Solvation thermodynamics: An approach from analytic temperature derivatives

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A method is presented that uses integral equation theory to determine analytic temperature derivatives of the radial distribution functions. It is illustrated by studying the solvation thermodynamics of monatomic solutes in aqueous solution. The results agree well with the density derivative method developed previously [Yu and Karplus, J. Chem. Phys. **89**, 2366 (1988)]. An expression for the solvation enthalpy is derived which allows direct comparison with experimental and isobaric–isothermal (NPT) ensemble simulation data. Satisfactory agreement with experiment is found for pure water and for the aqueous solvation of monovalent ions. Simple equations that exploit the site–site HNC closures are given for the decomposition of the potential of mean force into its enthalpic (or energetic) and entropic components. Since the extended RISM (HNC-RISM) theory yields an incorrect (trivial) value of the dielectric constant, two different ways to correct for the asymptotic behavior of the solute–solute potential of mean force are compared. They lead to similar results but the method in which the solvent dielectric constant is modified from the outset can be applied more generally. The interactions between nonpolar and between polar solutes in water are decomposed into enthalpic and entropic contributions. This is difficult to do by computer simulations because of the lack of precision in such calculations. The association of nonpolar solutes in water is found to have comparable enthalpic and entropic contributions; this result disagrees with the usual description of an entropy-dominated hydrophobic interaction. For ions, the somewhat surprising result is that the association of like-charged species is enthalpy driven while for oppositely charged ions entropic effects are dominant. The process of bringing two like-charged ions together leads to higher local charge density; the more favorable solvation enthalpy arising from this increase in charge density (q^2 dependence) more than compensates for the Coulombic repulsion. For oppositely charged ions, association leads to a partial charge neutralization in which the favorable Coulombic attraction is overwhelmed by the loss of stabilizing solvation enthalpy. The entropic increase is due to the greater freedom of the surrounding water molecules resulting from the partial charge neutralization.

I. INTRODUCTION

Integral equation theories have been shown to be applicable for the study of the solvation of nonpolar and polar solutes.[1-8] By use of the site–site Ornstein–Zernike (SSOZ) [the reference interaction site model (RISM)] integral equation[9] and its density expansion (δ_{ρ_u}),[8] the solvation free energy has been decomposed into energetic and entropic contributions. Examination of the solvent reorganization term for model infinite dilute solutions demonstrated that it is a significant component of the solvation energy. However, even at finite concentrations this term is canceled exactly by a corresponding contribution to the entropy and thus does not appear in the solvation free energy. In the present paper, we generalize the expansion approach and apply it to the temperature derivative (δ_T) of the radial distribution function. An expression for the solvation enthalpy is derived. This makes possible direct comparison with experimental data, in which the solvation free energy is usually decomposed into the entropy and the enthalpy, rather than the energy. The present formulation also leads to a convenient separation of the potential of mean force (PMF) into its enthalpic and entropic components. This can aid in under-standing the physical origin of solvent contribution to the PMF and supplement results available from numerical finite temperature difference calculations.[4,6,10] Further, the temperature derivative, in contrast to the density derivative discussed previously, makes it possible to decompose the solvation enthalpy (or energy) and entropy into contributions from atoms or functional groups in polyatomic molecule. This is of particular interest for the development of empirical potentials with solvation corrections that do not depend on the superposition approximation.[10]

An additional question addressed in this paper concerns the fact that the SSOZ integral equation with the hypernetted-chain closure (HNC-RISM) leads to an underestimate of the dielectric constant for a solvent with long-ranged interactions.[11,12] For the TIP3P model of water at 300 K and 1 atm, the calculated dielectric constant is only 18[4] compared to the simulation estimate of 53 for TIP4P[13] and the experimental value of 78. Thus, the calculated asymptotic amplitude of the PMF between charged solutes is too large by a factor of 4. Hirata et al.[3] have proposed and applied an *a posteriori* correction by modifying the Coulombic contribution to the PMF. The method is applicable only to solutes that have nonzero net charge at infinite separation. An alter-

native approach, which does not have this restriction, is to modify the closure at the level of the solvent correlation functions to achieve consistency with the desired macroscopic dielectric constant.[14–16] This builds in the correction *a priori* and is thus more general. For instance, since the solvent structure itself has been modified, the thermodynamic properties of single solute molecule will be corrected accordingly. This method can also be applied to chemical reactions in which charge transfer occurs such that the solute charges are nonzero at small separation but may be zero at infinite separation.[17,18]

In Sec. II, we develop the analytic temperature derivatives of the radial distribution functions as well as an expression for the enthalpy using the SSOZ integral equations.[9] The model solvent and solutes used for illustrative calculations in this study are described in Sec. III. The results and discussions are given in Sec. IV. The conclusions are summarized in Sec. V.

II. THEORY AND METHODS

In this section, we first review the relevant classical thermodynamics and then outline the method for calculating analytic temperature derivatives of the radial distribution functions using the HNC-RISM as a concrete example. The approach is the same as that used for finding analytic density derivatives.[2,8] In addition, we derive equations for calculating the enthalpy and the entropy. Finally, two different ways to correct the asymptotic behavior of the PMF for errors in the calculated solvent dielectric constant are summarized.

A. Solvation thermodynamics

The thermodynamics for a two components (u for solute and v for solvent) solution is reviewed;[19] the generalization to multicomponent systems is straightforward. The excess chemical potential $\Delta\mu_u$ for the solute in the solution is given by (all excess quantities are denoted by Δ)

$$\Delta\mu_u = \mu_u - \mu_u^{id}$$
$$= \left(\frac{\partial\mathscr{G}}{\partial N_u}\right)_{T,P,N_v} - k_B T \ln(\rho_u \Lambda_u^3 q_u)$$
$$= \left(\frac{\partial\mathscr{A}}{\partial N_u}\right)_{T,V,N_v} - k_B T \ln(\rho_u \Lambda_u^3 q_u), \quad (2.1)$$

where $\mathscr{G}$ and $\mathscr{A}$ are the Gibbs and the Helmholtz free energies, respectively; N, P, V and T are the number of molecules, pressure, volume and temperature, respectively; Λ is the thermal de Broglie wavelength, q_u is the intramolecular partition function, k_B is the Boltzmann constant, and $\rho_u = N_u/V$ is the solute number density. One way to decompose the excess chemical potential is to take the isochoric temperature derivative.[2,8] This leads to the *excess partial molecular* entropy $\Delta s_{u,V}$ at constant T, V and the *excess partial molecular* energy $\Delta\epsilon_u$,

$$\Delta s_{u,V} = -\left(\frac{\partial\Delta\mu_u}{\partial T}\right)_{\rho_u,\rho_v} = \left(\frac{\partial\Delta\mathscr{S}}{\partial N_u}\right)_{T,V,N_v}, \quad (2.2)$$

$$\Delta\epsilon_u = \left(\frac{\partial\Delta\mu_u/T}{\partial 1/T}\right)_{\rho_u,\rho_v} = \Delta\mu_u + T\Delta s_{u,V} = \left(\frac{\partial\Delta\mathscr{E}}{\partial N_u}\right)_{T,V,N_v}, \quad (2.3)$$

where $\Delta\mathscr{S}$ and $\Delta\mathscr{E}$ are the excess entropy and internal energy, respectively. Since experiments are most commonly done at constant T and P, it is convenient to introduce the alternative decomposition of the excess chemical potential into the *excess partial molecular* entropy $\Delta s_{u,P}$ at constant T, P and the *excess partial molecular* enthalpy Δh_u.[20] This can be achieved by use of an isobaric temperature derivative,

$$\Delta s_{u,P} = -\left(\frac{\partial\Delta\mu_u}{\partial T}\right)_{P,x_v} = \left(\frac{\partial\Delta\mathscr{S}}{\partial N_u}\right)_{T,P,N_v}, \quad (2.4)$$

$$\Delta h_u = \left(\frac{\partial\Delta\mu_u/T}{\partial 1/T}\right)_{P,x_v} = \Delta\mu_u + T\Delta s_{u,P} = \left(\frac{\partial\Delta\mathscr{H}}{\partial N_u}\right)_{T,P,N_v}, \quad (2.5)$$

where $\mathscr{H}$ is the enthalpy and x_v is the mole fraction of the solvent. For brevity, the phrase "*excess partial molecular*" will be omitted in the rest of the paper.

In Eqs. (2.2) and (2.4) we have used subscripts V and P to emphasize that the two entropic terms are *different*. Their difference is given by

$$T(\Delta s_{u,P} - \Delta s_{u,V})$$
$$= \Delta h_u - \Delta\epsilon_u$$
$$= T\alpha_{P,x_v}\left[\rho_v\left(\frac{\partial\Delta\mu_u}{\partial\rho_v}\right)_{T,\rho_u} + \rho_u\left(\frac{\partial\Delta\mu_u}{\partial\rho_u}\right)_{T,\rho_v}\right], \quad (2.6)$$

where $\alpha_{P,x_v} = [\partial \ln(V)/\partial T]_{P,x_v}$ is the isobaric thermal expansion coefficient of the solution. At infinite dilution, $\rho_u \to 0$ [denoted by superscript (0)], Eq. (2.6) reduces to

$$T(\Delta s_{u,P}^{(0)} - \Delta s_{u,V}^{(0)}) = \Delta h_u^{(0)} - \Delta\epsilon_u^{(0)}$$
$$= T\rho_v\alpha_{v,P}\left(\frac{\partial\Delta\mu_u^{(0)}}{\partial\rho_v}\right)_T, \quad (2.7)$$

where $\alpha_{v,P}$ is the isobaric thermal expansion coefficient of the pure solvent. Although $\alpha_{v,P}$ is generally rather small, the derivative term in parenthesis on the right-hand side of Eq. (2.7) is inversely related to the isothermal compressibility of the solvent, $\kappa_{v,T} = -[\partial \ln(V)/\partial P]_{T,N_v}$, which is also rather small except at a phase transition. Thus, one cannot be certain that their product is negligible. In the case of water at 298.15 K and 1 atm, $\alpha_{v,P} = 2.57 \times 10^{-4}$ K^{-1} and $[\partial\Delta\mu_u^{(0)}/\partial\rho_v]_T = 9.0$ kcal cm^3/mol g.[21] From Eq. (2.7), the difference between the enthalpy and energy is 0.69 kcal/mol, roughly 7% of the enthalpy, -9.97 kcal/mol.[20] For a hydrocarbon liquid such as methane at its boiling point, -111.66 K at 1 atm, the estimated difference based on $\kappa_{v,T} = 1.72 \times 10^{-4}$/atm calculated from a Monte Carlo simulation[22] is about 2 kcal/mol, comparable in magnitude to the solvation enthalpy of 1.8 kcal/mol.[20]

In earlier work,[8] we used Eqs. (2.2) and (2.3) to study the solvation thermodynamics. We develop here a method based on Eqs. (2.4) and (2.5) by means of analytic expressions involving temperature derivatives of the radial distribution functions. In principle the method can be applied at

finite concentrations as well as at infinite dilution; in practice, at finite concentrations data for α_{P,x_v} of the solution are required. Thus for simplicity we consider a two-component solution at the infinite dilution. The case of pure water is given as an example of a finite concentration system.

