

## Reply to Comment on “Electrostatic Potentials and Free Energies of Solvation of Polar and Charged Molecules”

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Calculation of single-ion free energies of solvation<sup>1</sup> requires careful treatment of electrostatic interactions. In computer simulations of ion solvation, only a finite number of solvent molecules are considered. To mimic an infinite system, periodic boundary conditions are generally employed. Ewald summation provides a consistent means to calculate electrostatic interactions under periodic boundary conditions. However, if an interaction cutoff is used instead, many additional details become relevant.<sup>2</sup> We recently concluded that application of an interaction cutoff between a solute ion and solvent water based on a molecular center of water induces an artificial surface dipole density at the cutoff sphere.<sup>3</sup> Ashbaugh and Wood independently came to the identical conclusion.<sup>4</sup> Both studies showed that this leads to artificial dependences on the choice of a molecular center. These studies also verify that the electrostatic potential at the center of a neutral Lennard-Jones particle in water is positive.<sup>3,5–8</sup> Åqvist and Hansson<sup>9</sup> had previously obtained a negative potential based on the choice of the water–oxygen atom as a molecular center.

The Comment by Åqvist and Hansson<sup>10</sup> acknowledges that center dependences of electrostatic potentials are undesirable. The Comment then attempts to correct the value obtained previously<sup>9</sup> for the electrostatic potential at the center of a neutral Lennard-Jones particle in water. However, the Comment also proposes a “unique” molecular center that presumably should give the correct result. In the following, we show how that particular choice of center leads to incorrect results. In doing so, we rederive the correction terms calculated before on a considerably more complicated basis by Ashbaugh and Wood<sup>4</sup> for a special case and in the Comment. These considerations do not change the fundamental point made in our paper<sup>3</sup> that electrostatic potentials should be based upon charge densities and boundary conditions for solutions of the Poisson equation and should be independent of the choice of a molecular center.

Consider a neutral system confined to a finite region of an infinite volume so that electrostatic potential fields may be computed by summation of elementary Coulomb fields due to finite charge elements. In addition, consider the special case

where the system may be treated as an ideal gas. The average electrostatic potential  $\Delta\phi$  at any point in a homogeneous ideal gas of isotropic water molecules should be zero since the mean charge density is identically zero. We will show below that the choice of a molecular center as proposed in the Comment leads to a nonzero average potential in this ideal gas system. That average potential is a generalization of the correction obtained by Ashbaugh and Wood<sup>4</sup> using a different procedure, for the special case of an oxygen atom center, and also in the Comment by Åqvist and Hansson.<sup>10</sup> Note, however, that the Comment simplifies the geometry of the solvent water molecules to a linear dipole with the hydrogen partial charges collapsed onto the hydrogen bisector.

When molecular centers are used, we can calculate the average potential from the potential  $\varphi(\mathbf{r})$  created by individual solvent molecules. After averaging isotropically over all orientations about the center, the potential of a molecule depends only on the distance  $r = |\mathbf{r}|$  from its center. The average potential inside the system volume is then

$$\Delta\phi = \rho \int d\mathbf{r} \varphi(r) \quad (1)$$

where  $\rho$  is the number density of the ideal gas of solvent molecules. The potential  $\varphi(r)$  of a molecule that rotates isotropically around a fixed center can be calculated easily, because the isotropic rotation leads to concentric shells of charge. The potential of a spherical shell with radius  $R$  of a homogeneously distributed charge  $q$  is constant,  $q/R$ , inside and  $q/r$  outside the shell. For a water molecule with three charge sites on the oxygen atom and the two hydrogen atom positions, we find (using Gaussian units for the electrostatics)

$$\varphi(r) = \begin{cases} 2q_H/R_H + q_O/R_O & \text{for } r < R_O \\ 2q_H/R_H + q_O/r & \text{for } R_O < r < R_H \\ 0 & \text{for } R_H < r \end{cases} \quad (2)$$

