Solvation Thermodynamics: Theory and Applications[†]

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Potential distribution and coupling parameter theories are combined to interrelate previous solvation thermodynamic results and derive several new expressions for the solvent reorganization energy at both constant volume and constant pressure. We further demonstrate that the usual decomposition of the chemical potential into noncompensating energetic and entropic contributions may be extended to obtain a Gaussian fluctuation approximation for the chemical potential plus an exact cumulant expansion for the remainder. These exact expressions are further related to approximate first-order thermodynamic perturbation theory predictions and used to obtain a coupling-parameter integral expression for the sum of all higher-order terms in the perturbation series. The results are compared with the experimental global solvation thermodynamic functions for xenon dissolved in *n*-hexane and water (under ambient conditions). These comparisons imply that the constant-volume solvent reorganization energy has a magnitude of at most $\sim kT$ in both experimental solutions. The results are used to extract numerical values of the solute−solvent mean interaction energy and associated fluctuation entropy directly from experimental solvation thermodynamic measurements.

1. Introduction

The solvation of a single molecule is the elementary process undelying all fluid chemical equilibria.[1−5] For example, the free energy of solvation dictates the equilibrium vapor pressure of a solute, as well as the partitioning of a solute between two fluid phases. In systems containing chemically reactive molecules, it is the difference between the chemical potentials of the products and the reactants which determines the equilibrium concentration of each species.

Theoretical expressions for the chemical potential may be derived using various quite different formulations.[1,6−9] For example, the chemical potential may be obtained from the solute-insertion Boltzmann factor (probability) averaged over preequilibrated solvent configurations using the Widom potential-distribution theorem.[10−12] Alternatively, the chemical potential may be related to the reversible work required to grow a solute within the solvent using Kirkwood coupling-parameter integration.[2,13] Although the resulting chemical potentials are necessarily equivalent, such alternative approaches provide different fundamental and physical insights into the solvation process.

A primary objective of the present work is to clarify and extend the results obtained using the above two strategies, particularly as they pertain to the separation of solute−solvent and solvent−solvent contributions to solvation entropies, energies, and enthalpies, evaluated in either the constant-volume or the constant-pressure ensembles. Although some of this terrain has been traversed in previous studies,[12−19] we establish new links between previously obtained results and derive a number of new expressions for the solute excess chemical potential and solvent reorganization energy. Moreover, we compare these results with liquid perturbation theory predictions, thereby clarifying the physical significance and interrelationship of various solvation thermodynamic quantities. Finally, we combine theoretical, simulation, and experimental results for the solvation of xenon in *n*-hexane and in water to extract noncompensating energetic and entropic contributions to the chemical potential directly from experimental data and test first-order perturbation theory predictions.

Unless otherwise noted, all of the results presented in this work pertain to the dilute solute limit. However, this limitation is not as restrictive as it may appear, because a solution of finite concentration may be treated as a dilute solution in a multi-component solvent, one of whose components happens to be the same as the solute. The only other significant restriction imposed in deriving some of the results in sections 3−5 is the implicit assumption that all intermolecular pair potential functions are temperature- and density-independent. In other words, any solvation-induced changes in the internal degrees of freedom of the solute and/or solvent molecules are assumed to be sufficiently small that they do not significantly affect the corresponding solvation thermodynamic functions (which is a quite reasonable approximation, because such effects are typically expected to be far smaller than thermal energies[20]).

The chemical potential results presented in section 2 pertain to a closed, constant-volume, isothermal system ($\{N\}$, V, T), where $\{N\}$ refers to the fixed number of particles of various species in the solution. Of course, the same chemical potential also pertains to other ensembles, such as ($\{N\}$, P, T), and so we do not sacrifice any generality in deriving statistical mechanical expressions for the chemical potential using a particular set of constraints. However, thermodynamic derivatives of the chemical potential (i.e., the solvation energy, enthalpy, entropy, and volume, as defined in sections 3−5) are, in general, ensemble-dependent,[16] although results pertaining

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to different ensembles may readily be interrelated[21] (as described in section 5). Thermodynamic perturbation theory not only clarifies the physical significance of various fundamental statistical mechanical quantities but also facilitates the extraction of repulsive, cohesive, local, and nonlocal contributions to experimental solvation thermodynamic functions (as described in sections 6−8).

2. The Chemical Potential of a Dilute Solute

The chemical potential, μ_u, of an infinitely dilute solute (subscript u) in a single component solvent (subscript w) evaluated in an ($\{N\}$, V, T) ensemble, in the thermodynamic limit, is

$$\mu_u = \left[\left(\frac{\partial A}{\partial N_u}\right)_{T,V,N_w}\right]_{N_u \to 0}$$
$$= A(T, V, N_w, N_u = 1) - A(T, V, N_w, N_u = 0) \quad (1)$$

where $A(T, V, N_w, N_u)$ is the Helmholtz free energy of a solution composed of N_w solvent molecules and N_u solute molecules at a fixed temperature T and volume V. The corresponding excess chemical potential of the solute is

$$\mu_u^\times = \left[\left(\frac{\partial A^\times}{\partial N_u}\right)_{T,V,N_w}\right]_{N_u \to 0}$$
$$= A^\times(T, V, N_w, N_u = 1) - A^\times(T, V, N_w, N_u = 0) \quad (2)$$

where the excess properties are defined relative to the ideal gas (I) limit in which all intermolecular interactions are turned off (while leaving the system composition, volume, and temperature fixed). Thus, $A^\times(T, V, N_w, N_u) = A(T, V, N_w, N_u) - A^I(T, V, N_w, N_u)$, and so, $\mu_u^\times = \mu_u - \mu_u^I$ represents the change in chemical potential induced by turning on solute−solvent and solvent−solvent coupling. Moreover, because the kinetic energy of the solute is unaffected by intermolecular coupling, $\mu_u^\times$ is equivalent to Ben-Naim's psuedochemical potential (PCP)[3] change associated with a constant-volume solvation process, $\Delta\mu_s^*$.

The excess Helmholtz free energy difference in eq 2 may also be expressed in terms of the following ratio of configurational integrals, $\mathscr{Z}$ (where $\beta \equiv 1/kT$, and k is Boltzmann's constant)

$$\beta\mu_u^\times = -\ln\{\mathscr{Z}(1)/\mathscr{Z}(0)\} \quad (3)$$

Here, $\mathscr{Z}(0)$ and $\mathscr{Z}(1)$ are the canonical configurational integrals of the system before and after turning on solute−solvent coupling. In other words, we envision the solute particle as being present in the both the (0) and (1) systems, but in the former case, the solute is a "ghost particle" that is completely decoupled from the solvent. The configurational integrals $\mathscr{Z}(0)$ and $\mathscr{Z}(1)$ may be considered as particular instances of a ξ-dependent configurational integral, $\mathscr{Z}(\xi)$, defined in terms of the potential energy function $\mathscr{U}(\xi)$ of the system

$$\mathscr{Z}(\xi) = \int dQ_u \int dQ_w \, e^{-\beta \mathscr{U}(\xi)} \quad (4)$$

where the integrations ($\int dQ_i \cdots$) are carried over the positions (r_i) and orientations (Ω_i) of the solute and solvent molecules. More specifically, dQ_u is understood to be shorthand notation for $d^3r_u \, d\Omega_u/V\Omega_u$, while dQ_w is shorthand notation for $d^3r_1 \, d\Omega_1 \, d^3r_2 \, d\Omega_2 \cdots/(V\Omega_w)^{N_w}$, where $\Omega_i \equiv \int d\Omega_i$.

The ξ-dependent interaction potential energy $\mathscr{U}(\xi)$ pertaining to a given system configuration may be further represented using the following linear coupling scheme, in which ξ can take on any value from 0 to 1:

$$\mathscr{U}(\xi) = \Phi + \xi\Psi \quad (5)$$

For a given configuration of the system, Φ corresponds to the total potential energy of interaction between the solvent molecules, while Ψ is the (fully coupled) potential energy of interaction between the solute and all the solvent molecules in the system. Notice that the above coupling scheme does not necessarily require pairwise additivity of the intermolecular potentials (as any nonpairwise additivity may be absorbed into the definition of Ψ).

