Tests of Dielectric Model Descriptions of Chemical Charge Displacements in Water

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A dielectric model of electrostatic solvation is applied to describe potentials of mean force in water along reaction paths for: a) formation of a sodium chloride ion pair; b) the symmetric SN2 exchange of chloride in methylchloride; and c) nucleophilic attack of formaldehyde by hydroxide anion. For these cases simulation and XRISM results are available for comparison. The accuracy of model predictions varies from spectacular to mediocre. It is argued that: a) dielectric models are physical models, even though simplistic and empirical; b) their successes suggest that second-order perturbation theory is a physically sound description of free energies of electrostatic solvation; and c) the most serious deficiency of the dielectric models lies in the definition of cavity volumes. Second-order perturbation theory should therefore be used to refine the dielectric models. These dielectric models make no attempt to assess the role of packing effects but for solvation of classical electrostatic interactions the dielectric models sometimes perform as well as the more detailed XRISM theory.

An important quality of water as a solvent is its ability to stabilize ions and polar molecules. Since displacement of electric charge is often central to chemical reactivity, water is a special solvent for chemical reactions in solution. An accurate molecular theory of water participation in chemical reactions in aqueous solution has not been established but a few possibilities are available. The range of theoretical approaches includes simulation calculations, integral equation theories, and dielectric models.

Comparison of the predictions of dielectric models with those of other methods in cases where thermal precision in solvation free energies is possible is the goal of this paper. For several molecular complexes we obtain
thermally accurate solutions of the governing macroscopic Poisson equation. 
The particular examples are chosen because of the availability of results 
from alternative methods. The comparison of dielectric model results with 
data from simulation calculations or with XRISM (1) results should teach 
us about the utility of the dielectric model and about fruitful directions for 
the discovery of better theories. Since the goal is unambiguous comparisons 
that test the performance of the dielectric model, the example problems are 
not discussed for their own sake.

**Dielectric models of electrostatic solvation free energies**

The dielectric model we apply is physically viewed as follows (2, 3). 
Attention is focused on a solute of interest. A solute volume is defined 
on the basis of its geometry. Partial charges describing the solute electric 
charge distribution are positioned with respect to this volume. For liquid 
water under the most common conditions it is known that the van der Waals 
volume of the molecule is a satisfactory choice for the molecular volume 
(4, 5). But that is coincidental and elaborations of the theory will have 
to consider more general possibilities. For the present applications, it is 
essential that the defined solute volume permit disconnection when the solute 
fragments are widely separated. We define the solute volume as the volume 
enclosed by spheres centered on solute atoms. The solvent is idealized as a 
continuous dielectric material with dielectric constant $\varepsilon$. The value $\varepsilon = 77.4$, 
appropriate to water at its triple point, is used everywhere below. The 
solvent is considered to be excluded from the solute volume and that region 
is assigned a dielectric constant of one, $\varepsilon = 1$.

**Methods.** The equation to be solved for the model is 

$$ \nabla \cdot \varepsilon(r) \nabla \Phi(r) = -4\pi \rho_f(r) $$

(1)
where \( \rho_f(r) \) is the density of electric charge associated with the solute molecule, the function \( \varepsilon(r) \) gives the local value of the dielectric constant, and the solution \( \Phi(r) \) is the electric potential. To solve this equation, we first cast it as an integral equation, e. g.

\[
\Phi(r) = \Phi_0(r) + \int_V G_0(r, r') \left( \frac{\nabla' \varepsilon(r')}{{4\pi\varepsilon(r')}} \right) \cdot \nabla' \Phi(r') d^3 r'.
\]

(2)

Here \( G_0(r, r') \) is the Green function for the Poisson equation with \( \varepsilon(r) = 1 \) and \( \Phi_0(r) \) is the electrostatic potential for that case. It is assumed that all the charges of \( \rho_f(r) \) are positioned in regions where \( \varepsilon(r) = 1 \). This equation is correct both for a localized distribution \( \rho_f(r) \) and zero boundary data on a surface everywhere distant and for periodic boundary conditions on a cell of volume \( V \). \( G_0(r, r') \) is different in those two cases as is \( \Phi_0(r) \). This equation is not the only such form that can be solved and more general considerations can be helpful. But we do not pursue those issues here.