The connection between classical thermodynamics and statistical mechanics can be made by invoking coupling parameter integration to relate the excess chemical potential to an average over the radial distribution functions, $g_{\alpha\gamma}^{(0)} = h_{\alpha\gamma}^{(0)} + 1$;[23] the subscripts α and γ associated with letters not in boldface refer to site labels. We specialize to spherically symmetric interaction sites to simplify the notation. For a solute dissolved in a solvent at infinite dilution, we have

$$\Delta\mu_{u,\text{sol}}^{(0)} = \rho_v \sum_{\alpha=1}^{n_u} \sum_{\gamma=1}^{n_v} \int_0^1 d\lambda \int dr \frac{\partial U_{\alpha\gamma}(r;\lambda)}{\partial\lambda} g_{\alpha\gamma}^{(0)}(r;\lambda).$$
(2.8)

Application of Eq. (2.3) leads to an expression for the solvation energy,

$$\Delta\epsilon_{u,\text{sol}}^{(0)} = \Delta\mu_{u,\text{sol}}^{(0)} - T\rho_v \sum_{\alpha=1}^{n_u} \sum_{\gamma=1}^{n_v} \int_0^1 d\lambda$$
$$\times \int dr \frac{\partial U_{\alpha\gamma}(r;\lambda)}{\partial\lambda} \delta_T h_{\alpha\gamma}^{(0)}(r;\lambda).$$
(2.9)

The enthalpy can be obtained from Eq. (2.7),

$$\Delta h_{u,\text{sol}}^{(0)} = \Delta\epsilon_{u,\text{sol}}^{(0)} + T\alpha_{v,P}\left[\Delta\mu_{u,\text{sol}}^{(0)} + \rho_v^2 \sum_{\alpha=1}^{n_u} \sum_{\gamma=1}^{n_v} \int_0^1 d\lambda\right.$$
$$\left.\times \int dr \frac{\partial U_{\alpha\gamma}(r;\lambda)}{\partial\lambda} \delta_{\rho_v} h_{\alpha\gamma}^{(0)}(r;\lambda)\right].$$
(2.10)

In the above, we have used $\delta_T h_{\alpha\gamma}^{(0)}(r)$ for the isochoric temperature derivative and $\delta_{\rho_v} h_{\alpha\gamma}^{(0)}(r)$ for the isothermal solvent density derivative of the radial distribution function. The coupling parameter λ transforms the system from the reference pure solvent plus a noninteracting solute ($\lambda = 0$) to the actual system with full interactions ($\lambda = 1$), corresponding to an infinite dilute solution. For nonrigid polyatomic solute, each different configuration can be treated as a separate species with a given subscript α.

B. Integral equation theory

To use Eqs. (2.9) and (2.10), we need to calculate the required derivatives of the distribution functions. This is done by exploiting the self-consistent nature of the integral equation theory; that is, we set up equations involving the derivatives and solve them iteratively. The approach corresponds to that used for the evaluation of density derivatives.[2,8]

We start with the SSOZ (RISM) integral equations[3,9,24,25] expressed in terms of the matrix of correlation functions (quantities in k space are indicated by a caret and matrices are denoted by boldfaced letters)

$$\hat{\chi} \equiv \rho\hat{w} + \rho\hat{h}\rho = \rho\hat{w} + \rho\hat{w}\hat{c}\hat{\chi} = \overline{\mathbf{Q}} + \overline{\mathbf{Q}}\hat{c}^*\hat{\chi},$$
(2.11)

where $\hat{w}$ is the matrix of intramolecular correlation functions; $\hat{h}$ is the matrix of intermolecular total correlation functions; ρ is the density; $\overline{\mathbf{Q}}$ is the chain sum of $\hat{\phi}'$[26] and

$\hat{c}^* = \hat{c} - \hat{\phi}'$. Here $\hat{c}$ is the matrix of direct correlation functions; $\hat{\phi}' = A\hat{\phi}$ with $\hat{\phi}_{\alpha\gamma}(k) = 4\pi\beta z_\alpha z_\gamma/k^2$; $\beta = 1/k_B T$ and z_α is the charge on site α. The symbol A is a site independent quantity introduced to modify the HNC closure [see Sec. I and Eq. (2.36)] such that the calculated correlation functions are consistent with an experimental value of the solvent dielectric constant. It is given by (see Appendix C)[3,14–16]

$$A = \frac{1 + \epsilon(3y - 1)}{3y(\epsilon - 1)} \quad \text{with} \quad y = \frac{4\pi\beta\rho_v\langle d_v^2\rangle}{9}, \quad (2.12)$$

where $\langle d_v^2\rangle$ is the average squared dipole moment of the solvent molecule. For $A = 1$ (i.e., no modification of the HNC closure) the dielectric constant ϵ is given by $\epsilon = 1 + 3y$, the gas phase dielectric constant of uncorrelated molecules, which we denote as ϵ_{RISM}. If a correction of the solvent dielectric constant is used, ϵ is an *input* value for the macroscopic dielectric constant that is denoted as ϵ_0. The matrix $\overline{\mathbf{Q}}$ in Eq. (2.11) is given by

$$\overline{\mathbf{Q}} \equiv \rho\hat{w} + \rho\hat{\mathbf{Q}}\rho = \rho\hat{w} + \rho\hat{w}\hat{\phi}'\overline{\mathbf{Q}}. \quad (2.13)$$

For rigid molecules, the matrix $\hat{w}$ has elements $\hat{w}_{\alpha\gamma}(k) = \sin(kL_{\alpha\gamma})/kL_{\alpha\gamma}$ with $L_{\alpha\gamma}$ the distance between sites α and γ.

To obtain the first order temperature derivatives, we differentiate Eqs. (2.11) and (2.13) with respect to the temperature once (see Appendix A),

$$\delta_T\hat{\chi} = \hat{\chi}\delta_T\hat{c}\hat{\chi} = \hat{\chi}\delta_T\hat{c}^*\hat{\chi} + \hat{\chi}\overline{\mathbf{Q}}^{-1}[\delta_T\overline{\mathbf{Q}}]\overline{\mathbf{Q}}^{-1}\hat{\chi} \quad (2.14)$$

and

$$\delta_T\overline{\mathbf{Q}} = \overline{\mathbf{Q}}\hat{\phi}''\overline{\mathbf{Q}} \quad \text{where} \quad \hat{\phi}'' = \left[\delta_T A - \frac{A}{T}\right]\hat{\phi}. \quad (2.15)$$

The δ_T represents the isochoric temperature derivative of the correlation functions. Equations for the second-order derivatives can be set up correspondingly to calculate the change in the heat capacity associated with the solvation process.

In this study, we consider the infinite dilution versions ($\rho_u \rightarrow 0$) of Eqs. (2.11) to (2.15) that separates the solvent–solvent (vv), solute–solvent (uv), and solute–solute (uu) parts of the full equations. The zeroth-order terms for the vv and uv parts are given by[3,8,25,27]

$$\hat{h}_{av}^{(0)} = \hat{Q}_{av}^{(0)} + [\hat{w}_a\hat{c}_{av}^{*(0)} + \hat{Q}_{av}^{(0)}\rho_v\hat{c}_{vv}^{*(0)}][\hat{w}_v + \rho_v\hat{h}_{vv}^{(0)}] \quad (2.16)$$

and

$$\hat{Q}_{av}^{(0)} = \hat{w}_a\hat{\phi}_{av}'[\hat{w}_v + \rho_v\hat{Q}_{vv}^{(0)}], \quad (2.17)$$

where $\{a\} = \{u,v\}$. The subscripts associated with matrices are used to denote species labels rather than site labels.

For the first-order temperature derivatives, Eq. (2.15) leads to

$$\delta_T\hat{Q}_{a\gamma}^{(0)} = \hat{w}_a[\hat{\phi}_{a\gamma}''\hat{w}_\gamma + \hat{\phi}_{av}''\rho_v\hat{Q}_{v\gamma}^{(0)}]$$
$$+ \hat{Q}_{av}^{(0)}\rho_v[\hat{\phi}_{v\gamma}''\hat{w}_\gamma + \hat{\phi}_{vv}''\rho_v\hat{Q}_{v\gamma}^{(0)}] \quad (2.18)$$

and Eq. (2.14) gives

$$\delta_T\hat{h}_{a\gamma}^{(0)} = \hat{w}_a[\delta_T\hat{c}_{a\gamma}^{(0)}\hat{w}_\gamma + \delta_T\hat{c}_{av}^{(0)}\rho_v\hat{h}_{v\gamma}^{(0)}]$$
$$+ \hat{h}_{av}^{(0)}\rho_v[\delta_T\hat{c}_{v\gamma}^{(0)}\hat{w}_\gamma + \delta_T\hat{c}_{vv}^{(0)}\rho_v\hat{h}_{v\gamma}^{(0)}], \quad (2.19)$$

where $\{\alpha,\gamma\} = \{u,v\}$ and $\delta_T\hat{c}^{(0)} = \delta_T\hat{c}^{*(0)} - \hat{\phi}''$. These three sets of equations must be augmented with a closure relating the $\delta_T h_{\alpha\gamma}^{(0)}$'s and the $\delta_T\hat{c}_{\alpha\gamma}^{(0)}$'s. For the purpose of applying the present approach to ionic solutions, we choose the site–site HNC closure[25] and determine its derivative version. The HNC closure has been applied to water and to ionic systems with some success.[4,28] Further, it has the advantage that the coupling parameter integration can be avoided because analytic expression are available for the calculation of the solvation thermodynamics.[29] The HNC closure and its temperature derivative are given by

$$h_{\alpha\gamma}^{(0)}(r) = \exp\{-\beta U_{\alpha\gamma}^*(r) + h_{\alpha\gamma}^{(0)}(r) - c_{\alpha\gamma}^{*(0)}(r)\} - 1 \tag{2.20}$$

and

$$\delta_T h_{\alpha\gamma}^{(0)}(r) = \left[\frac{\beta}{T} U_{\alpha\gamma}^*(r) + \delta_T h_{\alpha\gamma}^{(0)}(r) - \delta_T c_{\alpha\gamma}^{*(0)}(r) \right]$$
$$\times [h_{\alpha\gamma}^{(0)}(r) + 1], \tag{2.21}$$

respectively, where U^* is a short-range potential typically of the Lennard-Jones form.