The well-known Kirkwood coupling-parameter representation of the chemical potential follows directly from eqs 3 and 5 (as shown in Appendix 9.1).

$$\mu_u^\times = \int_0^1 d\xi \, \langle\Psi\rangle^{(\xi)} \quad (6)$$

The notation $\langle\cdots\rangle^{(\xi)}$ indicates an average obtained using the canonical distribution function $\exp\{-\beta\mathscr{U}(\xi)\}/\mathscr{Z}(\xi)$ pertaining to a given value of ξ

$$\langle\cdots\rangle^{(\xi)} = \frac{\int dQ_u \int dQ_w \cdots e^{-\beta\mathscr{U}(\xi)}}{\int dQ_u \int dQ_w \, e^{-\beta\mathscr{U}(\xi)}} \quad (7)$$

Thus, for example, $\langle\cdots\rangle^{(1)}$ and $\langle\cdots\rangle^{(0)}$ represent averages over equilibrium configurations of the system with solute−solvent coupling either fully turned on or fully turned off, respectively.

Equation 6 may further be rearranged (see Appendix 9.1) to obtain the following important result, which is closely related to an expression first obtained by Yu and Karplus for nondilute solutions[13] (a concise derivation of which is provided in Appendix 9.2).

$$\mu_u^\times = \langle\Psi\rangle^{(1)} + \beta \int_0^1 d\xi \xi K_2(\xi) \quad (8)$$

In the second term, we have introduced the ξ-dependent second-order cumulant of the solute−solvent interaction energy Ψ

$$K_2(\xi) \equiv \langle(\delta_\xi\Psi)^2\rangle^{(\xi)} = \langle\Psi^2\rangle^{(\xi)} - [\langle\Psi\rangle^{(\xi)}]^2 \quad (9)$$

The second equality in the last equation follows from the definition of the ξ-dependent fluctuation $\delta_\xi\Psi \equiv \Psi - \langle\Psi\rangle^{(\xi)}$. Moreover, because $K_2(\xi)$ is a second-order cumulant, *the second term in* eq 8 *is always positive*. A further integration by parts of eq 8 produces the following new expression

$$\mu_u^\times = \langle\Psi\rangle^{(1)} + \frac{\beta}{2}\langle(\delta\Psi)^2\rangle^{(1)} - \frac{\beta}{2}\int_0^1 d\xi\xi^2 \, d_\xi K_2(\xi) \quad (10)$$

where $\delta\Psi \equiv \delta_1\Psi = \Psi - \langle\Psi\rangle^{(1)}$ is the fluctuation of the solute−solvent energy in the fully coupled system (and $d_\xi \equiv \partial/\partial\xi$). Thus, $\langle(\delta\Psi)^2\rangle^{(1)} = K_2(1)$ represents the contribution of $\delta\Psi$ to the constant-volume solvation heat capacity. The third term in eq 10 is expected to be small, because it vanishes identically if the fluctuation in Ψ is purely Gaussian (as in the Gaussian bath approximation[22,23]).

At first sight, eqs 8 and 10 appear to be quite different from the expression

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$$\beta\mu_{u}^{\times} = -\ln\langle e^{-\beta\Psi}\rangle^{(0)} \qquad (11)$$

which follows directly from eq 3, as a straightforward consequence of Widom's potential-distribution theorem.[10−12] The connection between the two expressions becomes more apparent when eq 1 is expressed in inverse form[11]

$$\beta\mu_{u}^{\times} = \ln\langle e^{\beta\Psi}\rangle^{(1)}$$

$$= \beta\langle\Psi\rangle^{(1)} + \ln\langle e^{\beta\delta\Psi}\rangle^{(1)} \qquad (12)$$

Sanchez and co-workers previously obtained an expression equivalent to eq 12 for both single-component fluids and solutions,[19,24] and Guillot and Guissani had previously presented a closely related alternative expression.[15] It is again evident that the second term on the right-hand side of eq 12 is necessarily positive, because $\langle e^{x}\rangle \geq e^{\langle x\rangle} \geq 0$, and so $\langle e^{\beta\delta\psi}\rangle = \langle e^{\beta\Psi}\rangle/e^{\langle\beta\Psi\rangle} \geq 1$. The latter term may also be expanded in terms of centered cumulant averages[25] computed over fully coupled ($\xi = 1$) system configurations.

$$\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} = \langle e^{\beta\delta\Psi} - 1\rangle_{c}^{(1)} = \sum_{n\geq 2}\frac{\beta^{n}}{n!}\langle(\delta\Psi)^{n}\rangle_{c}^{(1)} \quad (13)$$

where the symbol $\langle\cdots\rangle_{c}^{(1)}$ indicates the cumulant average operation, and $\langle(\delta\Psi)^{n}\rangle_{c}^{(1)}$ is the n-order cumulant; in particular, the second cumulant is $K_{2}(1)$. Notice that truncation of eq 13 reduces eq 12 to a Gaussian fluctuation approximation that is identical to that obtained by neglecting the third term on the right-hand side of eq 10.

Ben-Naim has pointed out that $\mu_{u}^{\times}$ can also be represented in terms of the solute−solvent potential energy probability densities.[12] For example, we may re-express eq 11 in the following way

$$e^{-\beta\mu_{u}^{\times}} = \langle e^{-\beta\Psi}\rangle^{(0)} = \int_{-\infty}^{\infty}d\psi\, e^{-\beta\psi}p_{0}(\psi) \qquad (14)$$

where we have introduced the probability density, $p_{0}(\psi)$, that the solute−solvent interaction energy Ψ has a particular numerical value ψ, when sampling solvent configurations pertaining to the pure solvent at equilibrium (with solute−solvent coupling turned off).

$$p_{0}(\psi) \equiv \langle\delta(\psi - \Psi)\rangle^{(0)} \qquad (15)$$

Alternatively, the excess chemical potential of the solute at infinite dilution can be calculated from the first equality in eq 12. This may be expressed in terms of the probability density

$$p_{1}(\psi) \equiv \langle\delta(\psi - \Psi)\rangle^{(1)} \qquad (16)$$

that the solute−solvent potential energy, Ψ, has the numerical value ψ in a system in which the solvent configurations are sampled from the solution at equilibrium (with a fully coupled solute). The resulting expression for $\mu_{u}^{\times}$ is

$$e^{\beta\mu_{u}^{\times}} = \langle e^{\beta\Psi}\rangle^{(1)} = \int_{-\infty}^{\infty}d\psi\, e^{\beta\psi}p_{1}(\psi) \qquad (17)$$

The solvation potential energy probability densities in eqs 15 and 16 are related to each other in the following way

$$p_{1}(\psi) = \frac{\int dQ_{u}\int dQ_{w}\, e^{-\beta(\Phi+\Psi)}\,\delta(\psi - \Psi)}{\int dQ_{u}\int dQ_{w}\, e^{-\beta(\Phi+\Psi)}}$$

$$= e^{-\beta\psi}\frac{\int dQ_{u}\int dQ_{w}\, e^{-\beta\Phi}\,\delta(\psi - \Psi)}{\int dQ_{u}\int dQ_{w}\, e^{-\beta(\Phi+\Psi)}}$$

$$= e^{\beta[\mu_{u}^{\times}-\psi]}p_{0}(\psi) \qquad (18)$$

To obtain the last equality, we divided both numerator and denominator by the partition function $\mathcal{Z}(0)$ and made use of the first equality in eq 17.

In summary, the above results make it clear that the excess chemical potential $\mu_{u}^{\times}$ of the solute at infinite dilution may be decomposed into the sum of two terms

$$\mu_{u}^{\times} = \epsilon_{\mu}^{\times} - Ts_{\mu}^{\times} \qquad (19)$$

where

$$\epsilon_{\mu}^{\times} = \langle\Psi\rangle^{(1)} = \int_{-\infty}^{\infty}d\psi\,\psi\, p_{1}(\psi) \qquad (20)$$

and

$$-Ts_{\mu}^{\times} = \frac{1}{\beta}\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} = \beta\int_{0}^{1}d\xi\,\xi K_{2}(\xi) \qquad (21)$$

may be interpreted as the fundamental energetic and entropic contributions to the (excess) chemical potential of the solute.[13,15] The average solute−solvent potential energy of interaction $\epsilon_{\mu}^{\times}$ is usually negative, but is not restricted in sign, while the entropic term $Ts_{\mu}^{\times}$ is always positive.