where  $q_O$  and  $q_H$  are the partial charges on the oxygen and hydrogen atoms, respectively, with  $q_O = -2q_H$ ;  $R_O$  and  $R_H$  are the distance of the center from oxygen and hydrogen atoms, respectively, where the center is assumed to be on the symmetry axis of the molecule and  $R_H \geq R_O$ . (Those assumptions can easily be relaxed.) Integration then leads to an average potential

$$\Delta\phi = \frac{4\pi\rho}{3} q_H (R_O^2 - R_H^2) \quad (3)$$

or for a general neutral molecule with charges  $q_\alpha$  at distance  $R_\alpha$  from the center

$$\Delta\phi = -\frac{2\pi\rho}{3} \sum_{\alpha} q_{\alpha} R_{\alpha}^2 \quad (4)$$

This is exactly the contribution derived by Wilson et al.,<sup>2</sup> to correct for center dependences in calculations of surface potentials. What is more, eq 3 corresponds exactly to the result eq 6b found by Ashbaugh and Wood<sup>4</sup> on the basis of a more elaborate calculation, for the special case of a water–oxygen center ( $R_O = 0$ ). This is also the correction obtained in the Comment.<sup>10</sup> Equation 1 of the Comment corresponds to the case of  $R_O = g$ ; eq 7 of the Comment is the result for a “dipolar” molecule with the hydrogen charges collapsed onto the hydrogen bisector, corresponding to  $R_O = g$  and  $R_H = h_2$  in our eq 3

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using their notation. Equation 3 yields  $e\Delta\phi = -19.001$  kcal/mol for an oxygen center and SPC<sup>11</sup> water parameters; for the center proposed in the Comment,<sup>10</sup> we obtain  $e\Delta\phi = -12.667$  kcal/mol ( $e$  is the elementary charge), in agreement with the value of 12.7 kcal/mol calculated numerically in the Comment.

We note that  $\Delta\phi$  is nonzero even though each spherical shell of isotropic water molecules *far* from the observation point gives zero contribution. For shells close to the observation point, isotropically rotated water molecules overlap with the observation point, giving a nonzero contribution. We also point out that our approach is formally identical to those followed by Wilson et al.<sup>2</sup> as well as Ashbaugh and Wood.<sup>4</sup> Those approaches used the induced charge density to calculate  $\Delta\phi$ , which for a solute is nonzero near the cutoff  $R_c$  if a molecule-based cutoff is used.

Now that we have clarified the correction sought for the molecule-center-based calculations, we can go back to analyze the results and claims of the Comment. Given the foregoing, we regard the following claims in the Comment as incorrect: (1) that the quadrupole moment of water need not be considered for the center correction where, in fact, the correction eq 4 is proportional to the center-dependent trace of the quadrupole tensor;<sup>2</sup> (2) that the result of the Comment establishes an error in the analysis of Ashbaugh and Wood;<sup>4</sup> (3) that subtraction of  $\Delta\phi_{\text{AH}}$ , as defined in eq 1 of the Comment, from a *charge-based* potential  $\phi_q$  gives the correct potential, thereby subtracting from  $\phi_q$  the contributions of all partial charges within  $R_c$  belonging to molecules with centers within a spherical shell  $R_c - h < r < R_c + h$  (where  $R_c$  is the cutoff and  $h$  is the distance of the partial charge farthest from the molecular center). Correspondingly, the Comment's "corrected" result,

$$\phi_{\text{AH}} = \phi_q - \Delta\phi_{\text{AH}} = \phi_{\text{M}}(R_c - h) \quad (5)$$

corresponds to the result  $\phi_{\text{M}}(R_c - h)$  of applying a molecule-center-based cutoff  $R_c - h$ . A claim that  $\Delta\phi_{\text{AH}} = \phi_q - \phi_{\text{M}}(R_c - h)$  is center-independent is incorrect. For large values of the cutoff parameter  $R_c$  each of the terms in eq 5 will be insensitive to  $R_c$ . But the first and third terms will be center-dependent. The result quoted in the Comment ( $e\Delta\phi_{\text{AH}} = 12.7$  kcal/mol) corresponds specifically to a center halfway between the oxygen atom and the hydrogen bisector. For this and other centers, we can use eq 3 avoiding the numerical integration of the Comment.