For the enthalpy [Eq. (2.10)] we need in addition the derivative of the radial distributions functions with respect to the solvent density ρ_v. Structurally equivalent equations for the solute density derivative have been given as Eqs. (22a) and (22b) in Yu and Karplus[8] with $A = 1$. For a general A, we rewrite them here as (see also Appendix A)

$$\delta_{\rho_\eta}\hat{Q}_{\alpha\gamma}^{(0)} = \hat{Q}_{\alpha\eta}^{(0)}\hat{w}_\eta^{-1}\hat{Q}_{\eta\gamma}^{(0)} + [\hat{w}_\alpha(\hat{\phi}_{\alpha\gamma}^\eta\hat{w}_\gamma + \hat{\phi}_{\alpha v}^\eta\rho_v\hat{Q}_{v\gamma}^{(0)}) + \hat{Q}_{\alpha v}^{(0)}\rho_v(\hat{\phi}_{v\gamma}^\eta\hat{w}_\gamma + \hat{\phi}_{vv}^\eta\rho_v\hat{Q}_{v\gamma}^{(0)})] \tag{2.22}$$

with $\hat{\phi}_{\alpha\gamma}^\eta = (\delta_{\rho_\eta}A)\hat{\phi}_{\alpha\gamma}$ and

$$\delta_{\rho_\eta}\hat{h}_{\alpha\gamma}^{(0)} = \hat{w}_\alpha\delta_{\rho_\eta}\hat{c}_{\alpha\gamma}^{(0)}\hat{w}_\gamma + [\hat{w}_\alpha\delta_{\rho_\eta}\hat{c}_{\alpha v}^{(0)} + \hat{h}_{\alpha v}^{(0)}\rho_v\delta_{\rho_\eta}\hat{c}_{vv}^{(0)}]$$
$$\times\rho_v\hat{h}_{v\gamma}^{(0)} + \hat{h}_{\alpha\eta}^{(0)}\hat{w}_\eta^{-1}\hat{h}_{\eta\gamma}^{(0)}, \tag{2.23}$$

where $\{\alpha,\gamma,\eta\} = \{u,v\}$ and $\delta_{\rho_\eta}\hat{c}^{(0)} = \delta_{\rho_\eta}\hat{c}^{*(0)} + \hat{\phi}^\eta$. The corresponding density derivative of the HNC closure is

$$\delta_{\rho_\eta}h_{\alpha\gamma}^{(0)}(r) = [\delta_{\rho_\eta}h_{\alpha\gamma}^{(0)}(r) - \delta_{\rho_\eta}c_{\alpha\gamma}^{*(0)}(r)][h_{\alpha\gamma}^{(0)}(r) + 1]. \tag{2.24}$$

For $A = 1$, Eq. (2.8) for the solvation free energy can be integrated analytically over the coupling parameter to obtain[6,29]

$$\Delta\mu_{u,\text{sol}}^{(0)} = \frac{\rho_v}{\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int dr\{\tfrac{1}{2}[h_{\alpha\gamma}^{(0)}(r)]^2 - c_{\alpha\gamma}^{(0)}(r)$$
$$- \tfrac{1}{2}h_{\alpha\gamma}^{(0)}(r)c_{\alpha\gamma}^{(0)}(r)\}. \tag{2.25}$$

With Eq. (2.25) the solvation energy [Eq. (2.9)] and enthalpy [Eq. (2.10)] can be written as

$$\Delta\epsilon_{u,\text{sol}}^{(0)} = \rho_v\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int dr\, U_{\alpha\gamma}(r)g_{\alpha\gamma}^{(0)}(r)$$
$$+ \frac{T\rho_v}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int dr[c_{\alpha\gamma}^{(0)}(r)\delta_T h_{\alpha\gamma}^{(0)}(r)$$
$$- h_{\alpha\gamma}^{(0)}(r)\delta_T c_{\alpha\gamma}^{(0)}(r)], \tag{2.26}$$

$$\Delta h_{u,\text{sol}}^{(0)} = \Delta\epsilon_{u,\text{sol}}^{(0)} + T\alpha_{v,P}\left\{ \Delta\mu_{u,\text{sol}}^{(0)} \right.$$
$$+ \frac{\rho_v^2}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int dr\left[h_{\alpha\gamma}^{(0)}(r)\delta_{\rho_v}c_{\alpha\gamma}^{(0)}(r) \right.$$
$$\left.\left. - c_{\alpha\gamma}^{(0)}(r)\delta_{\rho_v}h_{\alpha\gamma}^{(0)}(r) \right] \right\}. \tag{2.27}$$

In Eq. (2.26) the first term is the average solute–solvent interaction energy and the second term is the solvent reorganization energy, previously denoted as $\Delta\epsilon_{\text{cavity}}^{(0)}$.[8] The corresponding solvation entropy can be obtained using Eqs. (2.3) and (2.5). Although the equations have been written for a two-component solution, their generalization to multicomponent systems is straightforward.

An advantage of the present approach, relative to the previous analysis of the solvation thermodynamics,[8] is its potential utility for separating the thermodynamic functions into contributions from various groups within a polyatomic solute. This is true because all terms in Eqs. (2.25) to (2.27) involve explicit summation over the solute sites, $\Sigma_{\alpha=1}^{n_u}$, that can be looked at individually or grouped chemically into functional units.[18] The earlier δ_{ρ_u} method[8] does not allow this for the energy and entropy since the solvent rearrangement term was calculated from an expansion of the solvent radial distribution functions to first order in the bulk solute density at infinite dilution. This density is a property of the whole solute molecule as a single entity and thus cannot be decomposed. This is clear from the expression [cf. Eq. (11a) of Yu and Karplus[8]]

$$\Delta\epsilon_{u,\text{sol}}^{(0)} = \rho_v\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int dr\, U_{\alpha\gamma}(r)g_{\alpha\gamma}^{(0)}(r)$$
$$+ \frac{\rho_v^2}{2}\sum_{\eta=1}^{n_v}\sum_{\gamma=1}^{n_v}\int dr\, U_{\gamma\eta}(r)\delta_{\rho u}h_{\gamma\eta}^{(0)}(r). \tag{2.28}$$

Although the first term in Eq. (2.28) can be grouped into sets of solute sites, the second term, due to solvent reorganization, cannot.

On the other hand, the advantage of Eq. (2.28) over Eq. (2.26) is that the former is in principle independent of the choice of closure, whereas the latter is true only for the site–site HNC closure. In Appendix B, we sketch the proof of the thermodynamically consistent $\mathscr{U}$ (energy) route and $\mathscr{A}$ (free energy) route to the solvation energy within the HNC-RISM integral equation theory, i.e., the SSOZ with site–site HNC closure when $A = 1$. The proof is a direct consequence of the works of Morita and Hiroike[30,31] and Singer and Chandler.[29] If A is itself a function of the coupling parameter, the proof as presented can no longer be carried out and the terms causing the inconsistency are indicated. Numerically, the observed inconsistency (see Sec. IV) may be viewed as providing a measure of the error in the solvation thermodynamic results obtained from integral equation theory.

Once the various radial distribution functions have been determined, the potential of mean force (PMF) between sites α and γ on different solute molecules u and u' is by definition

$$W_{\alpha_u \gamma_{u'}}(r) = -\frac{1}{\beta} \ln \left[1 + h^{(0)}_{\alpha_u \gamma_{u'}}(r) \right]$$

$$= U^*_{\alpha_u \gamma_{u'}}(r) - \frac{1}{\beta} \left[h^{(0)}_{\alpha_u \gamma_{u'}}(r) - c^{*(0)}_{\alpha_u \gamma_{u'}}(r) \right]. \tag{2.29}$$

For the energy contribution to the PMF, an isochoric temperature derivative of $W_{\alpha_u \gamma_{u'}}(r)$ gives

$$E_{\alpha_u \gamma_{u'}}(r) = \frac{T}{\beta} \frac{\delta_T h^{(0)}_{\alpha_u \gamma_{u'}}(r)}{1 + h^{(0)}_{\alpha_u \gamma_{u'}}(r)}$$

$$= U^*_{\alpha_u \gamma_{u'}}(r) + \frac{T}{\beta} \left[\delta_T h^{(0)}_{\alpha_u \gamma_{u'}}(r) - \delta_T c^{*(0)}_{\alpha_u \gamma_{u'}}(r) \right]. \tag{2.30}$$

Similarly the enthalpy contribution is obtained from an isobaric temperature derivative of $W_{\alpha_u \gamma_{u'}}(r)$ [cf. Eq. (2.7)]

$$H_{\alpha_u \gamma_{u'}}(r) = E_{\alpha_u \gamma_{u'}}(r) + \frac{T \rho_v \alpha_{v,P}}{\beta} \frac{\delta_{\rho_v} h^{(0)}_{\alpha \gamma}(r)}{1 + h^{(0)}_{\alpha_u \gamma_{u'}}(r)}$$

$$= E_{\alpha_u \gamma_{u'}}(r) + \frac{T \rho_v \alpha_{v,P}}{\beta} \left[\delta_{\rho_v} h^{(0)}_{\alpha_u \gamma_{u'}}(r) \right.$$

$$\left. - \delta_{\rho_v} c^{*(0)}_{\alpha_u \gamma_{u'}}(r) \right]. \tag{2.31}$$

In Eqs. (2.29) to (2.31) the HNC closure (2.20) and its derivatives, Eqs. (2.21) and (2.24), were used to obtain the second equalities.

For a solute in a polar solvent, it has been shown that when $A = 1$ the asymptotic amplitude of the PMF, Eq. (2.29), between site α_u on solute u and site $\gamma_{u'}$ on solute u' is given by[11,32]

$$W_{\alpha_u \gamma_{u'}}(r) \to \frac{1}{\epsilon_{\mathrm{RISM}}} \frac{Z_u Z_{u'}}{r} \quad \text{for large } r \tag{2.32}$$

where $Z_u = \Sigma^{n_u}_{\alpha_u = 1} z_{\alpha_u}$ is the net charge on solute u and z_{α_u} is the charge on site α_u. To correct for the underestimated solvent dielectric constant in the HNC-RISM formulation, we can follow Hirata et al.[3] and modify Eq. (2.29) to

$$W'_{\alpha_u \gamma_{u'}}(r) = W_{\alpha_u \gamma_{u'}}(r) + \frac{Z_u Z_{u'}}{r} \left[\frac{1}{\epsilon_0} - \frac{1}{\epsilon_{\mathrm{RISM}}} \right], \tag{2.33}$$

where ϵ_0 is the correct dielectric constant of the solvent. The modified energy and enthalpy are then

$$E'_{\alpha_u \gamma_{u'}}(r) = E_{\alpha_u \gamma_{u'}}(r) + \frac{Z_u Z_{u'}}{r}$$

$$\times \left[\frac{1}{\epsilon_0} + \frac{T}{\epsilon_0} \left(\frac{\partial \ln(\epsilon_0)}{\partial T} \right)_{\rho_v} - \frac{1}{\epsilon^2_{\mathrm{RISM}}} \right], \tag{2.34}$$

$$H'_{\alpha_u \gamma_{u'}}(r) = H_{\alpha_u \gamma_{u'}}(r) + \frac{Z_u Z_{u'}}{r} \left[\frac{1}{\epsilon_0} + \frac{T}{\epsilon_0} \left(\frac{\partial \ln(\epsilon_0)}{\partial T} \right)_P \right.$$

$$\left. - \frac{1}{\epsilon^2_{\mathrm{RISM}}} - T \alpha_{v,P} \left(1 - \frac{1}{\epsilon_{\mathrm{RISM}}} \right) \right]. \tag{2.35}$$