Notice that Φ does not appear explicitly in any of the above expressions for $\epsilon_{\mu}^{\times}$ and $Ts_{\mu}^{\times}$, and thus, *the chemical potential is not affected by solute-induced changes in the solvent−solvent interaction energy.*[12,13,15−17,19] We will also see that the above energetic and entropic contributions to $\mu_{u}^{\times}$ are not necessarily equivalent to the solvation energy and entropy (pertaining either to a constant volume or a constant pressure solvation process). This is because terms involving solute-induced changes in Φ may contribute to both the solvation energy and entropy, but only in such a way that they exactly cancel (compensate) when combined to form the chemical potential.[12,13,15−17,19]

3. Solvation Energy at Constant Volume

The excess solvation energy in a constant-volume system, $\epsilon_{u}^{\times}$, may be derived from $\mu_{u}^{\times}$ using the Gibbs−Helmholtz relation

$$\epsilon_{u}^{\times} = \left[\frac{\partial(\mu_{u}^{\times}/T)}{\partial(1/T)}\right]_{V,N_{w},N_{u}} = \left[\frac{\partial(\beta\mu_{u}^{\times})}{\partial\beta}\right]_{V,N_{w},N_{u}} \qquad (22)$$

By invoking the second equality in eq 2 and applying the Gibbs−Helmholtz relation to each of the corresponding Helmholtz free energies $A^{\times}$, it follows that

$$\epsilon_{u}^{\times} = U^{\times}(T, V, N_{w}, N_{u} = 1) - U^{\times}(T, V, N_{w}, N_{u} = 0) \quad (23)$$

$$= \langle\Phi + \Psi\rangle^{(1)} - \langle\Phi\rangle^{(0)}$$

$$= \langle\Psi\rangle^{(1)} + \langle\Phi\rangle^{(1)} - \langle\Phi\rangle^{(0)}$$

$$= \langle\Psi\rangle^{(1)} + \Delta\langle\Phi\rangle \qquad (24)$$

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Again, the above equations may be viewed as pertaining to a process in which a stationary solute is transferred into the solvent (at constant volume and temperature).

Comparison of the last equality in eq 24 with eq 20 makes it clear that $\epsilon_u^\times$ differs from $\epsilon_\mu^\times$ by a quantity, $\Delta\langle\Phi\rangle = \epsilon_u^\times - \epsilon_\mu^\times$, which represents the solute-induced change in the solvent−solvent interaction energy. This so-called solvent reorganization energy remains the subject of current interest and debate, because its quantitative evaluation is a challenge, both experimentally[24] and by numerical simulation.[15,17,19] Moreover, it appears that both the sign and the magnitude of $\Delta\langle\Phi\rangle$ can vary significantly with the molecular identity of the solvent and solute, as well as the density and temperature of the system. Notice that $\Delta\langle\Phi\rangle$ represents the solvent reorganization energy in a *constant-volume* solvation process, and so, it should not be confused with the corresponding quantity pertaining to a *constant-pressure* solvation process. The difference between the two solvent reorganization energies, which is often quite significant (several times *kT*), derives from the energy associated with the relaxation of the system volume in a constant-pressure process. This volume relaxation energy may be expressed in terms of the partial molar volume of the solute and bulk properties of the solvent (as further described in section 5).

If the solvent−solvent, Φ, and solute−solvent, Ψ, interaction terms in the Hamiltonian of the system are assumed to be pairwise additive, then

$$\Phi = \sum_a \sum_{b>a} u_{ww}(a, b) \tag{25}$$

$$\Psi = \sum_a u_{uw}(c, a) \tag{26}$$

where $u_{ww}(a, b)$ is the potential energy of interaction between two solvent molecules a and b, while $u_{uw}(c, a)$ is the potential energy of interaction between the solute molecule c and a solvent molecule a. Each of the individual pair potentials are understood to be *T*- and ρ-independent. Notice that the molecular labels a, b, and c inside the parentheses specify both the location and orientation of the molecules.

The solvent reorganization energy, $\Delta\langle\Phi\rangle$, may be expressed in terms of the solvent−solvent *generic* two-particle molecular distribution function, $\rho_{ww}(a, b)$ (see Appendix 9.3 for details)

$$\Delta\langle\Phi\rangle = \int da \int db \, u_{ww}(a, b)[\rho_{ww}^{(1)}(a, b) - \rho_{ww}^{(0)}(a, b)] \tag{27}$$

Moreover, the distribution function $\rho_{ww}^{(1)}(a, b)$ can also be expressed in terms of the solute−solvent-solvent three-particle reduced distribution function according to

$$\rho_{ww}^{(1)}(a, b) = \int dc \, \rho_{uww}^{(1)}(c, a, b) \tag{28}$$

where $\rho_{uww}(c, a, b)$ stands for the probability density of finding the solute (c) and any two solvent molecules (a, b) at locations/orientations specified by the set of variables (a, b, c). For the distribution function $\rho_{ww}^{(0)}(a, b)$, we can write

$$\rho_{ww}^{(0)}(a, b) = \frac{1}{V\Omega_u}\int dc \, \rho_{ww}^{(0)}(a, b) = \int dc \, \rho_u^{(1)}(c)\rho_{ww}^{(0)}(a, b) \tag{29}$$

where we have identified the one-particle solute generic distribution function $\rho_u^{(1)}(c) = \rho_u^{(0)}(c) = (V\Omega_u)^{-1}$, given that the pure solvent is uniform and isotropic. In view of these representations, we can write

$$\rho_{ww}^{(1)}(a, b) - \rho_{ww}^{(0)}(a, b)$$

$$= \int dc \, \rho_u^{(1)}(c)\left[\frac{\rho_{uww}^{(1)}(c, a, b)}{\rho_u^{(1)}(c)} - \rho_{ww}^{(0)}(a, b)\right]$$

$$= \frac{1}{V}\int \frac{dc}{\Omega_u}[\rho_{ww}^{(1)}(a, b| c) - \rho_{ww}^{(0)}(a, b)] \tag{30}$$

Thus, by combining eqs 27 and 30, we obtain

$$\Delta\langle\Phi\rangle = \frac{1}{V}\int da \int db \int \frac{dc}{\Omega_u} u_{ww}(a, b)[\rho_{ww}^{(1)}(a, b| c) - \rho_{ww}^{(0)}(a, b)] \tag{31}$$

Several additional expressions for $\Delta\langle\Psi\rangle$ may be obtained using alternative starting points and approaches. For example, we may begin with the Kirkwood coupling-parameter representation of $\Delta\langle\Phi\rangle$

$$\Delta\langle\Phi\rangle = \int_0^1 d\xi \, d_\xi\langle\Phi\rangle^{(\xi)} \tag{32}$$

Evaluation of the derivative in the integrand leads to the following result (obtained as described in the Appendix 9.1):

$$\Delta\langle\Phi\rangle = -\beta \int_0^1 d\xi \, [\langle\Phi\Psi\rangle^{(\xi)} - \langle\Phi\rangle^{(\xi)}\langle\Psi\rangle^{(\xi)}] \tag{33}$$

A similar result was originally derived by Yu and Karplus for nondilute solutions.[13]

Alternatively, we may obtain the following expression for $\langle\Phi\rangle^{(1)}$ in terms of the solvation energy distribution function, $p_1(\psi)$

$$\langle\Phi\rangle^{(1)} = \int_{-\infty}^{\infty} d\psi \, \langle\Phi\delta(\psi - \Psi)\rangle^{(1)}$$

$$= \int_{-\infty}^{\infty} d\psi \, \langle\delta(\psi - \Psi)\rangle^{(1)}\langle\Phi\delta(\psi - \Psi)\rangle^{(1)}/$$

$$\langle\delta(\psi - \Psi)\rangle^{(1)}$$

$$= \int_{-\infty}^{\infty} d\psi p_1(\psi)\langle\Phi|\Psi = \psi\rangle^{(1)} \tag{34}$$

where $\langle\Phi|\Psi = \psi\rangle^{(1)}$ is the *conditional* expectation value of the potential energy of interaction between the solvent molecules, Φ, *given* that the solute−solvent potential energy of interaction has the numerical value ψ. Because $p_1(\psi)$ is normalized, we can also write

$$\Delta\langle\Phi\rangle = \int_{-\infty}^{\infty} d\psi \, p_1(\psi)[\langle\Phi|\Psi = \psi\rangle^{(1)} - \langle\Phi\rangle^{(0)}] \tag{35}$$

We may obtain an additional expression for $\Delta\langle\Phi\rangle$ by taking the derivative of both sides of eq 14 with respect to β at constant V and number of particles. From the left-hand side of eq 14, we obtain

$$-d_\beta[\beta\mu_u^\times] \, e^{-\beta\mu_u^\times} = -\epsilon_u^\times \, e^{-\beta\mu_u^\times}$$

and from the right-hand side of eq 14, we obtain

$$-\int_{-\infty}^{\infty} d\psi\psi \, e^{-\beta\psi}p_0(\psi) + \int_{-\infty}^{\infty} d\psi \, e^{-\beta\psi} \, d_\beta p_0(\psi)$$

We can now exploit the energy distribution conversion eq 18 to derive the following expression for the excess partial internal energy of the solute at infinite dilution

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$$\epsilon_u^\times = \int_{-\infty}^{\infty} d\psi \psi p_1(\psi) - \int_{-\infty}^{\infty} d\psi p_1(\psi) \, d_\beta \ln p_0(\psi) \quad (36)$$

The first term is clearly $\langle\Psi\rangle^{(1)}$, and so by comparing the above result with eq 24, we conclude that

$$\Delta\langle\Phi\rangle = -\int_{-\infty}^{\infty} d\psi p_1(\psi) \, d_\beta \ln p_0(\psi) \quad (37)$$

Notice that the above expression for $\Delta\langle\Phi\rangle$ does not depend explicitly on Φ. The same is true of following result obtained by combining eqs 12 and 22 with the second cumulant (Gaussian fluctuation) approximation.

$$\Delta\langle\Phi\rangle = \beta \, d_\beta\langle\Psi\rangle^{(1)} + d_\beta \ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$$

$$\approx \beta\Big\{\langle\Psi^2\rangle^{(1)} - [\langle\Psi\rangle^{(1)}]^2 + [1 - \beta\langle\Psi\rangle^{(1)}]d_\beta\langle\Psi\rangle^{(1)} + \frac{\beta}{2}d_\beta\langle\Psi^2\rangle^{(1)}\Big\} \quad (38)$$

which again does not explicitly include Φ. However, Φ is clearly an implicit variable in both of the above equations, because the corresponding solvent configuration averages obviously depend on solvent structure.