How does the Comment identify a "unique" center for the calculation of these electrostatic potentials? It determines the correction  $\Delta\phi$  for a linear dipole with a partial charge  $q_{\text{O}}$  located at the oxygen atom and a partial charge  $2q_{\text{H}}$  at the H-H bisection point. Using our eq 4 or their eq 7, we can see that the correction would be zero for a molecular center chosen halfway between the two charges. This is a simplification of the actual water molecule geometry. The potential correction for (nonlinear) three- or four-site water molecules will be different.

For the geometry of the particular molecular model used, there is a choice that would give the value *zero* as the correction for center dependence: that is the point equidistant from the water oxygen and hydrogen sites of the particular water model ( $R_{\text{O}} = R_{\text{H}}$ ). Unfortunately, for molecules with different symmetry such centers cannot be identified in general. For instance, no such center exists for a linear triatomic molecule such as hydrogen cyanide, HCN. Any such center would have to satisfy that each spherical shell around the center is neutral for the isolated molecule.

For three-site water models, one can construct many other reasonable but incorrect centers, one of which has been proposed in the Comment. As the symmetry of the molecule is reduced and the complexity increased, construction of such reasonable but incorrect centers becomes impossible. For complex molecules, no symmetric point exists at which the extended dipole moment could be positioned. Accordingly, the Comment does not give a general recipe for more realistic models of water (or, e.g., whole proteins, etc.) with many charge sites, spatially extended charge distributions, polarizabilities, or internal flexibility.

We point out that center dependences in molecule-based potential calculations arise not only from molecules at the cutoff but also from the artificial center-based ordering of charges in the first solvation shell around the solute. This can be seen clearly in Figure 2 of ref 3: For a center close to the oxygen, the first shell gives a negative potential; for centers closer to the hydrogens, the potential contribution of the first shell is less negative. That center dependence persists to the cutoff because the water molecules of the second shell and beyond give only small additional contributions, as they are almost isotropically oriented around an uncharged spherical solute.

We emphasize that electrostatic potentials have to be measured with respect to a reference value. The average potential in an homogeneous ideal gas of isotropically oriented polar molecules provides that reference point. In a charge-based scheme, electrostatic potentials are determined by integration over charge densities. Charge-based integration readily gives a zero potential for the ideal gas. When charges are grouped together as molecules, and spherical cutoffs are applied, the average calculated potential in the ideal gas is in general nonzero. This leads to a simple correction that depends on the particular choice of the center used for the molecule-based cutoff.

In summary, the "unique" center identified in the Comment has a nonzero correction for center dependence. The potentials calculated based on that center are too negative.  $e\Delta\phi = -12.667$  kcal/mol should be subtracted from the result given in the Comment, and  $-19.001$  kcal/mol should be subtracted from the previous results<sup>9</sup> of Åqvist and Hansson. The center recommended in the Comment corresponds to the point halfway between the oxygen atom and the hydrogen bisector. That center would give a zero potential correction only if water were a linear dipole with the hydrogen charges collapsed onto the hydrogen bisector. Centers that do not require a correction are equidistant from the oxygen and hydrogen atoms. For general molecules, in particular whole proteins or even amino acid residues, such centers cannot be found. We recommend again, as in our previous papers,<sup>3,5,6,12</sup> that the problems of identifying molecular centers can be avoided by using Ewald summation or reaction field methods.<sup>3,5-8,12-14</sup> If the use of a spherical cutoff is unavoidable in the analysis of simulation structures for electrostatic potential calculations, integration of charge densities gives correct results for large cutoffs. This was shown by the consistency of a variety of center-independent procedures that check alternatives for exterior boundary conditions.<sup>3,5,6,12</sup>

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