The $W'_{\alpha_u \gamma_{u'}}(r)$, $E'_{\alpha_u \gamma_{u'}}(r)$ and $H'_{\alpha_u \gamma_{u'}}(r)$ refer to an infinite separation of sites α_u and $\gamma_{u'}$ on different solute molecules u and u' as the zero of their energy scale. A decomposition of

Eq. (2.33) into energy and entropy contributions has been made previously with numerical finite difference temperature derivatives.[4,6,10]

Alternatively one may correct the asymptotic behavior of the PMF by choosing A as given by Eq. (2.12) to impose $c_{vv}(r) \to A\phi_{vv}(r)$ for large r;[14–16] that is, we rewrite the HNC closure in Eq. (2.20) as

$$h^{(0)}_{vv}(r) = \exp\{ -\beta U^*_{vv}(r) + A\phi_{vv}(r)$$

$$+ h^{(0)}_{vv}(r) - c^{(0)}_{vv}(r) \} - 1 \tag{2.36}$$

for the pure solvent correlation functions. This allows one to construct solvent correlation functions via the SSOZ equation with long-ranged behavior that are consistent with the macroscopic dielectric constant ϵ_0 while introducing only small alterations in the short-ranged part.[16] It is important to note that the solvation thermodynamic properties of the solutes are also corrected accordingly; such a correction is not made in the scheme used by Hirata et al.[3] Since Eq. (2.36) involves just the solvent–solvent part of the SSOZ equation, only derivatives of A with respect to T or ρ_v that are associated with the pure solvent correlation functions are needed. Thus, in Eqs. (2.13), (2.15), (2.18), (2.19), and (2.23), the following conditions apply

$$\hat{\phi}'_{vv} = A\hat{\phi}_{vv}; \quad \hat{\phi}'_{u\gamma} = \hat{\phi}_{u\gamma} \quad \text{with } \gamma = \{u,v\}, \tag{2.37}$$

$$\hat{\phi}''_{vv} = \left[\delta_T A - \frac{A}{T} \right] \hat{\phi}_{vv};$$

$$\hat{\phi}''_{u\gamma} = \frac{-1}{T} \hat{\phi}_{u\gamma} \quad \text{with } \gamma = \{u,v\}, \tag{2.38}$$

$$\hat{\phi}^\eta_{\alpha\gamma} = 0 \quad \text{unless } \{\eta,\alpha,\gamma\} = \{v\}. \tag{2.39}$$

With A specified by Eq. (2.12), Eq. (2.29) directly yields a PMF that has the appropriate asymptotic behavior, $W_{\alpha_u \gamma_{u'}}(r) \to Z_{\alpha_u} Z_{\gamma_v}/\epsilon_0 r$ for large r. This second method for the correction of a PMF can be readily used for chemical reactions where site charges z_{α_u} vary as a function of the value of the reaction coordinate.[17,33]

For monatomic solutes where $\hat{w}_u = 1$, no explicit knowledge of the solute–solute radial distribution function and its derivatives is needed to calculate the PMF and its decomposition when the HNC closure, Eqs. (2.20) or (2.36), is used. This is a consequence of the fact that Eqs. (2.29) to (2.31) depend only on the difference between the total and direct correlation functions, which from Eqs. (2.19) and (2.23) does not involve the solute–solute correlation functions directly.[3]

III. MODELS

To facilitate comparison with our earlier work that uses density derivatives,[8] we analyze the solvation thermodynamics for the same model solutions. The solvent is a three-site water model similar to Jorgensen's TIP3P water.[34] The solutes are Lennard-Jones spheres the size of a chloride ion with charges 0, + 1, and − 1. The model ions Br⁻, Na⁺, and K⁺ are also studied and compared with available experimental data. The standard core potential combination rules ($\epsilon_{\alpha\gamma} = \sqrt{\epsilon_\alpha \epsilon_\gamma}$ and $\sigma_{\alpha\gamma} = (\sigma_\alpha + \sigma_\gamma)/2$) are used; the parameters are given in Table I.

TABLE I. Model potential parameters.

	ϵ (kcal/mol)	σ (Å)	q (e)
H_2O^a			
O	0.152	3.15	− 0.834
H	0.046	0.40	0.417
Cl^+	0.107	4.446	1.0
Cl^0	0.107	4.446	0.0
Cl^-	0.107	4.446	− 1.0
Br^-	0.090	4.624	− 1.0
$Na^{+\ b}$			1.0
O	0.118	2.29	
H	0.390	2.22	
$K^{+\ b}$			1.0
O	0.113	3.17	
H	0.373	3.10	

$^a R_{OH} = 0.9572$ Å,$\angle_{HOH} = 104.52°$.
^{b} From Ref. 4.

All calculations were done at 298.15 K and ρ_{H_2O} = 0.997 g/cm^3, for which ϵ_{RISM} = 19.7 for the water model used here. The isochoric temperature derivative of ϵ_0 for pure water required in Eq. (2.34) can be calculated via

$$\left(\frac{\partial \ln(\epsilon_0)}{\partial T} \right)_{\rho_v} = \left(\frac{\partial \ln(\epsilon_0)}{\partial T} \right)_P - \left(\frac{\partial \ln(\epsilon_0)}{\partial P} \right)_T$$
$$\times \left(\frac{\partial P}{\partial \rho_v} \right)_T \left(\frac{\partial \rho_v}{\partial T} \right)_P. \tag{3.1}$$

For the temperature and pressure dependence of ϵ_0, we use the equation of Owen et al;[35] it gives ϵ_0 = 78.4 at 298.15 K and 1 atm. To construct water correlation functions that are consistent with this ϵ_0, an A = 0.959 is needed; operationally it is equivalent to scaling the water site charges by $\sqrt{A}$ = 0.9795 in solving for the pure water correlation functions.[16] The small change in A needed is a result of Eq. (2.12) in which $A \sim 1$ when $\epsilon \gg 1$. For the temperature and pressure dependence of the water density, the equations given by Kell[36] were used.

IV. RESULTS AND DISCUSSION

A. Thermodynamics

Table II shows the solvation thermodynamics for the infinite dilute model solutions described in Sec. III. The results reported include the dielectric correction using Eq. (2.12) unless otherwise specified. For the solvation free energy, $\Delta\mu_{u,sol}^{(0)}$, correcting the water dielectric constant from 19.7 to 78.4 generally leads to more favorable solvation for ionic species; the change is in the range 2 to 3.5 kcal/mol for all of the ions studied. This is consistent with the Born theory of solvation in which a larger solvent dielectric constant increases the solvation free energy.[37] For monatomic ions, the corrections can be evaluated by changing the $(1 - 1/\epsilon_{RISM})$ to $(1 - 1/\epsilon_0)$ in the Born solvation formula (Born radii of 1.74, 1.83, 1.71, and 2.11 in Å for Cl^-, Br^-, Na^+ and K^+, respectively, would yield the calculated values). The viability of such simple correction suggests that the values of Born radii are insensitive to the asymptotic correction and is consistent with little alteration in the short-ranged part of the radial distribution functions.[16] For nonpolar solute Cl^0

TABLE II. Aqueous solvation thermodynamics at infinite dilution from $\mathcal{U}$ and $\mathcal{A}$ routes.[a]

Solute	H_2O	Cl^+	Cl^0	Cl^-	Br^-	Na^+	K^+
$- \Delta\mu_{u,sol}^{(0)}$	$(6.32)^b$			$(80.5^c,73.9^d)$	$(74.2^c,70.6^d)$	$(89.6^c,96.4^d)$	$(72.7^c,78.9^d)$
$A = 1$	6.13	42.0	− 12.1	78.3	73.8	80.6	62.7
$A = $ Eq. (2.12)		44.2	− 12.2	81.9	77.2	84.0	65.6
$- \Delta\epsilon_{u,sol}^{(0)}$	$(10.7)^b$						
$A = 1$	$\mathcal{U}$ 14.2	55.7	− 2.14	92.6	88.0	89.9	72.5
	$\mathcal{A}$ 14.2	55.7	− 2.14	92.6	88.0	89.9	72.5
$A = $ Eq. (2.12)	$\mathcal{U}$	58.1	− 2.25	96.7	92.0	93.7	75.8
	$\mathcal{A}$	56.0	− 2.19	93.3	88.8	90.6	73.1
$- \Delta h_{u,sol}^{(0)}$	$(9.97)^b$			$(88.2^c,81.8^d)$	$(80.8^c,78.4^d)$	$(99.9^c,106.6^d)$	$(80.3^c,86.6^d)$
$A = 1$	$^e\Delta$ 12.9	52.6	− 5.29	90.3			
	$\mathcal{A}$ 12.9	53.0	− 5.32	90.2	85.4	90.0	71.8
$A = $ Eq. (2.12)	$\mathcal{U}$	55.3	− 5.44	94.1	89.2	93.6	75.0
	$\mathcal{A}$	53.2	− 5.37	90.8	86.6	90.5	72.2
$- \Delta s_{u,sol,P}^{(0)}$	$(12.24)^b$			$(25.8^c,26.5^d)$	$(22.1^c,26.2^d)$	$(34.5^c,34.2^d)$	$(25.5^c,25.8^d)$
$A = 1$	$\mathcal{A}$ 22.7	37.1	22.9	40.1	39.2	31.5	30.6
$A = $ Eq. (2.12)	$\mathcal{U}$	37.3	22.7	41.2	40.4	32.4	31.5
	$\mathcal{A}$	30.4	23.0	29.9	31.6	21.8	22.4

$^a \Delta\mu_{u,sol}^{(0)}$, $\Delta\epsilon_{u,sol}^{(0)}$ and $\Delta h_{u,sol}^{(0)}$ are in kcal/mol and $\Delta s_{u,sol,P}^{(0)}$ is in cal/mol · K. For ions, the experimental data have been adjusted to correspond to infinite dilute solution.
^{b} Experimental data from Ref. 20.
^{c} From Refs. 38 and 39.
^{d} From Ref. 40.
$^e \Delta$ stands for finite difference approximation to the $\mathcal{A}$ route (see the text).

where correcting the solvent dielectric constant should have little or no effect, the solvation free energies with and without the correction are 12.2 and 12.1 kcal/mol, respectively. The agreement of the calculated $\Delta\mu_{u,\text{sol}}^{(0)}$ with more recent experiments[38,39] is within 10% in all cases and is somewhat better for Cl^- and Br^- ($<4\%$) than for Na^+ and K^+; the agreement with earlier experimental data[40] is worse but still within 17% in all cases. It is also of interest to compare the difference between ions which can be obtained directly from simulations. For $Cl^- \rightarrow Br^-$ the theory predicts a $\Delta\Delta\mu_{u,\text{sol}}^{(0)}$ of -4.7 kcal/mol compared with -3.6 kcal/mol from molecular dynamics simulation with the same parameters;[41] the experimental data range from -3.3^{40} to -6.3 kcal/mol.[38,39] For $Na^+ \rightarrow K^+$ the $\Delta\Delta\mu_{u,\text{sol}}^{(0)}$ is -18.4 with experiments range from $-16.9^{38,39}$ to -17.5^{40} kcal/mol.