All of the above expressions for the constant-volume solvent reorganization energy, $\Delta\langle\Phi\rangle$, are of course necessarily equivalent to each other and to those previously obtained by Ben-Naim, Yu-Karplus, and others.[15,19,24] However, the above representations of $\Delta\langle\Phi\rangle$, all of which are substantially new, serve to extend and interconnect the results presented by previous authors.

4. Other Constant-Volume Functions

The excess solvation entropy of a dilute solute in a constant-volume fluid is

$$s_u^\times \equiv -\left(\frac{\partial\mu_u^\times}{\partial T}\right)_V = S^\times(T, V, N_w, N_u = 1) - S^\times(T, V, N_w, N_u = 0) \quad (39)$$

This quantity may also be obtained directly from the results in sections 2 and 3, because $Ts_u^\times = \epsilon_u^\times - \mu_u^\times$. Thus, for example, we may obtain the following Kirkwood coupling-parameter expression for $Ts_u^\times$ by combining eqs 8, 24, and 33, which is equivalent to the corresponding Yu–Karplus result[13] when using the linear coupling scheme defined by eq 5.

$$Ts_u^\times = -\beta \int_0^1 d\xi[\langle\Phi\Psi\rangle^{(\xi)} - \langle\Phi\rangle^{(\xi)}\langle\Psi\rangle^{(\xi)}] - \beta \int_0^1 d\xi\xi K_2(\xi) \quad (40)$$

On the other hand, we may use the Widom potential-distribution theorem approach to obtain the following alternative expressions for $Ts_u^\times$, by combining eqs 11, 12, and 24.

$$Ts_u^\times = \langle\Psi\rangle^{(1)} + \Delta\langle\Phi\rangle + \frac{1}{\beta}\ln\langle e^{-\beta\Psi}\rangle^{(0)}$$

$$= \Delta\langle\Phi\rangle - \frac{1}{\beta}\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} \quad (41)$$

The first of the above equalities is equivalent to that previously obtained by Ben-Naim,[12] while eqs 21 and 33 identify the two terms in eq 41 with the corresponding terms in eq 40. Moreover, notice that the same solvent reorganization energy $\Delta\langle\Phi\rangle$ also appears in the solvation energy, eq 24, and thus exactly cancels

when combining $\mu_u^\times = \epsilon_u^\times - Ts_u^\times = \epsilon_\mu^\times - Ts_\mu^\times$. In other words, although $\Delta\langle\Phi\rangle$ does not contribute to $\mu_u^\times$, $\epsilon_\mu^\times$, or $s_\mu^\times$, it may significantly contribute to both $\epsilon_u^\times$ and $s_u^\times$.

A constant-volume solvation process is in general accompanied by a change in the pressure of the system

$$p_u^\times \equiv -\left(\frac{\partial\mu_u^\times}{\partial V}\right)_{T,N_w,N_u} = P^\times(T, V, N_w, N_u = 1) - P^\times(T, V, N_w, N_u = 0) \quad (42)$$

The energy associated with this pressure change, $Vp_u^\times$, can also be expressed as a derivative of $\mu_u^\times$ with respect to the solvent number density, ρ, because $\partial\rho/\rho = \partial\rho_u/\rho_u$, where $\rho_u = 1/V$ is the number density of the single solute molecule in the system of volume V.

$$Vp_u^\times = \rho\left(\frac{\partial\mu_u^\times}{\partial\rho}\right)_T \quad (43)$$

The above partial derivative implicitly pertains to a closed system (at constant N_w and N_u).

The change in Gibbs free energy, $g_u^\times|_V \equiv (\partial G^\times/\partial N_u)_{V,T,N_w}$, and enthalpy, $h_u^\times|_V \equiv (\partial H^\times/\partial N_u)_{V,T,N_w}$, associated with a constant-volume solvation process may be expressed as linear combinations of the above quantities.

$$g_u^\times|_V = \mu_u^\times + Vp_u^\times = \epsilon_u^\times + Vp_u^\times - Ts_u^\times \quad (44)$$

$$h_u^\times|_V = \epsilon_u^\times + Vp_u^\times = \mu_u^\times + Vp_u^\times + Ts_u^\times \quad (45)$$

5. Constant-Pressure Solvation

The solvation of a molecule at constant pressure generally produces a change in the volume of the system, which is equivalent to the experimental partial molar volume

$$v_u \equiv \left(\frac{\partial\mu_u}{\partial P}\right)_{T,N_w,N_u} = V(T, P, N_w, N_u = 1) - V(T, P, N_w, N_u = 0) \quad (46)$$

This partial molar volume can be expressed as the sum of excess, $v_u^\times$, and ideal, v_u^I, contributions, and is related in a simple way to the partial molar pressure change, $p_u = p_u^\times + p_u^I = p_u^\times + kT$, associated with the corresponding constant-volume process.

$$Pv_u = P\left(\frac{\partial\mu_u}{\partial\rho}\right)_T\left(\frac{\partial\rho}{\partial P}\right)_T = P\kappa_T\rho\left(\frac{\partial\mu_u}{\partial\rho}\right)_T \quad (47)$$

$$= P(v_u^\times + v_u^I) = P\kappa_T\left[\rho\left(\frac{\partial\mu_u^\times}{\partial\rho}\right)_T + kT\right] \quad (48)$$

$$= P\kappa_T[Vp_u] \quad (49)$$

where $\kappa_T = -1/V(\partial V/\partial P)_T = 1/\rho(\partial\rho/\partial P)_T$ is the isothermal compressibility of the fluid. Notice that the above relations imply that $v_u^\times = \kappa_T\rho(\partial\mu_u^\times/\partial\rho)_T$ corresponds to the partial molar volume of a *stationary* solute in the fluid phase, while $v_u^I = \kappa_T kT$ is the additional volume induced by turning on the solute's translational kinetic energy (where κ_T is the compressibility of the fluid).[3]

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The constant-volume solvation energy and entropy may be converted to the constant-pressure partial molar enthalpy, $h_u|_P$, and entropy, $s_u|_P$, using the following thermodynamic identities pertaining to the volume-relaxation energy associated with a constant-pressure solvation process,[21] where $\alpha_P = 1/V(\partial V/\partial T)_P = -1/\rho(\partial \rho/\partial T)_P$ is the solvent isobaric thermal expansion coefficient (and the notation $|_V$ has been appended to the quantities defined sections 3 and 4, as a reminder that they pertain to a constant-volume process).

$$s_u|_P - s_u|_V = \left(\frac{\alpha_P}{\kappa_T}\right)v_u = \alpha_P\rho\left(\frac{\partial \mu_u}{\partial \rho}\right)_T \tag{50}$$

$$h_u|_P - \epsilon_u|_V = T\left(\frac{\alpha_P}{\kappa_T}\right)v_u = T\alpha_P\rho\left(\frac{\partial \mu_u}{\partial \rho}\right)_T \tag{51}$$

$$\epsilon_u|_P - \epsilon_u|_V = (T\alpha_P - P\kappa_T)\left(\frac{v_u}{\kappa_T}\right) = (T\alpha_P - P\kappa_T)\rho\left(\frac{\partial \mu_u}{\partial \rho}\right)_T \tag{52}$$

Notice that the above results imply that the solvent reorganization energy and entropy associated with a constant-pressure solvation process are $\Delta\Phi + [T\alpha_P - P\kappa_T]v_u/\kappa_T$ and $\Delta\langle\Phi\rangle/T + (\alpha_P/\kappa_T)v_u$, respectively.

