5.0		1.0	

 $<sup>^</sup>a$  MST calculations have been performed by using both SC and DC charge renormalization methods. Absolute and relative p $K_a$  values are given in Roman and in italics, respectively.  $^b$  Data taken from refs 45 and 46.  $^c$  A correction term of 1.9 kcal/mol was added to the gas-phase free-energy difference to account for the change in standard states at 298.15 K.  $^d$  Values taken from ref 50.  $^e$  rms: root-mean-square deviation. mse: mean signed deviation.

TABLE 4: Calculated and Experimental Free Energies of Tautomerization between Neutral and Zwitterionic Forms of Nicotinic (NA) and Isonicotinic (INA) Acids<sup>a</sup>

compound	$\Delta G_{ m gas}{}^b$	$\Delta G_{ m sol}({ m A})$	$\Delta G_{\rm sol}({\rm AH^+})~({\rm SC})$	$\Delta G_{\mathrm{aq}}\left(\mathrm{SC}\right)$	$\Delta G_{\rm sol}({\rm AH^+})~({\rm DC})$	$\Delta G_{\rm aq}$ (DC)	$\Delta G_{ m aq}({ m exptl})^b$
NA (A)	33.3	-9.3	-42.6	0.0	-45.3	-2.7	-2.0
(B)	33.5	-9.0	-42.6	0.0	-45.3	-2.7	
INA	35.1	-8.6	-42.1	1.6	-45.4	-1.7	-2.5

<sup>&</sup>lt;sup>a</sup> MST calculations were performed by using both SC and DC charge renormalization methods. <sup>b</sup> Data taken taken from ref 47.

the molecule. For our purposes here, such a comparison was performed by including exclusively those points generated by scaling the atomic radii of atoms in group X. Moreover, we have determined the well depth  $(E_{\min})$  of the molecular interaction potential<sup>49</sup> in the vicinity of group X for the solutes interacting with classical probe particles O<sup>-</sup> (cations) and H<sup>+</sup> (anions). Finally, the results are examined in light of the solvent's net apparent charge  $(Q_{\sigma})$  induced on the surface

elements spread on the portion of the cavity created from group X. The results are shown in Table 5.

Not unexpectedly, there is close similarity in the results obtained from the two charge renormalization schemes for CH<sub>3</sub>-NH<sub>3</sub><sup>+</sup> and CH<sub>3</sub>OH<sub>2</sub><sup>+</sup>. However, there are notable differences when the largest members of the congeneric series, CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>-NH<sub>3</sub><sup>+</sup> and CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>OH<sub>2</sub><sup>+</sup>, are considered. Thus, the electrostatic potential around group X is more positive when the DC

TABLE 5: Differences in the Electrostatic Potential Computed in Layers around the Molecule, the Well Depth of the Molecular Interaction Potential, and the Net Apparent Charge Induced on the Cavity Surface for a Series of Congeneric Ionic Compounds

		rmsd <sup>a</sup> in layer			$E_{\min}^{\ \ b}$		$Q_{\sigma}(\mathrm{X})^c$		
compound	X	×1.4	×1.6	×1.8	×2.0	MST-SC	MST-DC	MST-SC	MST-DC
CH <sub>3</sub> NH <sub>3</sub> <sup>+</sup>	NH <sub>3</sub> <sup>+</sup>	0.0	0.0	0.0	0.0	-123.8	-123.8	-0.71	-0.71
$CH_3(CH_2)_6NH_3^+$	$NH_3^+$	2.1	1.8	1.6	1.4	-118.6	-121.5	-0.53	-0.65
CH <sub>3</sub> OH <sub>2</sub> <sup>+</sup>	$OH_2^+$	0.5	0.4	0.3	0.3	-130.1	-129.7	-0.57	-0.59
$CH_{3}(CH_{2})_{6}OH_{2}^{+}$	$\mathrm{OH_2}^+$	3.6	3.0	2.5	2.2	-127.1	-127.5	-0.39	-0.53
CH <sub>3</sub> NH <sup>-</sup>	$NH^{-}$	6.6	5.5	4.4	3.7	-187.6	-192.3	+0.91	+0.78
$CH_3(CH_2)_6NH^-$	$NH^-$	1.6	1.3	1.1	0.9	-190.6	-190.6	+0.79	+0.72
CH <sub>3</sub> O <sup>-</sup>	$O_{-}$	0.9	0.8	0.6	0.5	-169.6	-168.5	+0.81	+0.77
$CH_3(CH_2)_6O^-$	$O_{-}$	0.6	0.5	0.5	0.4	-168.2	-168.2	+0.76	+0.75

a rmsd between the electrostatic potentials computed from the wave functions determined from MST-SC and MST-DC calculations for the ionic compounds. Layers defined by scaling the van der Waals radii by 1.4, 1.6, 1.8, and 2.0. Minimum energy of the molecular interaction potential for the ionic compounds interacting with classical probe particles O<sup>-</sup> (cations) and H<sup>+</sup> (anions). <sup>c</sup> Net apparent charge spread on the cavity surface of group X determined from both SC and DC charge renormalization schemes.