For the $\Delta\epsilon_{u,\text{sol}}^{(0)}$ we listed two sets of values calculated from the earlier analytic isothermal solute density derivative ($\mathcal{U}$-route[42]) method[8] and the analytic isobaric temperature derivative ($\mathcal{A}$-route[42]) method developed in this paper. For the $\Delta h_{u,\text{sol}}^{(0)}$, the analytic isobaric temperature derivative method is compared with its finite difference approximation (Δ). The latter was done by calculating the solvation free energies at 293.15 and 303.15 K with water densities at their respective temperatures at 1 atm pressure.[6] For $\Delta\epsilon_{u,\text{sol}}^{(0)}$ with $A = 1$, the difference between the analytic $\mathcal{U}$ and $\mathcal{A}$ routes are less than 0.02 kcal/mol, whereas with A specified by Eq. (2.12) they can be of the order of 2 to 3.5 kcal/mol for ions, about 4% of the solvation energy or enthalpy (see entries for Cl^+ and Cl^- in Table II). The thermodynamic consistency of the two routes in the calculation with $A = 1$ is outlined analytically in Appendix B, whereas in the case of $A \neq 1$ the terms causing inconsistency are isolated. The $\Delta\Delta h_{u,\text{sol}}^{(0)}$ for $Cl^- \rightarrow Br$ are -4.2 ($\mathcal{U}$ route) and -4.9 ($\mathcal{A}$ route) kcal/mol compared with the experimental range -3.4^{40} to $-7.4^{38,39}$ kcal/mol. For $Na^+ \rightarrow K^+$, they are -18.7 ($\mathcal{U}$ route) and -18.2 ($\mathcal{A}$ route) kcal/mol compared with $-19.6^{38,39}$ to -20^{40} kcal/mol from experiments.

Results for pure water are included to show that when $A = 1$ the method is not restricted to the limit of infinite dilution. The $\Delta\mu_{u,\text{sol}}^{(0)}$ of -6.13 is in surprisingly good agreement with the experimental value of -6.32 kcal/mol.[20] For the $\Delta h_{u,\text{sol}}^{(0)}$, the -12.9 calculated is 30% larger than -9.97 kcal/mol from experiment.[20] This is consistent with the fact that the HNC-RISM theory overestimates the hydrogen bonding interaction in water; the first maximum in the hydrogen–oxygen radial distribution function is at $r_{\text{max}} = 1.5$ Å and has a height $g_{\text{max}} = 2.3$; simulations[43,44] give ($r_{\text{max}}, g_{\text{max}}$) of (1.8–1.9Å,1.1–1.4) while experimental data yield (1.85–1.95 Å, 0.8~1.4).[45,46,54] The difference between the calculated solvation enthalpy and energy for water of 1.26 kcal/mol is somewhat larger than the experimental estimate of 0.69 kcal/mol; this translates into the calculated isothermal compressibility being 45% too low [see Eq. (2.7)]. Simulation results underestimate the value by about 60%.[43]

B. Distribution functions

The analytic temperature derivative method provides structural information in addition to the solvation thermo-

dynamics; the results complement those obtained from the analytic density derivatives.[8]

In Figs. 1(a) to 1(c) we present the site–site distribution functions and their temperature derivatives for pure water. The solid lines correspond to $g(r)$ for the case of $A = 1$ and the dotted lines are obtained when A is given by Eq. (2.12). The height of the hydrogen bonding peak is reduced by 4% [see Fig. 1(b)] when the radial distribution functions are required to be consistent with the macroscopic dielectric constant for water. This reduction, though small, is in the correct direction to improve agreement with experiment and simulations. The other $g(r)$ peaks have magnitudes that are within 1% of each other for the two forms of A. This confirms the relatively weak coupling between long-ranged and short-ranged behavior of the radial distribution functions.[16] The $\delta_T h_{\alpha\gamma}$'s for an increase in temperature are shown as dashed lines; they have been multiplied with $T = 298.15$ K [cf. Eqs. (2.25) and (2.26)] and shifted by $+1.0$ to facilitate comparisons with the $g_{\alpha\gamma}$'s. The two different A's gave $\delta_T h_{\alpha\gamma}$'s that are indistinguishable on the scale of the figure. That the $\delta_T h_{\alpha\gamma}$'s are out of phase with the $g_{\alpha\gamma}$'s reflects the fact that an increase in temperature decreases the correlation among water sites. Both the hydrogen-bonding peak at 1.5 Å in g_{OH} and the tetrahedral coordination peak at 4.3 Å in g_{OO} are thus diminished. The innermost peaks in the $\delta_T h_{\alpha\gamma}$'s are a result of the increased probability of sampling more of the repulsive configurations at elevated temperatures.

For the *chlorides* (see Fig. 2), the positions of g_{Cl-H} and g_{Cl-O} are 2.0 and 3.5 Å, respectively, as compared with experimental data of 2.25 and 3.6 Å.[47] The $\delta_T h_{uv}^{(0)}$'s have the same out-of-phase relationship with respect to the g_{uv}'s as the water results, but the magnitudes of $\delta_T h_{uv}^{(0)}$'s are somewhat larger.

C. Potential of mean force

The PMF (W,–), enthalpy (H,--) and entropy ($-TS_p$,–·–) are shown for all possible *chloride* pairs with A specified by Eq. (2.12) in Figs. 3(a)–3(f); the thin lines give the corresponding W', H' and $-TS'_p$ for $A = 1$. For the PMF involving at least one nonpolar solute Cl^0 (i.e., Cl^0–Cl^0 and Cl^0–$Cl^\pm$), Figs. 3(a) to 3(c), the two are nearly indistinguishable on the scale of the graph. For ionic species, Figs. 3(d) to 3(f), the two asymptotic corrections for the PMF gave quantitative agreement down to a value of r in the range of the van der Waals' contact; the only difference is inside the core. The disagreement at small r may be related to the way Eq. (2.33) is used; that is, the asymptotic correction was employed for even the unphysical region inside the core.

Figures 3(a)–3(c), when compared with Figs. 3(d)–3(f), show that the association of pairs involving at least one Cl^0 have comparable enthalpies and entropies of mean force, in contrast to those involving only charged solutes. In the latter, the entropy of mean force is repulsive for like-charged pairs while it is attractive for the oppositely charged pair. The minimum in the PMF for Cl^0–Cl^0 is *deeper* than that for Cl^0–Cl^- and Cl^0–Cl^+ by 0.3 kcal/mol (see Table III). This may reflect the negative solvation free energies of isolated Cl^- and Cl^+ ions in water, which favors the situation where

(a)   r (Å)

(c)   r (Å)

(b)   r (Å)

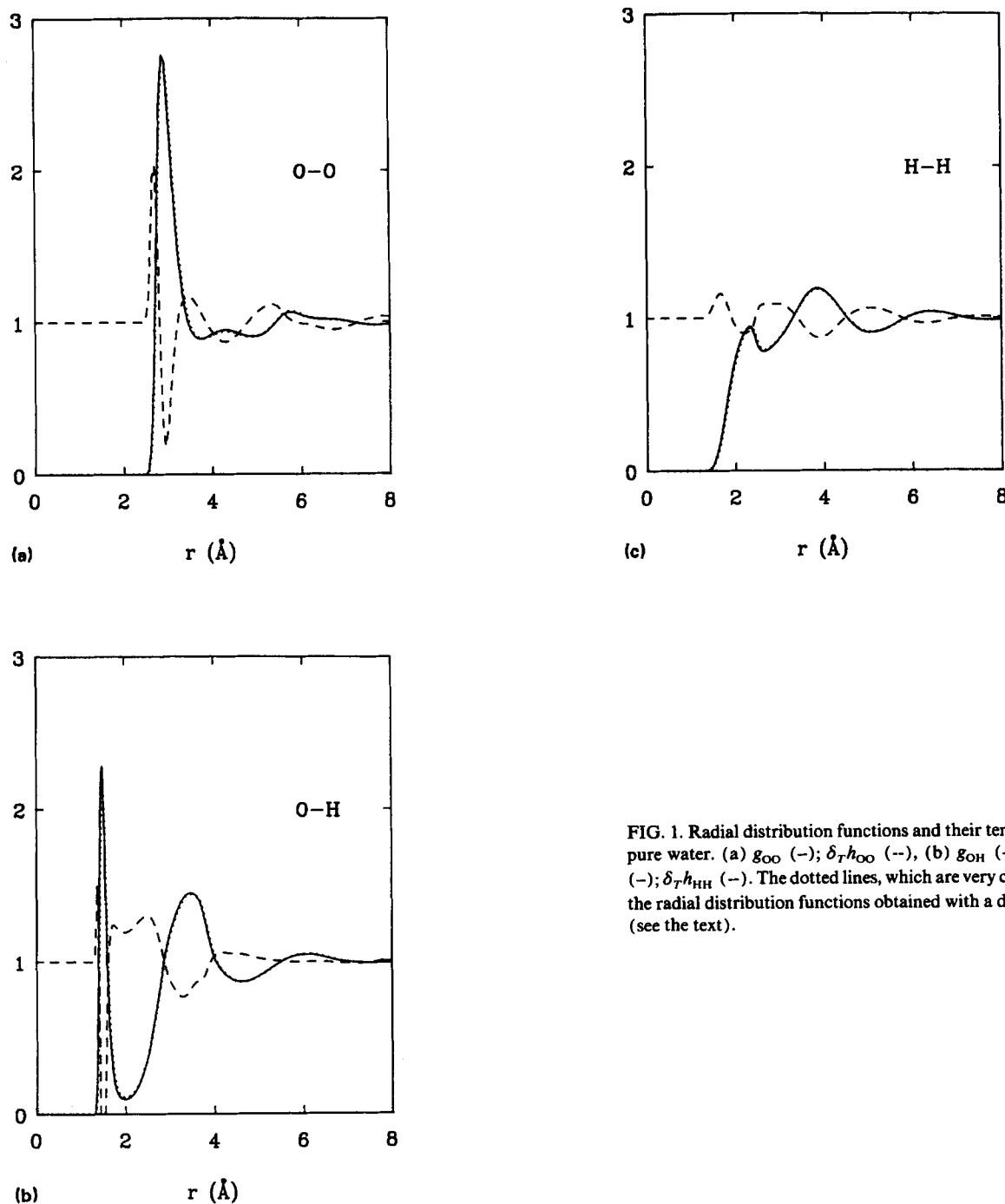FIG. 1. Radial distribution functions and their temperature derivatives for pure water. (a) g_{OO} (–); $\delta_T h_{OO}$ (--), (b) g_{OH} (–); $\delta_T h_{OH}$ (--), (c) g_{HH} (–); $\delta_T h_{HH}$ (--). The dotted lines, which are very close to the solid line, give the radial distribution functions obtained with a dielectric constant of 78.4 (see the text).

the ion is surrounded by water instead of being associated with a Cl^0. The narrower well for Cl^0–Cl^- compared to Cl^0–Cl^0 and Cl^0–Cl^+ implies a spatially more restricted solvent cage around the Cl^0–Cl^- pair due to a smaller $Cl^- \cdots H$ separation than for $Cl^+ \cdots O$. This would be expected to lead to a higher frequence of oscillation for Cl^0–Cl^-.