The corresponding excess quantities are associated with the transfer of a *stationary* solute into the fluid.[3]

$$h_u^\times|_P - \epsilon_u^\times|_V = Ts_u^\times|_P - Ts_u^\times|_V$$

$$= T\left(\frac{\alpha_P}{\kappa_T}\right)v_u^\times = T\alpha_P\rho\left(\frac{\partial \mu_u^\times}{\partial \rho}\right)_T$$

$$= T\left(\frac{\alpha_P}{\kappa_T}\right)(v_u - kT\kappa_T)$$

$$= T\alpha_P\left[\rho\left(\frac{\partial \mu_u}{\partial \rho}\right)_T - kT\right] \tag{53}$$

$$\epsilon_u^\times|_P - \epsilon_u^\times|_V = (T\alpha_P - P\kappa_T)\left(\frac{v_u^\times}{\kappa_T}\right)$$

$$= (T\alpha_P - P\kappa_T)\rho\left(\frac{\partial \mu_u^\times}{\partial \rho}\right)_T \tag{54}$$

Thus, the solvent reorganization energy associated with the solvation of a stationary molecule at a constant-pressure process is $\Delta\langle\Phi\rangle + [T\alpha_P + P\kappa_T]^{v_u^\times}/\kappa_T$. Also note that the fluid α_P and κ_T values are to be used even when calculating ideal-gas (translational) contribution to the partial molar volume. This is because the concentration of the solute necessarily scales with the density of the fluid.

The partial molar excess Helmholtz free energy, $a_u^\times|_P$, and potential energy, $\epsilon_u^\times|_P$, are expressible as linear combinations of the above partial molar quantities.

$$a_u^\times|_P = \mu_u^\times - Pv_u^\times = h_u^\times|_P - Pv_u^\times - Ts_u^\times|_P \tag{55}$$

$$\epsilon_u^\times|_P = a_u^\times|_P + Ts_u^\times|_P = \mu_u^\times - Pv_u^\times + Ts_u^\times|_P \tag{56}$$

Other solvation thermodynamic quantities, such as the partial molar excess heat capacity and compressibility, represent higher-order derivatives of $\mu_u^\times$ with respect to T and P.[3] Fundamental expressions for such quantities are implicit in the above results, because first-order solvation thermodynamic functions evaluated over a range of T and P values are equivalent to higher-order

derivatives of $\mu_u^\times$ pertaining to a given thermodynamic state. Further discussion of the large positive partial molar heat capacity associated with hydrophobic solvation processes is presented at the end of section 8.

All the equations in this section are valid for both dilute and concentrated solutions, as long as ρ, α_P, and κ_T are understood to pertain to the solution and $(\partial \mu_u/\partial \rho)_T$ is evaluated at constant composition. In the infinite dilution limit, ρ, α_P, and κ_T reduce to the corresponding pure solvent values.

6. Solvation Perturbation Theory

To further illustrate the physical significance of the above results, we apply them to fluids which can be described using first-order thermodynamic perturbation theory, much in the same spirit as originally proposed by Pratt and Chandler in deriving their theory of the hydrophobic effect[14] (whose key elements have more recently been validated and extended by Garde and co-workers[26]). More specifically, we define three increasingly detailed first-order generalized van der Waals (GvdW) solvation models, followed by the derivation of an exact expression for the sum of all higher-order terms in the perturbation series. Practical applications of the GvdW results are illustrated using experimental examples in section 7.

For a dilute solution consisting of particles of arbitrary shape, the excess chemical potential of a solute may be represented as the following sum of a reference system excess chemical potential, μ_u^R, plus a first-order (mean-field) perturbation potential energy[14,26] (using notation defined in Appendix 9.3)

$$\mu_u^\times = \mu_u^R + \rho\int d^3\mathbf{r}\int\frac{d\Omega_u}{\Omega_u}\int\frac{d\Omega_w}{\Omega_w}u_{uw}^A(r, \Omega_u, \Omega_w)\,g_{uw}^R(r, \Omega_u, \Omega_w) \tag{57}$$

where u_{uw}^A is the solute−solvent perturbation pair potential. For a fluid composed of spherical particles, eq 57 reduces to

$$\mu_u^\times = \mu_u^R + \rho\int_0^\infty u_{uw}^A(r)g_{uw}^R(r)\,4\pi r^2\,dr \tag{58}$$

The above expression could, for example, be used to describe the chemical potential of xenon in argon or a more complex fluid composed of nonspherical molecules whose interactions are approximated by spherical potentials obtained using an appropriate course-graining procedure.[27,28]

Both of the above first-order perturbation expressions may, without loss of generality, be written as

$$\beta\mu_u^\times = \gamma - a\beta\rho \tag{59}$$

The dimensionless quantities γ and $-a\beta\rho$ represent the reference and perturbation contributions to $\mu_u^\times$, respectively. In general, γ and a may each be functions of ρ and T (as well as the molecular properties of the fluid constituents).

A fluid in which both the solvent−solvent and solute−solvent interactions are represented by hard-sphere core plus long-range (van der Waals mean-field) cohesive interaction potentials may be accurately represented by the following GvdW0 approximation. In this limit, the parameter γ reduces to a T-independent function of ρ only, and a becomes a ρ- and T-independent constant (see Appendix 9.4 for details). Thus, we obtain the following GvdW0 expressions for the solvation energy and entropy in a constant-volume system (from the derivative of $\beta\mu_u^\times$ with respect to β at constant ρ).

$$\beta\epsilon_u^\times|_V^{GvdW0} = -a\beta\rho \tag{60}$$

$$\beta Ts_u^\times|_V^{GvdW0} = -\gamma \tag{61}$$

Comparison of eqs 58 and 59 indicates that $-a\beta\rho$ is precisely the average solute−solvent interaction potential energy in a GvdW0 fluid, and thus, eqs 19−21 imply the following relation between the GvdW parameters and the noncompensating energetic and entropic contributions to the chemical potential.

$$-a\rho = \epsilon_\mu^\times = \langle\Psi\rangle^{(1)} \tag{62}$$

$$\gamma k = -s_\mu^\times = k\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} \tag{63}$$

Comparison of eqs 60−63 makes it clear that in a GvdW0 fluid there is no solvent reorganization contribution to the solvation energy and entropy at constant volume. However, a compensating volume-relaxation energy can contribute significantly to constant-pressure solvation processes, as implied by the following GvdW0 expressions for $h_u^\times|_P$, $\epsilon_u^\times|_P$, and $Ts_u^\times|_P$, obtained using eqs 53 and 54 (or equivalently by direct differentiation of $\beta\mu_u^\times$ with respect to β and P).

$$\beta h_u^\times|_P^{GvdW0} = -a\beta\rho + T\alpha_P\left[\rho\left(\frac{\partial\gamma}{\partial\rho}\right)_T - a\beta\rho\right] \tag{64}$$

$$\beta\epsilon_u^\times|_P^{GvdW0} = -a\beta\rho + (T\alpha_P - P\kappa_T)\left[\rho\left(\frac{\partial\gamma}{\partial\rho}\right)_T - a\beta\rho\right] \tag{65}$$

$$\beta Ts_u^\times|_P^{GvdW0} = -\gamma + T\alpha_P\left[\rho\left(\frac{\partial\gamma}{\partial\rho}\right)_T - a\beta\rho\right] \tag{66}$$

Notice that $\epsilon_u^\times|_P$ would become equivalent to $\epsilon_u^\times|_V$ in a hard-sphere solvent, even if solute−solvent interactions were cohesive. This is because in such a fluid $T\alpha_P = P\kappa_T$ (see Appendix 9.4), and so, the second term in eq 65 would vanish. On the other hand, in ambient liquids, it is generally the case that $|T\alpha_P| \gg P\kappa_T > 0$ (except in rare situations such as water at $T \approx 4$ °C), and so under standard experimental conditions, it is typically the case that $\epsilon_u|_P \neq \epsilon_u|_V$, but the solvation enthalpies and energies are essentially equivalent to each other, $h_u|_P \cong \epsilon_u|_P$.