scheme is used, which reflects the more negative apparent charge induced on the cavity surface around the NH<sub>3</sub><sup>+</sup> and OH<sub>2</sub><sup>+</sup> groups. In fact, by enlarging the size of the side chain, there is a reduction of 25–32% in  $Q_{\sigma}(X)$  when the SC scheme is used, which is notably larger than the 8-10% variation found for the DC results.

For anions, the differences between the two charge renormalization schemes are clear even for the parent anions, CH<sub>3</sub>NH<sup>-</sup> and CH<sub>3</sub>O<sup>-</sup>, and tend to decrease as the size of the ionic compound is enlarged. This is particularly true for the former anion, CH<sub>3</sub>NH<sup>-</sup>, where the solvent apparent charge determined in the SC scheme ( $Q_{\sigma}(NH^{-}) = +0.91$ ) is sensibly larger than that obtained in the DC formalism  $(Q_{\sigma}(NH^{-}) =$ +0.78). A detailed inspection of the results reveals that such a difference stems from the solvent reaction field created in the portion of the cavity associated to the hydrogen atom. Thus, when the DC scheme is used, the solvent reaction field is mainly concentrated in the surface elements pertaining to the nitrogen atom, giving rise to an apparent charge of +0.80, whereas the apparent charge on the portion of the cavity created by the hydrogen atom is only -0.02. In contrast, when the SC scheme is considered, both nitrogen and hydrogen atoms contribute markedly to the solvent reaction field, as noted in the apparent charges of +0.69 and +0.22, respectively. This different distribution of the reaction field in the surroundings of the NH group gives rise to differences in the electrostatic properties of the solute (see Table 5), leading in turn to different solutesolvent interaction energy.

In summary, the preceding results clearly point out that the explicit treatment of anisotropy in the charge distribution leads to subtle, but nonnegligible, differences in the solvent reaction field, which in turn might modulate the calculation of the solvent-induced change in the solute's properties, as noted in the case of the group contributions to the solvation free energy.<sup>48</sup>

# **Concluding Remarks**

A satisfactory agreement between predicted and experimental hydration free energies of univalent ions can be obtained by means of a simple, conservative adjustment in the definition of the cavity used to obtain the electrostatic contribution within the framework of the MST model. Such a refinement implies a reduction in the cavity of 8% relative to the standard scaling used for neutral species and is limited to the atom(s) that bear the formal charge. This allows us to retain the original simplicity of the approach and to exploit the same set of scaling factors that modulate the cavity definition for the calculation of the electrostatic term in the MST model.

The results point out the need to explicitly account for the anisotropies in the charge distribution of ionic species in order to correct the effects due to the solute's charge density that lies outside the cavity. The explicit consideration of the anisotropy in the charge distribution of the ionic compounds leads to a subtle, but nonnegligible, improvement in the calculated electrostatic component of the hydration free energy. Moreover, it also modulates the magnitude of the solvent reaction field, which in turn influences the solvent-induced change in the solute's properties. On the other hand, the IEF values are very close to and exhibit high correlation with the MST-DC results, which are, on the average, around 2% larger (in absolute value) than the hydration free energies determined by using the IEF formalism. Therefore, these findings point out that the optimized cavities should be largely transferable between the two computational schemes.

The optimized MST-DC method leads to an average relative error of 4.7% in the hydration free energy for the series of univalent ions containing a variety of functional groups and molecular sizes. The basic strategy proposed here is still open to further refinement, at least for the prediction of the hydration free energy, through the adjustment of the atomic surface tensions used for the charged atoms. However, this refinement would require the existence of a larger database of experimental values to avoid overtrained models than can fail when applied to compounds very different to those used in the parametrization of the model. In any case, the robustness of the strategy is supported by the results obtained for the absolute and relative  $pK_a$ 's of carboxylic acids and substituted pyridines, as well as for the tautomeric equilibrium between neutral and zwitterionic forms of nicotinic and isonicotinic acids. These examples suffice to point out that the MST model can be used confidently to measure the magnitude of the solvent influence of chemically relevant properties and to use this continuum method as an interpretative tool able to gain insight into the influence of solvation on chemical processes of ionic species.

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