The integrand of equation 2 is concentrated on the interface between the solute volume and the solvent. We can then use boundary element ideas to solve it (6-11). The principal novelty in our numerical methods is that we use a sampling method based upon quasi-random number series (12) to evaluate the surface integral rather than more specialized methods. Advantages of our method are that it facilitates systematic studies of numerical convergence and exploitation of systematic coarse-graining. More specific discussion of numerical methods can be expected at a later date.

With the solution of equation 2 in hand we obtain the desired potential of mean force as

\[
W = U + \left( \frac{1}{2} \right) \int_V \rho_f(r) (\Phi(r) - \Phi_0(r)) d^3 r
\]

(3)
where $U$ is the static energy in the absence of the solvent. Since for the present examples $\rho_f(r)$ is a sum of partial charges, the integral in equation 3 is a sum over those partial charges.

Results

a) Pairing of sodium and chloride ions in water. Dielectric model results for the $Na^+ \cdot \cdot Cl^-$ potential of average force in water are shown in Figure 1. The radii used were those recommended by Rashin and Honig (5). See also Pratt, et al. (Pratt, L. R., Hummer, G., and Garcia, A. E., Biophys. Chem., in press). These results agree with those of Rashin who studied a similar dielectric model (13). Rashin assumed a somewhat different solute volume and his predicted potential of mean force displayed a more prominent barrier to escape from the contact minimum. Those results were similar to XRISM (14). The dielectric model results are surprising in showing minimum free energies both at ion contact and at a larger distance that indicates a solvent-separated pairing. Although surprising, these results are not in quantitative agreement with simulation calculations of solvation free energies of ion pairing (Hummer, G., Soumpasis, D. M., and Neumann, M., Mol. Phys., in press). Most importantly, the contact minimum is much deeper than the simulation results. We note also that the simulation results were obtained for finite concentrations of NaCl. Thus, the large distance behavior of that potential of mean force is influenced by ionic screening. The dielectric models and this XRISM result conforms to the asymptotic variation expected at infinite dilution.

A particular concern over recent years has been sensitivity of the molecular results for potentials of mean force to modelled intermolecular interactions (15). Figure 1 does not attempt to give the wide range of results that have
been obtained. However, to the extent that such sensitivity is considered important, it highlights a fundamental deficiency of the dielectric models. Those molecular details are not present in the dielectric models as currently applied. The dielectric models do depend on the dielectric constant of the solvent but for many applications that dependence is not decisive because of the high values of the dielectric constant that are typically relevant.

b) Symmetric $S_N2$ chloride exchange in methyl chloride. Following the efforts of Chandrasekhar, et al. (16), this example has been taken as a theoretical model of reactions in solutions over recent years (17-18). We used radii of $R_H = 1.00\, \text{Å}$, $R_C = 1.85\, \text{Å}$, $R_{Cl} = 1.937\, \text{Å}$, and partial charges of Chandrasekhar, et al. (16) (Figure 2) and Huston, et al. (18) (Figure 2 inset). As Figure 2 shows, the agreement between dielectric model and simulation results is close, no less satisfactory than the agreement between XRISM and simulation. As is discussed in the paper of Huston, et al. (18) the original assignment of partial charges of the reacting complex in the neighborhood of the barrier leads to the prediction of the notch in the potential of the mean force by the XRISM theory. This is also true of the dielectric model, as is seen in Figure 2. Huston, et al. (18) reanalyzed this modeling of solute-solvent interactions and proposed alterations of the original parameterization. The results for this alternative description of the barrier region are shown in the inset.

c) Nucleophilic attack of $HO^-$ on $H_2CO$. This example has been previously studied as a prototype of an initial step in the formation and destruction of the peptide unit (19, 20). We used radii of $R_{O(hydroxide)} = 1.65\, \text{Å}$, $R_C = 1.85\, \text{Å}$, and $R_H = 1.0\, \text{Å}$, and $R_{O(carbonyl)} = 1.60\, \text{Å}$, and the partial charges and geometries of Madura and Jorgensen (19). The results are shown in Figure 3. The predictions of the dielectric model are qualitatively
similar to those of the Monte Carlo simulation and of the XRISM theory, particularly in predicting the existence of a solvation barrier prior to contact of the reacting species.