A somewhat more general GvdW1 class of fluids are ones in which the GvdW0 approximation is applied only to the solute−solvent interaction potential, while the solvent−solvent interactions are represented at an arbitrary level of accuracy. In such a fluid, the parameter a remains a constant, but γ may be a function of both ρ and T. Because γ represents the free energy required to form a cavity sufficiently large to accommodate a hard-sphere solute (of the same size as the solute−solvent core), the temperature dependence of the γ parameter in a GvdW1 fluid reflects the solvent reorganization energy associated with the creation of such a cavity. In particular, the constant-volume solvation energy and entropy in a GvdW1 fluid are

$$\beta\epsilon_u^\times|_V^{GvdW1} = -T\left(\frac{\partial\gamma}{\partial T}\right)_\rho - a\beta\rho \tag{67}$$

$$\beta Ts_u^\times|_V^{GvdW1} = -T\left(\frac{\partial\gamma}{\partial T}\right)_\rho - \gamma \tag{68}$$

The first term on the right-hand-side of eq 67 represents the constant-volume solvent reorganization energy.

$$\Delta\langle\Phi\rangle|^{GvdW1} = -\frac{T}{\beta}\left(\frac{\partial\gamma}{\partial T}\right)_\rho = \left(\frac{\partial\gamma}{\partial\beta}\right)_\rho \tag{69}$$

Equation 68 indicates that this reorganization energy also induces a precisely compensating contribution to the solvation entropy in a GvdW1 fluid. Moreover, the constant-pressure solvation enthalpy, energy, and entropy in a GvdW1 fluid are identical to those in a GvdW0 fluid, eqs 64−66, except for the additional $-T(\partial\gamma/\partial T)_\rho$ term which appears in each for the corresponding GvdW1 expressions.

A further generalization, GvdW2, may be used to describe fluids in which both solute−solvent and solvent−solvent interaction potentials are treated as smooth continuous functions with soft-repulsive and cohesive interactions of arbitrary length scale. Such a GvdW2 fluid could, for example, be one composed of particles whose pair potentials are represented by Lennard-Jones, generalized Lennard-Jones,[29,30] or more general anisotropic functions (with the Weeks−Chandler−Andersen procedure used to separate repulsive and attractive portions of the potential[29−32]). In a GvdW2 fluid, both γ and a may in general be functions of both T and ρ, and thus, the resulting total solvation energy and entropy become

$$\beta\epsilon_u^\times|_V^{GvdW2} = -a\beta\rho - T\left(\frac{\partial\gamma}{\partial T}\right)_\rho + \beta\rho\left[T\left(\frac{\partial a}{\partial T}\right)_\rho\right] \tag{70}$$

and

$$\beta Ts_u^\times|_V^{GvdW0} = -\gamma - T\left(\frac{\partial\gamma}{\partial T}\right)_\rho + \beta\rho\left[T\left(\frac{\partial a}{\partial T}\right)_\rho\right] \tag{71}$$

The last term in each of the above equations derives from the temperature dependence of the average perturbation energy, which in turn results from the finite length scales of the solute−solvent repulsive and cohesive interactions. Moreover, the second term, $T(\partial\gamma/\partial T)_\rho$, may now contain a contribution from the softness of the solute−solvent repulsive core potential. Thus, the compensating solvation energy and entropy in a GvdW2 fluid may in general contain both solvent−solvent and solute−solvent contributions, which do not affect $\mu_u^\times$. Notice that the volume-relaxation energy values which dictate the difference between the constant-volume and constant-pressure solvation quantities are the same in all of the above first-order thermodynamic perturbation theoretic model fluids.

The above results pertain only to fluids which are described well by first-order perturbation theory. The fundamental common feature of all such fluids is that the solute−solvent perturbation potential, u_{uw}^A, does not induce a significant change in solvent configurational entropy. Although the remarkable success of first-order perturbation theories in describing the equations of state of simple fluids is well-known,[6] the results presented in section 7 suggest that this approximation strategy is also appropriate for representing the solvation of nonpolar solutes in nonspherical solvents such as *n*-hexane and strongly associated fluids such as water.

More generally, an exact expression for the sum of all the higher-order terms in the perturbation series may be obtained by following a procedure similar to that used to derive eq 8. This begins by expressing the solute−solvent potential energy as $\Psi = \Psi^R + \Psi^A$, where Ψ^R is the solute−solvent interaction energy in the reference system and $\Psi^A \equiv \Psi - \Psi^R$ is the corresponding perturbation energy. We may now write the ξ-dependent total interaction potential energy in the form

$$\mathcal{U}(\xi) = \mathcal{U}^R + \xi\Psi^A \tag{72}$$

where $\mathcal{U}^R \equiv \Phi + \Psi^R$. Proceeding in a way similar to the derivation of eq 8, and defining $K_2^A(\xi) \equiv \langle(\Psi^A)^2\rangle^{(\xi)} - [\langle\Psi^A\rangle^{(\xi)}]^2$, we can show that

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$$\mu_u^\times = \mu_u^R + \langle \Psi^A \rangle^{(0)} - \beta \int_0^1 d\xi (1 - \xi) K_2^A(\xi) \qquad (73)$$

where $\langle \Psi^A \rangle^{(0)}$ now represents an average performed over configurations of the reference system ($\mathscr{U}^R$), which *includes the reference solute* and thus corresponds to the integral in eq 57. The last term on the right-hand side represents an explicit expression for the sum of the remaining perturbation series and so is the exact correction to the first-order perturbation theory result. In other words, the above expression may be rewritten as

$$\beta \mu_u^\times = \gamma - a\beta\rho - \beta^2 \int_0^1 d\xi (1 - \xi) K_2^A(\xi) \qquad (74)$$

Notice that, because $0 \leq (1 - \xi) \leq 1$, the correction term is always negative, which is consistent with the fact that first-order perturbation theory produces an upper bound to the true $\mu_u^\times$.[6]

7. Experimental Applications

The results presented in sections 2−5 provide exact statistical mechanical expressions for various experimentally measurable solvation thermodynamic quantities, at both constant-volume and constant-pressure. However, not all of the fundamentally identified quantities can be independently determined using purely experimental methods. For example, experimentally measured functions such as $\mu_u^\times = \langle \Psi \rangle^{(1)} + kT \ln \langle e^{\beta \delta \Psi} \rangle^{(1)}$ and $h_u^\times|_P = \langle \Psi \rangle^{(1)} + \Delta \langle \Phi \rangle + T(\alpha_P/\kappa_T)v_u^\times$ are composed of the solute−solvent average interaction energy, $\langle \Psi \rangle^{(1)}$, fluctuation entropy, $-k \ln \langle e^{\beta \delta \Psi} \rangle^{(1)}$, solvent reorganization energy at constant volume, $\Delta \langle \Phi \rangle$, and volume-relaxation energy, $T(\alpha_P/\kappa_T)v_u^\times$. However, although the latter quantity is experimentally measurable, the evaluation of $\langle \Psi \rangle^{(1)}$, $\ln \langle e^{\beta \delta \Psi} \rangle^{(1)}$, and/or $\Delta \langle \Phi \rangle$ in general requires additional theoretical and/or simulation input (except in special cases, as discussed below and in section 8).

To illustrate the way in which experimental functions may be decomposed into the above fundamental components, we consider the solvation of xenon in *n*-hexane and water (at 298 K and 1 atm) as representative examples of nonpolar and hydrophobic solvation processes. To facilitate the decomposition, we use independent theoretical and/or simulation estimates of the cavity distribution function in the two pure solvents (as described in Appendix 9.4), combined with first-order perturbation theory (described in section 6). Although previous estimates of $\Delta \langle \Phi \rangle$ for the solvation of xenon in water range from about −5 to 5 kT (as discussed in section 8), the following results suggest that $\Delta \langle \Phi \rangle \approx 0 \pm 1 \, kT$ for both of the above solvation processes. This finding implies that the two processes may be described using the GvdW0 approximation and thus that one may equate $\Delta E^*|_V \approx \langle \Psi \rangle^{(1)}$ and $\Delta S^*|_V \approx k \ln \langle e^{\beta \delta \Psi} \rangle^{(1)}$, as explained below.

The experimental pure solvent parameters for *n*-hexane and water (at 25 °C and 1 atm) are collected in Table 1.[33] The corresponding experimental xenon solvation thermodynamic functions are listed in Table 2.[19,34,35] The latter parameters all pertain to a standard solvation process as defined by Ben-Naim.[3] More specifically, the Ben-Naim solvation thermodynamic functions are equivalent to our excess solvation functions (expressed in molar units): $\Delta G^*|_P = \Delta A^*|_V = N_A \mu_{xe}^\times$, $\Delta E^*|_V = N_A \epsilon_{xe}^\times|_V$, $\Delta H^*|_P = N_A h_{xe}^\times|_P$, and $\Delta S^*|_{P \text{ or } V} = N_A s_{xe}^\times|_{P \text{ or } V}$, while $V^* = N_A v_u^\times$ is the partial molar volume of a stationary solute (moreover, because $P\kappa_T \ll T\alpha_P$, one may also accurately approximate $\Delta E^*|_V \approx \Delta H^*|_V$ and $\Delta H^*|_P \approx \Delta E^*|_P$).