It is of interest that for the like-charged ionic association, Cl^-–Cl^- and Cl^+–Cl^+, the enthalpy is the driving force despite the bare repulsive Coulombic interaction; for oppositely charged ions the contrary is true. This originates from the approximately quadratic dependence of the solvation thermodynamics on the solute charge.[8,37,48] The process of bringing two like-charged ions together leads to higher local charge density; the more favorable solvation enthalpy arising from the q^2 dependence more than compensates for the Coulombic repulsion. For oppositely charged ions, association leads to a partial charge neutralization in which the favorable Coulombic attraction is overwhelmed by the loss of stabilizing solvation enthalpy. The trend for the entropy can be understood in terms of the difference in the strength of the electrostatic field being exerted on the water solvent by the various contact ion pairs. For instance, the entropy driven association of the Cl^- and Cl^+ is a consequence of the decrease in the electrostatic field resulting from formation of the Cl^-–Cl^+ pair. This allows more freedom for the neighboring water molecules than for the separated pair.

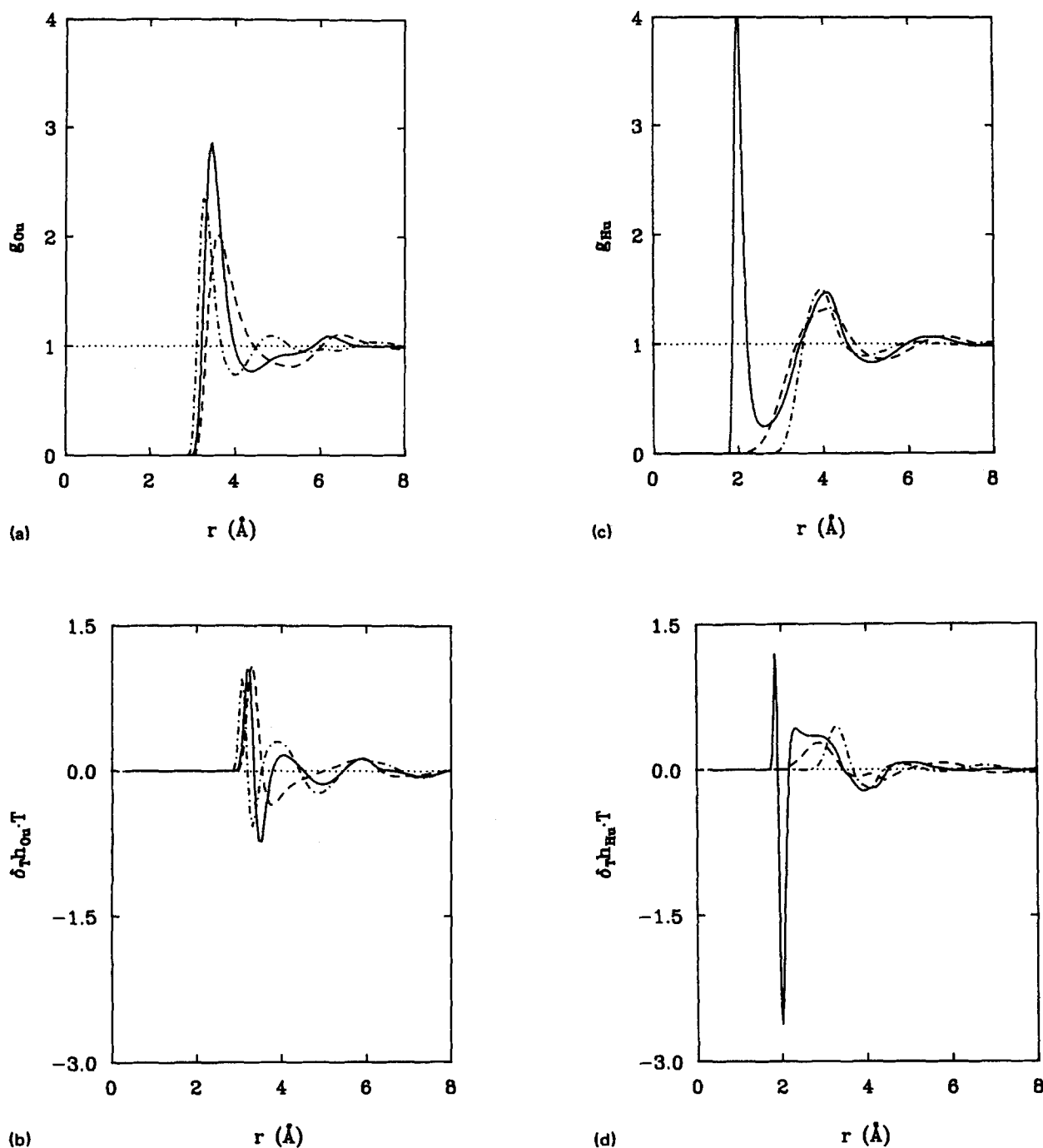FIG. 2. Radial distribution functions and their temperature derivatives for *chlorides*. (a) g_{O-Cl} (–); $g_{O-Cl''}$ (--); $g_{O-Cl'}$ (-·-); (b) $\delta_T h_{O-Cl}$ (–); $\delta_T h_{O-Cl''}$ (--); $\delta_T h_{O-Cl'}$ (-·-); (c) g_{H-Cl} (–); $g_{H-Cl''}$ (--); $g_{H-Cl'}$ (-·-); (d) $\delta_T h_{H-Cl}$ (–); $\delta_T h_{H-Cl''}$ (--); $\delta_T h_{H-Cl'}$ (-·-).

In Table III we summarize information on the *total* PMF's for the various species [see Eq. (2.29)]. The value of r at the first minimum and the various contributions to the PMF for both $A = 1$ and A given by Eq. (2.12) are shown. The asymmetric charged sites in the water model induces different features with respect to the anion and cation pairs. For example, the bifunctional water, in the sense of having two positively charged hydrogen sites, enable the $Cl^- - Cl^-$ pair to come much closer (to a distance of 3.97 Å) as compared to that of the $Cl^+ - Cl^+$ pair minimum at 5.47 Å.[49,50]

This difference of 1.5 Å in the minimum is likely to be an overestimation due to the shorter hydrogen bonding distance of 1.5 Å in the RISM model (see above).

For the monatomic solutes studied here at infinite dilution there is no need to solve explicitly for the solute–solute radial distribution function to calculate the PMF and its decomposition.[3] This means the contribution of the short-ranged solute–solute core potential can be chosen independent of the solvent contribution. To illustrate this, we compare the present study of $Cl^- - Cl^-$ with the HNC-
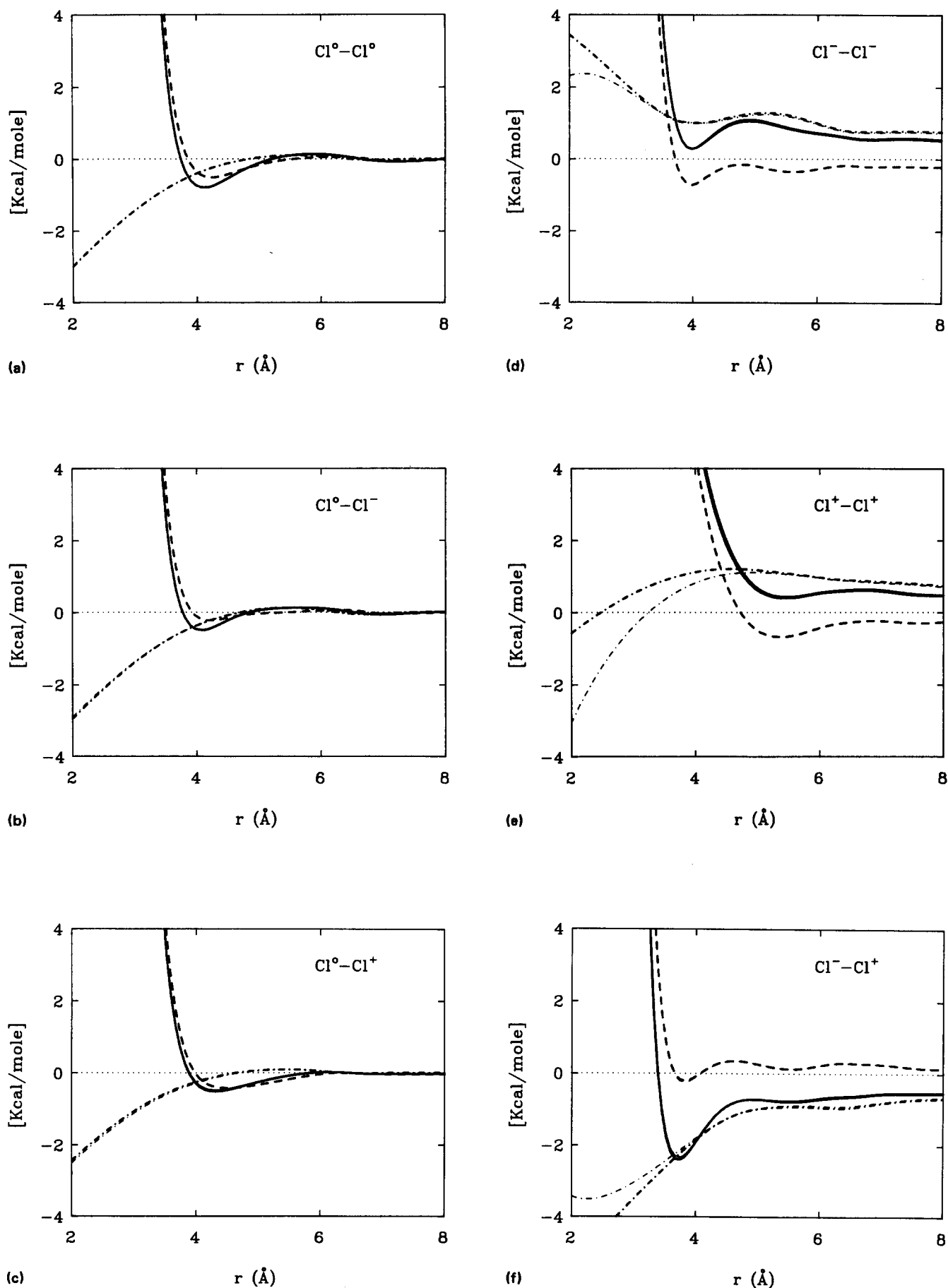
FIG. 3. Thermodynamic components of the asymptotically corrected PMF for *chlorides*. W (–); H (--) and $- TS_P$ (---) for A given by Eq. (2.12). W' (–); H' (--) and $- TS'_P$ (-·-) for $A = 1$. (a) Cl^0–Cl^0; (b) Cl^0–Cl^-; (c) Cl^0–Cl^+; (d) Cl^-–Cl^-. (e) Cl^+–Cl^+; (f) Cl^-–Cl^+.

TABLE III. Summary for the potential of mean force decomposition in water.