The results of the dielectric model are not quantitatively accurate in this case, however. It seems clear that adjustment of the cavity radii at each geometry could bring the model results into agreement with the simulation data. Recently, a new proposal was given for achieving a physically valid parameterization of the model on the basis of additional molecular information (Pratt, L. R., Hummer, G., and Garcia, A. E., *Biophys. Chem.*, in press); that proposal is discussed below. As an observation preliminary to attempts to parameterize the dielectric model on more basic information, we demonstrate here that reasonable radii can achieve excellent agreement with the data. To do this we adjusted the radii of the hydroxide oxygen to reproduce at a coarse level of calculation the simulation results at a few points along the potential of mean force shown, used a simple interpolation for radii at other points, and observed the variation of the hydroxide oxygen radius. The adjusted radii are shown in Figure 4 and the results for the potential of mean force are the circles of Figure 3. This type of comparison can be misleading. Agreement just as good would be achieved even if the model result were physically wrong, *e.g.*, if we had mistakenly done the calculation for acetaldehyde rather than formaldehyde. However, the typical rough expectation for cavity radii for these models is between the van der Waals radius and the distance of closest approach for solvent molecular centers. To the extent that the radii are treated as truly adjustable, the model has more than enough flexibility to match the data with reasonable changes in those radii.
Discussion

The importance of the dielectric models is that they provide free energies of solvation for cases that are not accessible by alternative methods. The free energies obtained from the dielectric model are quadratic functionals of the charge distribution of the solute. It has been pointed out previously (Pratt, L. R., Hummer, G., and Garcia, A. E., *Biophys. Chem.*, in press) that this indicates that the dielectric models correspond to a modelistic implementation of second-order perturbation theory for the excess chemical potential of the solute. Thus, the successes of dielectric models suggest that second-order thermodynamic perturbation theory is a physically sound theory for the desired solvation free energy due to electrostatic interactions. But in addition to the second-order limitation, dielectric models also drastically eliminate molecular detail of the solvation structures. This detail can be restored by implementing second-order thermodynamic perturbation theory on a molecular basis. The fundamental formula for that approach is

\[
\Delta \mu \approx \Delta \mu_0 + \left\langle \sum_{C=\text{constituents}} \varphi(C) \right\rangle_0 \\
- \left( \frac{\beta}{2} \right) \left\langle \left( \sum_{C=\text{constituents}} \varphi(C) - \left\langle \sum_{C'=\text{constituents}} \varphi(C') \right\rangle_0 \right)^2 \right\rangle_0 .
\]  

(4)

This approximation has been discussed previously by Levy, *et al.* (23). Here the subscript ‘0’ indicates quantities obtained for the reference system in which no electrostatic interactions are expressed between the solution constituents and a designated solute molecule. The \( \varphi(C) \) are the electrostatic potential energies of interaction between the constituent \( C \) of the solution and that solute. Several aspects of this molecular approach should be noted. First, it requires knowledge of \( \Delta \mu_0 \), the solvation free energy when electrostatic interactions are neglected. This is not supplied by the dielectric mod-
els. Second, the molecular approach includes a term linear in the charges; this involves the potential at zero charge induced by short ranged forces. This term is generally present, non-zero, dependent upon molecular geometry and thermodynamic state, but the dielectric models assume that it vanishes. Third, the second-order term corresponds to the quantities usually obtained from dielectric models but this formula avoids the classic empirical adjustments of cavity radii. From the perspective of a continuum approach, this second order term incorporates nonlocality of the polarization response of the solution.

In view of the corresponding molecular theory, a natural way to improve dielectric model results is first to obtain molecular results for the second-order term to better establish the solute volume on a proper molecular basis. Cavity radii thus determined will be dependent upon the thermodynamic state just as empirical cavity radii must generally be considered functions of thermodynamic state. For example, evaluation of enthalpies by temperature differentiation should include derivatives of the cavity radii with respect to temperature (22). After definition of that solute volume is better controlled, an alternative source of information on the leading two terms must be developed. At this level, the cavity radii are independent of charges and charge distributions of the solute. Finally, the importance of succeeding terms in the perturbation theory must be assessed (Pratt, L. R., Hummer, G., and Garcia, A. E., Biophys. Chem., in press, Rick, S. W., and Berne, B. J., J. Am. Chem. Soc., in press). Those succeeding terms are likely to be especially troublesome for circumstances where composition fluctuations are physically important, e. g., for mixed solvents.