TABLE 1: Liquid (Solvent) Parameters at 25 °C

solvent:	*n*-hexane	water	units
ρ^a	0.655 (4.58)	0.997 (33.3)	g/cm^3 (1/nm^3)
α_P^a	1.41×10^{-3}	0.256×10^{-3}	1/K
κ_T^a	1.67×10^{-3}	0.452×10^{-3}	1/MPa
$T(\alpha_P/\kappa_T)$	0.252	0.169	kJ/cm^3
$RT\kappa_P$	4.14	1.12	cm^3/mol
$T\alpha_P$	0.420	0.076	
$P\kappa_T$	1.67×10^{-4}	4.52×10^{-5}	

^{a} Pure solvent density (in both mass and number density units), isobaric thermal expansion and isothermal compressibility at 25 °C and 1 atm.[33]

TABLE 2: Xenon Solvation Thermodynamics at 25 °C

solvent:	*n*-hexane	water	units
$\Delta A^*|_V = \Delta G^*|_P{}^a$	−3.6	5.6	kJ/mol
$\Delta H^*|_P \cong \Delta E^*|_P{}^a$	−10	−16	kJ/mol
$\Delta E^*|_V \cong \Delta H^*|_V{}^b$	−21	−24	kJ/mol
$T\Delta S^*|_P{}^a$	−6	−22	kJ/mol
$T\Delta S^*|_V{}^b$	−17	−29	kJ/mol
$V^*{}^c$	45	46	cm^3/mol

^{a} Experimental excess thermodynamic functions pertaining to the Ben-Naim standard solvation process (data from Tables 2.6 and 2.22 in of Ben-Naim's *Solvation Thermdynamics* book[3] and references therein). ^{b} Obtained using eq 53 with the experimental V^* and $T(\alpha_P/\kappa_T)$ (Table 1). ^{c} $V^* = \bar{V} - RT\kappa_T$, where $\bar{V} = N_A v_u$ is the exerimental partial molar volume of xenon in each solvent.[34,35]

Simulation measurements[36] of the probability of finding a cavity the size of xenon ($\sigma_{xe} \approx 0.392$ nm)[37] in *n*-hexane imply that $kT\gamma = +17$ kJ/mol (see Appendix 9.4 for details). Notice that the latter quantity is equal to the experimental value of $-T\Delta S^*|_V$ (see Table 2). This agreement implies that $\Delta \langle \Phi \rangle = (\partial \gamma / \partial \beta) \approx 0$ and thus is consistent with GvdW0 predictions. Equivalently, we may combine the above estimate of γ with the general first-order perturbation theory expression (eq 59) and the experimental solvation free energy of xenon in *n*-hexane, $\Delta G^*|_P = -3.6$ kJ/mol, to obtain $\langle \Psi \rangle^{(1)} \approx -a\rho = -21$ kJ/mol, which is equivalent to the experimental value of $\Delta E^*|_V$ (see Table 2). This again implies that $\Delta \langle \Phi \rangle \approx 0$, as predicted by GvdW0 (eq 60). Moreover, using a reference hard-sphere fluid estimate of $kT\kappa_T\rho(\partial \gamma / \partial \rho)_T \approx 83$ cm^3/mol (obtained as described in Appendix 9.4), the GvdW0 approximation predicts a partial molar volume for xenon in *n*-hexane of $V^* \approx kT\kappa_T[\rho(\partial \gamma / \partial \rho)_T - a\beta\rho] \approx 47$ cm^3/mol, which is very close to the experimentally measured value of 45 cm^3/mol. The small difference between the predicted and experimental volumes is not significant given that decreasing the effective hard-sphere diameter of *n*-hexane by 0.002 nm (less than 0.5%) would be sufficient to produce an exact agreement between the experimental and predicted volumes (without significantly affecting any of the other solvation thermodynamic predictions).

The solvation of xenon in water differs both qualitatively and quantitatively from that in *n*-hexane (see Table 2). First of all, the solvation free energy of xenon in water is positive (rather than negative as in *n*-hexane). Moreover, the corresponding solvation enthalpy and entropy are significantly more negative than those in *n*-hexane. These experimental results cannot be reproduced using the same hard-sphere reference fluid approximation procedure that was successfully applied to the solvation of xenon in *n*-hexane. The source of the difficulty may be traced to the fact that cavity fluctuations in water differ significantly from those in a hard-sphere (or nonassociated) fluids of the same core diameter, density, and temperature.[19,38−40] The enhancement of cavity fluctuations in water is driven by the strong cohesive interactions between water molecules, which

promote water clustering and thus the enhanced formation of interstitial cavities.[19] As a result, the probability of finding cavities the size of xenon (~0.4 nm) in water[41,42] is comparable to the probability of finding cavities of 0.3-nm diameter in a hard-sphere or Lennard-Jones fluid of the same density and diameter as water.[19,43,44] This phenomenon is also closely related to the onset of hydrophobic dewetting, which Lum–Chandler–Weeks[45] and Stillinger[46,47] predicted should take place around nonpolar solutes of diameters larger than ~1 nm and which was subsequently confirmed by computer simulation[48−51] and X-ray scattering studies.[52] Moreover, recent simulations by Huang, Margulis, and Berne[53,54] have found evidence for dewetting in the hydration shell around neopentane, which is only slightly larger than xenon.[37,55] Thus, it appears that the enhanced probability of observing xenon-sized cavities in water foreshadows the onset of hydrophobic dewetting.

Given that cavity fluctuations in water are quite different from those in a hard-sphere reference fluid, it makes sense to use water simulation results, rather than a hard-sphere model, to represent the cavity size distribution in water. Simulations of hard-sphere cavity formation free energies[36,56,57] and partial molar volumes[58] in water imply that the solvation of a hard-sphere the size of xenon (0.392 nm[37]) is characterized by $kT\gamma = 29$ kJ/mol and $kT\kappa_T\rho(\partial\gamma/\partial\rho) = 55$ cm^3/mole (see Appendix 9.4 for details). Again, we find that $kT\gamma \approx -T\Delta S^*|_V$ and so $\Delta\langle\Phi\rangle \approx 0$, or equivalently combining γ with the experimental $\Delta G^*|_P$, we predict $\langle\Psi\rangle^{(1)} \approx -a\rho = -24$ kJ/mol, which is equivalent to the experimental value of $\Delta E^*|_V$. Moreover, the predicted partial molar volume of xenon in water, $V^* \approx kT\kappa_T[\rho(\partial\gamma/\partial\rho)_T - a\beta\rho] = 43$ cm^3/mol, is again in reasonably good agreement with the experimental value of 46 cm^3/mol. Because these results rely on cavity formation data in a realistic model of water, they may be viewed as pertaining to the GvdW1 rather than the GvdW0 approximation. However, because the results imply that $\Delta\langle\Phi\rangle \approx 0$, the GvdW1 predictions are essentially equivalent to those obtained using GvdW0, except that cavity fluctuations in water are more realistically represented.

The above results indicate that the solvation of xenon in both *n*-hexane and water may be accurately described using first-order perturbation theory with a near-zero value of $\Delta\langle\Phi\rangle$. However, it is important to note that these results pertain to the solvation of xenon under ambient conditions. So, the range of validity of the GvdW0 approximation (with $\Delta\langle\Phi\rangle = 0$) and more general first-order perturbation theories (with $\Delta\langle\Phi\rangle \neq 0$) remains to be determined.

The approach described above could readily be extended to other solvation processes in order to extract values of $\langle\Psi\rangle^{(1)}$, $\ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$, and $\Delta\langle\Phi\rangle$, as well as to test the limits of applicability of various GvdW and other approximations. More specifically, simulation results for γ may be compared with the experimental results for $\Delta S^*|_V$, $\Delta G^*|_P$, and/or $\Delta E^*|_V$ to determine $\Delta\langle\Phi\rangle$. If the value of $\Delta\langle\Phi\rangle$ is near zero, that immediately suggests that the GvdW0 approximation is applicable and thus that $\Delta E^*|_V \approx \langle\Psi\rangle^{(1)}$ and $\Delta S^*|_V \approx k \ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$. On the other hand, if $\Delta\langle\Phi\rangle$ differs significantly from zero, then the comparison of the predicted and measured partial molar volumes may be used to critically test the applicability of the GvdW1 approximation. Testing GvdW2 predictions requires more detailed comparisons of experimental, simulation, and theoretical results over a range of temperatures (and pressures).

It is also important to note that eq 74 may be used to quantify the error associated with invoking any first-order perturbation theory. More specifically, the first-order perturbation approximation implies that cohesive solute−solvent interactions

do not contribute to the constant-volume solvation entropy, and so, $\gamma \approx \ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$. The accuracy of this approximation could be determined using an independent simulation and/or integral-equation-based estimates of $-\beta\int_0^1 d\xi(1 - \xi)K_2^A(\xi)$, which represents a quantitative measure of the cohesive solute−solvent contributions to $\ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$.