Contact pair	r_{min}[a] (Å)	W	H (kcal/mol)	E	S_P	S_V (cal/mol K)
Cl^0–Cl^0	4.14[b]	− 0.81	− 0.50	− 0.42	1.02	1.28
	(4.14)[c]	(− 0.82)	(− 0.50)	(− 0.43)	(1.04)	(1.30)
Cl^0–Cl^-	4.06	− 0.50	− 0.18	− 0.11	1.08	1.32
	(4.06)	(− 0.52)	(− 0.19)	(− 0.12)	(1.10)	(1.35)
Cl^0–Cl^+	4.30	− 0.51	− 0.40	− 0.32	0.34	0.62
	(4.30)	(− 0.54)	(− 0.41)	(− 0.33)	(0.43)	(0.70)
Cl^-–Cl^-	3.97	0.28	− 0.73	− 0.60	− 3.38	− 2.96
	(3.97)	(0.27)	(− 0.74)	(− 0.61)	(− 3.41)	(− 2.98)
Cl^-–Cl^+	3.74	− 2.42	− 0.18	− 0.16	7.51	7.58
	(3.74)	(− 2.35)	(− 0.21)	(− 0.17)	(7.19)	(7.30)
Cl^+–Cl^+	5.47	0.41	− 0.67	− 0.62	− 3.64	− 3.48
	(5.47)	(0.38)	(− 0.68)	(− 0.64)	(− 3.55)	(− 3.42)

[a] Position of the first minimum in the PMF.
[b] A as given by Eq. (2.12).
[c] $A = 1$.

RISM calculation of Pettitt and Rossky;[4] they found a stable minimum of − 1.4 kcal/mol at 3.5 Å, while we find only a local minimum that is overall repulsive (relative to infinite separation) at 3.97 Å [see Fig. 3(d) and Table III]; the well depth is − 0.7 kcal/mol relative to a barrier at 5.3 Å. The difference in the two results can be traced back to the different short-ranged core potentials. Figure 4(a) shows the Huggins–Mayer potential (− −) adopted in the study of Pettitt and Rossky and the Lennard-Jones form (—) used here; the former has a much smaller repulsive core. In Fig. 4(b) we show the PMF and its decomposition for the smaller core size Huggins–Mayer potential. The entropic component (-·-) remains the same as that in Fig. 3(d) since it is independent of the choice of core potential. The PMF, however, now has a net stability of − 1.5 kcal/mol at 3.55 Å, slightly more favorable (by 0.1 kcal/mol) than the result of Pettit and Rossky. The latter seems to be a consequence of the different water models used, i.e., the oxygen charge used here is q_O = − 0.834 versus − 0.80 proton units in their study.

The very different PMF's in Figs. 3(d) and 4(b) clearly demonstrates the importance of the choice of short-ranged core potentials in RISM calculations, quite independent of the solute–solvent interactions. Explicit molecular dynamics simulation with the Huggins–Mayer core potential used by Pettitt and Rossky[4] gave a PMF with a minimum of − 1.2 ± 0.6 kcal/mol at 3.5 Å that agrees well with their HNC-RISM calculation.[49,50] However, recent Monte Carlo simulation using Lennard-Jones core parameters of (ϵ, σ) = (0.118 kcal/mol, 4.471 Å) for Cl^- in TIP4P water gave a PMF for Cl^-–Cl^- with a deep minimum of − 4.2 kcal/mol near 4.8 to 5.0 Å;[51] the two simulations thus gave very different solvent contributions. Although it had been suggested that difference in core potentials may be the cause,[51] at infinite dilution the Cl^-–Cl^- potential does not
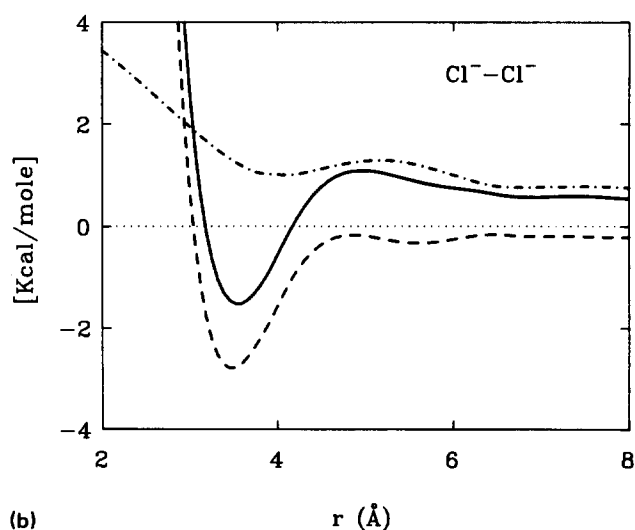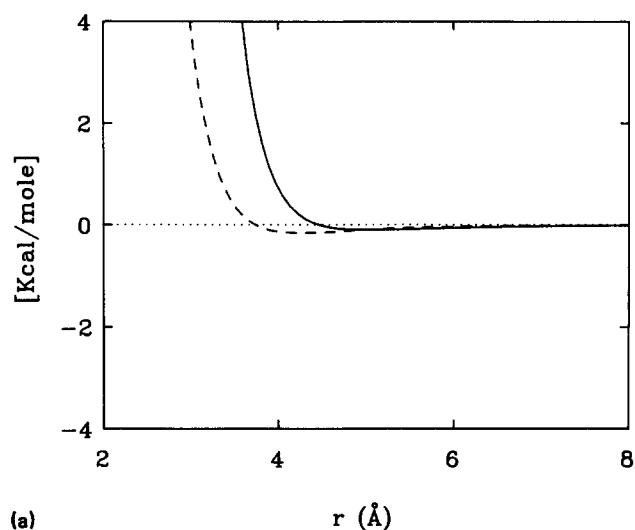
FIG. 4. Thermodynamic components of the PMF for Cl^- with the Huggins–Mayer core. (a) Short-ranged core potentials. Lennard-Jones (−); Huggins–Mayer (--), (b) Huggins–Mayer core. W (-); H (--); $- TS_P$ (-·-).

affect the solvent contribution to the Cl^-–Cl^- PMF; the latter is determined solely by the solvent–solvent and solute–solvent potentials. In the Monte Carlo study[51] the Cl^-–Cl^- potential never comes directly into the simulation whereas in the molecular dynamics study[49,50] the simulation was done with umbrella sampling using the PMF from HNC-RISM calculation as the biasing function; i.e., the Cl^-–Cl^- potential is present explicitly in the simulation and its effect was removed by subsequent data processing. Since the difference of 1.3 to 1.5 Å in the positions of minima between the two simulations seems larger than can be accounted for by the difference in the Cl^- water or water–water potentials (the present calculation shows a shift of 0.5 Å using the Lennard-Jones core), it is likely that difference in methodology also contributed to the observed discrepancy in the simulations.

V. CONCLUSIONS

In this paper, we have demonstrated how analytic temperature derivatives of the radial distribution functions can be used to study the solvation thermodynamics. The present formulation thus complements the earlier work using density derivatives. The agreement of the results obtained with the two approaches for $A = 1$ reflects the thermodynamic consistency between the $\mathscr{U}$ and $\mathscr{A}$ routes. The method of density derivatives provides more information that may be interpreted as solvent structure breaking or promotion induced by the solute. The temperature derivative approach has the advantage that when applied to polyatomic solutes it can lead to detailed partitioning of the solvation thermodynamic results into contributions from various functional groups, e.g., for the interaction of amino acids with water, the thermodynamics can be analyzed in terms of contribution from the main chain peptide $N\text{-}H$,$C\!\!=\!\!O$ and the various side chains.[18] In the earlier solute density derivative method only the free energy can be decomposed in this way; the energy and entropy could not be decomposed because the bulk solute density is a property of the solute molecule as a whole.

Two asymptotic corrections of the PMF for infinite dilute ionic solutes are compared and found to give similar results except for the unphysical region inside the repulsive core. The method in which modified site–site HNC closures are used to impose a dielectric constant consistent with macroscopic experimental data has the advantage that it may be applied to complex chemical reactions in which the site charges vary as a function of the reaction coordinate. This approach has been applied to the nucleophilic addition of hydorxide to formaldehyde and to the solvation of N-methyl acetamide.[17,18]

A method is developed which enabled the calculation of the solvation enthalpy in addition to other thermodynamic quantities. This allows direct comparison with a wider range of experimental solvation data than the energy results; satisfactory agreement ($\sim 10\%$) for both anions and cations was found. The usefulness of the present approach is demonstrated by a decomposition of the potential of mean force into its thermodynamic components for various solute pairs. By studying them with the same Lennard-Jones interaction parameters but varied charges, we are able to determine the effect of charges on the solute aggregation and dissociation. For cation–anion pairs, it is not the enthalpy, as one might have expected (based on the favorable bare Coulombic interaction), but the entropy that leads to their enhanced association over nonpolar and like-charged solute pairs. The enhancement is a consequence of partial charge neutralization in cation–anion pairs that leads to greater orientational freedom of the surrounding water molecules. This behavior corresponds to that found in a continuum theory in which the effect of solvent is represented by its dielectric constant. For two solutes with charges q_i and q_j, the solvent-mediated Coulombic interaction is

$$W_{ij}(r) = q_i q_j/\epsilon r = E_{ij}(r) - TS_{ij}(r),\qquad (5.2)$$

where the entropic contribution is given by

$$S_{ij}(r) = -\frac{\partial W_{ij}(r)}{\partial T} = \frac{q_i q_j}{\epsilon r}\left(\frac{1}{\epsilon}\frac{\partial \epsilon}{\partial T}\right).\qquad (5.3)$$

As the solvent dielectric constant in general decreases with increasing temperature, $S_{ij}(r)$ is positive for $q_i q_j < 0$, i.e., for oppositely charged species.

Enthalpy and entropy were found to make comparable contribution to the association of nonpolar solute in water. This observation disagrees with the conventional description of an entropy driven hydrophobic interaction and is the subject of a future study.[52]

Since we have used the experimental dielectric constant (instead of that given by the HNC-RISM theory or simulation) and isobaric thermal expansion coefficient for water as input in our calculation, the present approach has a semiempirical element. It can thus be made more consistent (and perhaps more accurate) by use of experimental information for the water radial distribution functions[1] (including their derivatives[53] if sufficiently accurate) to eliminate some of the deficiencies in the theory; e.g., the incorrectly predicted position of the hydrogen bonding peak, the lack of stoicheometric consistency (i.e., the mismatch of coordination numbers for oxygen and hydrogen in the water radial distribution functions).

Finally, we note that although we have used the site–site Ornstein–Zernlike integral equation and the site–site HNC closure for the study here, the method is not restricted to them. For example, the approach is applicable to site–site Percus–Yevick-like closures.

ACKNOWLEDGMENT

APPENDIX A: DERIVATIVES OF THE SSOZ EQUATION

In this Appendix, we outline a convenient scheme for deriving Eqs. (2.14) to (2.19), (2.22) and (2.23).