We note again that the reactions and models studied here were chosen solely because of the availability of molecularly detailed simulation data and
of results of integral equation theory. Since testing of the dielectric model by comparing its predictions to simulation and integral equation results is the objective, the same model systems must be treated by the various methods. Solute geometries and partial charges must be accepted for the test. Because of the simplicity of the dielectric model, however, we do not expect that conclusions regarding the utility of the model for description of charge displacement in aqueous solutions would be significantly changed if more elaborate models of these reactions were available. For example, the generalization of equation 4 to apply when solute-solvent electrostatic interactions are described with the aid of higher order multipole moments of the solute charge distribution is straightforward.

Conclusions

To the extent that the dielectric model is physically sound, second-order thermodynamic perturbation theory should provide an accurate description of free energies due to electrostatic interactions between the solute and the solution. Second-order thermodynamic perturbation theory restores molecular detail of the solvation structures that is discarded when the dielectric model is used. More fundamentally, second-order thermodynamic perturbation theory identifies the potential at zero charge that is neglected in the dielectric model.

Despite their simplistic character, dielectric models provide a physically sound description of chemical charge displacements in water. Because of these qualities they can be helpful where only rough but physical results are required; for example, they might be expected to provide serviceable umbrella functions (23) for more accurate molecular calculations of free energies along reaction paths of the sort considered here. It should be rec-
ognized, however, that stratification of the reaction coordinate is typically more important (24, 25).

Considered directly the dielectric models are not reliably accurate for thermal level energy changes. A large part of the unreliability of the dielectric model predictions is surely due to the assignment of cavity radii; the predictions of the model are sensitive to those parameters, they clearly ought to vary along a reaction path, and the determination of proper values for the radii comes from outside the model. Although the dielectric model does not attempt to assess the importance of packing effects on solvation properties, it is sometimes of comparable accuracy to the more detailed XRISM theory for treatment of electrostatic contributions. The dielectric model also has the advantage of being simple and physical when used for those purposes.

Acknowledgments. We are grateful for helpful discussions with Drs. J. Blair, S.-H. Chou, P. Leung, D. Misemer, J. Stevens, and K. Zaklika of 3M Corporation on the topics of solvation and reaction chemistry in solution. LRP thanks Gerhard Hummer and Angel E. Garcia for helpful discussions and acknowledges partial support for this work from the Tank Waste Remediation System (TWRS) Technology Application program, under the sponsorship of the U. S. Department of Energy EM-36, Hanford Program Office, and the Air Force Civil Engineering Support Agency. This work was also supported in part by the US-DOE under LANL Laboratory Directed Research and Development funds.

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**Figure Captions**

Figure 1: Potentials of the mean forces between ion pairs Na\(^+\)· · ·Cl\(^−\) in water. The XRISM results are redrawn from Reference 14; the MD results are redrawn from Pratt, *et al.* (Pratt, L. R., Hummer, G., and Garcia, A. E., *Biophys. Chem.*, in press). Those original MD results are to be found in Hummer, *et al.* (Hummer, G., Soumpasis, D. M., and Neumann, M., *Mol. Phys.*, in press).

Figure 2: Potential of the mean force along a reaction path for symmetric S\(_{N2}\) replacement of the Cl\(^−\) ion in CH\(_3\)Cl. \(\Delta W \equiv W - U\). See References 16 and 18.

Figure 3: Potential of the average force along a reaction path for nucleophilic attack of H\(_2\)CO by HO\(^−\) according to the dielectric model, simulation (19), and XRISM theory (20). The circles are the results of the dielectric
model with empirical adjustment of the radius of the hydroxide oxygen. See the text and Figure 4.

Figure 4: Variation of the hydroxide-oxygen radius adjusted to fit the simulation data for the potential of mean force in example c. See Figure 3.
Figure 1
Figure 2
Figure 3
Figure 4