The basic structure of Ornstein–Zernlike-like equations in k space [e.g., Eq. (2.11)] is

$$Z = X + XYZ.\qquad (A1)$$

Applying an arbitrary variation denoted by δ to the above equation leads to

$$
\begin{aligned}
\delta Z &= XY\delta Z + X\delta YZ + \delta X[1 + YZ]\\
&= [1 - XY]^{-1}X\delta YZ\\
&\quad + [1 - XY]^{-1}\delta X[1 + YZ]\\
&= Z\delta YZ + [1 + ZY]\delta X[1 + YZ]\\
&= Z\delta YZ + ZX^{-1}\delta XX^{-}Z.
\end{aligned}\qquad (A2)
$$

As concrete examples, the following table lists the application of the above two equations to derive Eqs. (2.14), (2.15), (2.19), (2.22), and (2.23).

Eq.	δ	X	Y	Z
(2.14)	δ_T	$\overline{\hat{Q}}$	$\hat{c}^*$	$\overline{\hat{\chi}}$
(2.15)	δ_T	$\rho\hat{w}$	$A\hat{\phi}$	$\overline{\hat{Q}}$
(2.19)	δ_T	$\rho\hat{w}$	$\hat{c}$	$\overline{\hat{\chi}}$
(2.22)	δ_{ρ_u}	$\rho\hat{w}$	$A\hat{\phi}$	$\overline{\hat{Q}}$
(2.23)	δ_{ρ_u}	$\rho\hat{w}$	$\hat{c}$	$\hat{\chi}$

Equations for higher derivatives can be obtained in a similar way.

APPENDIX B: THERMODYNAMIC CONSISTENCY OF $\mathscr{U}$ AND $\mathscr{A}$ ROUTE IN THE HNC-RISM THEORY

We follow the works of Morita and Hiroike[30,31] and Singer and Chandler[29] to show the thermodynamic consistency of $\mathscr{U}$ (energy) route and $\mathscr{A}$ (Helmholtz free energy) route[42] to the solvation energy in the HNC-RISM theory. For illustration we treat a two components polyatomic liquid.

The $\mathscr{U}$ route is given by the definition of the solvation energy density which can be written as

$$\left\{ \frac{\Delta\mathscr{E}}{V} \right\}_{\mathscr{U}} = \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int d\mathbf{r}\, \rho_M U_{\alpha_M\gamma_{M'}}(r)$$
$$\times [h_{\alpha_M\gamma_{M'}}(r) + 1]\rho_{M'}. \tag{B1}$$

The $\mathscr{A}$ route makes use of the temperature derivative of the excess Helmholtz free energy density

$$\left\{ \frac{\Delta\mathscr{E}}{V} \right\}_{\mathscr{A}} = \left(\frac{\partial\beta\Delta\mathscr{A}/V}{\partial\beta} \right)_\rho. \tag{B2}$$

Within the HNC-RISM theory the free energy density is[29]

$$\frac{-\beta\Delta\mathscr{A}}{V} = \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int d\mathbf{r}\, \rho_M \left[c_{\alpha_M\gamma_{M'}}(r) - \tfrac{1}{2}h^2_{\alpha_M\gamma_{M'}}(r) \right]\rho_{M'} - \frac{1}{2}\int \frac{d\mathbf{k}}{(2\pi)^3}\{ \mathrm{Tr}[\rho\hat{w}\hat{c}] + \ln(\det[1-\rho\hat{w}\hat{c}]) \}$$

$$- \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int_0^1 d\lambda \int d\mathbf{r}\, \rho_M g_{\alpha_M\gamma_{M'}}(r;\lambda) \frac{\partial(A-1)\phi_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\lambda}\rho_{M'}$$

$$= \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int d\mathbf{r}\, \rho_M \left\{ [f_{\alpha_M\gamma_{M'}}(r) + 1]e^{t_{\alpha_M\gamma_{M'}}(r) + (A-1)\phi_{\alpha_M\gamma_{M'}}(r)} \right.$$

$$\left. - 1 - t_{\alpha_M\gamma_{M'}}(r) - h_{\alpha_M\gamma_{M'}}(r)t_{\alpha_M\gamma_{M'}}(r) + \tfrac{1}{2}h^2_{\alpha_M\gamma_{M'}}(r) \right\}\rho_{M'}$$

$$- \frac{1}{2}\int \frac{d\mathbf{k}}{(2\pi)^3}\{ \mathrm{Tr}[(\rho\hat{w} + \rho\hat{h}\rho)\hat{c}] + \ln(\det[1-\rho\hat{w}\hat{c}]) \}$$

$$- \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int_0^1 d\lambda \int d\mathbf{r}\, \rho_M g_{\alpha_M\gamma_{M'}}(r;\lambda) \frac{\partial(A-1)\phi_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\lambda}\rho_{M'}$$

$$\equiv \mathscr{F}[c,h,t,f,\rho,\beta,A] \tag{B3}$$

with $t = h - c$ and $f = e^{-\beta U} - 1$. For $A = 1$, Singer and Chandler has shown that the $\mathscr{F}$ is stationary with respect to variations of the c, h and t in the HNC-RISM integral equation theory. For $A \neq 1$, the $\mathscr{F}$ is again stationary with respect to variations in c and t but is no longer so for h due to the presence of the third term in Eq. (B3). Eq. (B2) then leads to

$$\left\{ \frac{\Delta\mathscr{E}}{V} \right\}_{\mathscr{A}} = -\left(\frac{\partial\mathscr{F}}{\partial\beta} \right)_\rho = \left\{ \frac{\Delta\mathscr{E}}{V} \right\}_{\mathscr{U}} + \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int d\mathbf{r}\, \rho_M g_{\alpha_M\gamma_{M'}}(r) \frac{\partial(A-1)\phi_{\alpha_M\gamma_{M'}}(r)}{\partial\beta}\rho_{M'}$$

$$+ \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int_0^1 d\lambda \int d\mathbf{r}\, \rho_M \frac{\partial g_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\beta}\left[\frac{\partial(A-1)\phi_{\alpha_M\gamma_{M'}}(r;\lambda)/\partial\lambda}{\partial\beta} \right]\rho_{M'}. \tag{B4}$$

Thus, unless the sum of the last two terms in Eq. (B4) vanishes (e.g., as when $A = 1$) one would find thermodynamic inconsistency between the two routes. When $A = 1$, Eq. (B4) gives the analog in the HNC-RISM theory of the thermodynamic consistency between the $\mathscr{U}$ route and $\mathscr{A}$ route to the internal energy first demonstrated by Morita and Hiroike for simple liquids in the HNC approximation.[30,31]

The excess chemical potential for solute (u) is obtained by a derivative of $\mathscr{F}$ with respect to ρ_u,

$$-\beta\Delta\mu_u = \left(\frac{\partial\mathscr{F}}{\partial\rho_u} \right)_{\beta,\rho_v} = \sum_M^{u,v} \sum_{\alpha=1}^{n_u} \sum_{\gamma=1}^{n_M} \int d\mathbf{r}\left[c_{\alpha_u\gamma_M}(r) - \tfrac{1}{2}h^2_{\alpha_u\gamma_M}(r) + \tfrac{1}{2}h_{\alpha_u\gamma_M}(r)c_{\alpha_u\gamma_M}(r) \right]\rho_M$$

$$- \frac{1}{2} \sum_M^{u,v} \sum_{\alpha=1}^{n_u} \sum_{\gamma=1}^{n_M} \int_0^1 d\lambda \int d\mathbf{r}\, g_{\alpha_u\gamma_M}(r;\lambda) \frac{\partial(A-1)\phi_{\alpha_u\gamma_M}(r;\lambda)}{\partial\lambda}\rho_M$$

$$- \frac{1}{2} \sum_{M,M'}^{u,v} \sum_{\alpha=1}^{n_M} \sum_{\gamma=1}^{n_{M'}} \int_0^1 d\lambda \int d\mathbf{r}\, \rho_M \left\{ g_{\alpha_M\gamma_{M'}}(r;\lambda) \frac{\partial\left[(\partial A/\partial\rho_u)_{\beta,\rho_v} - 1 \right]\phi_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\lambda} \right.$$

$$\left. + \left(\frac{\partial g_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\rho_u} \right)_{\beta,\rho_v} \frac{\partial(A-1)\phi_{\alpha_M\gamma_{M'}}(r;\lambda)}{\partial\lambda} \right\}\rho_{M'} \tag{B5}$$

The excess solvation energy for the solute is given either as a temperature derivative of Eq. (B5) or a ρ_u density derivative of Eq. (B1). When $A = 1$ and at the limit of $\rho_u \to 0$, the former leads to Eq. (2.26) and the latter leads to Eq. (2.28).

APPENDIX C: DIELECTRIC CORRECTION

In this Appendix, we briefly outline the dielectric correction introduced by the modified solvent site–site HNC closures, Eq. (2.36).[3,14–16]

Chandler[11] has derived a correlation function formula for the dielectric constant ϵ:

$$\frac{1}{\epsilon} - 1 = \text{Tr}\{\Psi\hat{\chi}^{(2)}\} \quad \text{with} \quad \Psi_{\alpha_M\gamma_M} = -4\pi\beta z_{\alpha_M}z_{\gamma_M},$$

(C1)

where Tr stands for taking the trace of a matrix. The function $\hat{\chi}^{(2)}$ is the second moment in the small k expansion of $\hat{\chi}$. In RISM theory, the dielectric constant ϵ is given by the ideal gas value of $\epsilon_{\text{RISM}} = 1 + 3y$.[11]

The use of Eq. (2.36) can be mapped to that of using a *normal* site–site HNC closure by scaling the physical charges z_{α_M} of the solvent by $z'_{\alpha_M} = \sqrt{A}\, z_{\alpha_M}$.[16] From Eq. (C1), the dielectric constant ϵ'_{RISM} of the modified solvent (denoted by the prime) is given by

$$\frac{1}{\epsilon'_{\text{RISM}}} - 1 = \text{Tr}\{\Psi'\hat{\chi}'^{(2)}\} = \text{Tr}\{A\Psi\hat{\chi}'^{(2)}\},$$

(C2)

where ϵ'_{RISM} is $1 + 3Ay$ and y is calculated from the physical charges of the solvent [see Eq. (2.12)].

When the modified solvent structure χ' is used together with a *normal* site–site HNC closure [Eq. (2.20)] between solute and solvent, the asymptotic amplitude of the potential of mean force between site α_u on solute u and site $\gamma_{u'}$ on solute u' is given by [c.f. Eq. (2.32)][11]

$$W_{\alpha_u\gamma_{u'}}(r) \to \frac{1}{\epsilon_0}\frac{Z_u Z_{u'}}{r} \quad \text{for large } r,$$

(C3)

where ϵ_0 is related to $\hat{\chi}'$ by

$$\frac{1}{\epsilon_0} - 1 = \text{Tr}\{\Psi\hat{\chi}'^{(2)}\} = \frac{-3y}{1 + 3Ay}.$$

(C4)

Note that it is Ψ, instead of Ψ', in Eq. (C4) since the solutes see the physical charges of the solvent. Eq. (2.12) is obtained by solving Eq. (C4) for A. For water at 298.15 K and 1 atm, the experimental dielectric constant $\epsilon_0 = 78.4$ can be used to fit the value of A needed in Eq. (2.36).

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