8. Summary and Discussion

In keeping with previous analyses,[13,15,19] we have shown that $\mu_u^\times$ may be resolved into noncompensating energetic, $\epsilon_\mu^\times = \langle\Psi\rangle^{(1)}$, and entropic, $s_\mu^\times = -k \ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$, contributions, which derive from the average value and fluctuation, respectively, of the solute−solvent interaction energy, Ψ. Moreover, we have further expanded $Ts_\mu^\times$ into a leading Gaussian fluctuation term, $(\beta/2)\langle(\delta\Psi)^2\rangle^{(1)} = (\beta/2)K_2(1)$, plus a coupling-parameter integral representing the exact sum of all higher cumulant expansion coefficients (see eqs 10−13).

However, as stressed in previous studies,[13,15,19] the energetic and entropic components of $\mu_u^\times$ can, in general, differ from the corresponding solvation thermodynamic functions, because the latter may include an additional contribution arising from the solute-induced change in the solvent−solvent interaction energy at constant volume $\Delta\langle\Phi\rangle = \langle\Phi\rangle^{(1)} - \langle\Phi\rangle^{(0)}$, which contributes equally to both $\epsilon_u^\times|_V$ and $Ts_u^\times|_V$, and so exactly cancels when combining $\mu_u^\times = \epsilon_u^\times|_V - Ts_u^\times|_V$. We have obtained several new expressions for this constant-volume reorganization energy, $\Delta\langle\Phi\rangle$ (see section 3). In a constant-pressure solvation process, the solvent reorganization energy contains an additional volume-relaxation term,[21] $T(\alpha_P/\kappa_T)v_u^\times$ (see section 5), which again contributes equally to both $h_u^\times|_P$ and $Ts_u|_P$, and so again exactly cancels when combining $\mu_u^\times = h_u^\times|_P - Ts_u|_P$.

Moreover, we have shown how the above exact statistical thermodynamic quantities correlate with repulsive (reference system) and cohesive (perturbation) terms appearing in the first-order thermodynamic perturbation theory, thus facilitating the decomposition of the experimental solvation thermodynamic functions into fundamental statistical mechanical components, as illustrated in section 7. More generally, we have connected the cumulant and perturbation expansion results to identify a coupling-parameter integral representation for the sum of all higher-order terms in the perturbation series (see eq 74).

For a general solvation processes, it is often not possible to obtain $\langle\Phi\rangle^{(1)}$, $\ln\langle e^{\beta\delta\Psi}\rangle^{(1)}$, and $\Delta\langle\Phi\rangle$ directly from experimental measurements alone (except in the special case of a single-component solvation process[24] or when $\Delta\langle\Phi\rangle \approx 0$, as described in section 7 and further discussed below). In other words, although composite terms such as $\langle\Psi\rangle^{(1)} + \Delta\langle\Phi\rangle$ and $\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} - \beta\Delta\langle\Phi\rangle$ may be determined experimentally, $\Delta\langle\Phi\rangle$ cannot, in general, be determined without the aid of an independent theoretical calculation or simulation measurement. Moreover, $\Delta\langle\Phi\rangle$ is a notoriously difficult parameter to accurately simulate. For example, simulation-based estimates of $\Delta\langle\Phi\rangle$ for the hydration of xenon range over about 0 ± 5 kT,[15,19,59] while the hydration energy of a 0.3-nm diameter hard sphere (which is about the same size as a water molecule) has been somewhat more accurately determined to be on the order of -0.5 ± 0.5 kT.[38,57] On the other hand, $\langle\Psi\rangle^{(1)}$ may be more easily determined by computer simulation, and thus, comparisons with the experimental $\epsilon_u^\times|_V$ (obtained from $h_u^\times|_P$, $v_u^\times$, α_P, and κ_T) could provide an alternative route to the estimation of $\Delta\langle\Phi\rangle \approx \epsilon_u^\times|_V - \langle\Psi\rangle^{(1)}$. As an example, simulations of the solvation on xenon in SPC/E water yield $\langle\Psi\rangle^{(1)} \approx -21$ kJ/mol[15,19], which implies that $\Delta\langle\Phi\rangle \approx -2$ kT (when compared with the corresponding

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experimental constant-volume solvation energy, Table 2). However, given that both the experimental and simulation results have uncertainties (both random and systematic) of at least kT, the above estimate of $\Delta\langle\Phi\rangle$ is probably only reliable to $\pm 2\,kT$. As another source of comparison, Sanchez and co-workers have shown that the experimental equations of the state of nonaqueous single-component fluids imply $\Delta\langle\Phi\rangle \leq +kT$ (up to triple-point densities).[24] However, our comparisons with perturbation theory predictions (described in section 7) suggest that $\Delta\langle\Phi\rangle \approx 0$ ($\pm kT$) for the solvation of xenon in both *n*-hexane and water (at 298 K and 1 atm). This implies that such solvation processes may be represented using the GvdW0 approximation and thus that $kT\langle\Psi\rangle^{(1)} \approx \Delta E^*|_V = \Delta H^*|_P - T(\alpha_P/\kappa_T)V^*$ and $k\ln\langle e^{\beta\delta\Psi}\rangle^{(1)} \approx \Delta S^*|_V = \Delta S^*|_P - (\alpha_P/\kappa_T)V^*$ may be determined directly from experimental solvation thermodynamic measurements.

More generally, the difference between $\Delta H^*|_P$ and $\Delta E^*|_V$ (or $T\Delta S^*|_P$ and $T\Delta S^*|_V$) in *any* solvation process may be used to distinguish local- and nonlocal-contribution solvation thermodynamics.[20] Local solvation thermodynamic properties are those which derive strictly from the interactions between the solute and its surrounding solvation shell(s). Nonlocal solvation thermodynamic properties derive from structural changes in solvent molecules that are arbitrarily far from the solute. For example, in a constant-volume system, the insertion of a solute into the solvent must, in general, produce a change in solvent density both near and far from the solute. Although the magnitude of the nonlocal-solvation-induced density change must necessarily approach zero as the system size approaches the macroscopic limit, the nonlocal energy is at the same time spread over an increasing number of solvent molecules, and so, the nonlocal energy associated with a constant-volume solvation process need not vanish, even in the macroscopic limit. On the other hand, in a constant-pressure solvation process, the solvation energy is strictly local, because solvent molecules far from the solute necessarily remain in an identical thermodynamic state before and after the addition of a solute. Thus, the difference between the solvation energy in a constant-volume and constant-pressure process represents the nonlocal contribution to the constant-volume solvation energy, $-[T\alpha_P - P\kappa_T]V^*/\kappa_T \approx -T(\alpha_P/\kappa_T)V^*$. Moreover, if $\Delta\langle\Phi\rangle \approx 0$ (as our results suggest may often be the case), then the local and nonlocal contributions to the constant-volume solvent reorganization energy must be exactly equal in magnitude and opposite in sign. In other words, whenever $\Delta\langle\Phi\rangle \approx 0$, the *local* contribution to the solvent reorganization energy in *both* a constant-volume and a constant-pressure solvation process must be approximately equal to $T(\alpha_P/\kappa_T)V^*$. Thus, the *local* solvent reorganization energy induced by the solvation of xenon is ~11 kJ/mol in *n*-hexane and ~8 kJ/mol in water. Physically, this energy represents the loss in local solvent−solvent cohesive interaction energy induced by the solvation of xenon.

Finally, no discussion of hydrophobic solvation would be complete without mentioning the partial molar heat capacity, $c_P^\times$, whose large positive value is considered to be a classic signature of the hydrophobic effect.[60] Recall that this parameter is related to the second temperature derivative of the solvation free energy, because $c_P^\times = T(\partial s_u^\times|_P/\partial T)_P = -T(\partial^2 \mu_u^\times/\partial T^2)_P$ (and so is relatively difficult to accurately measure and/or simulate). Moreover, because $s_u^\times|_P = s_u^\times|_V + (\alpha_P/\kappa_T)V^*$, we may decompose $c_P^\times$ into the two corresponding terms. Previous studies have noted that hydrophobic heat capacities are primarily dictated by the second term in the above expression (which represents the volume-relaxation entropy and constant-pressure solvent reorganization entropy).[18,19,38,59,61] This suggests that

$\Delta C_P^* = N_A c_P^\times$ may be approximated by $\Delta C_P^* \approx [(T/\kappa_T)(\partial\alpha_P/\partial T)_P]\ V^*$. This approximation, combined with the required experimental parameters (from Tables 1 and 2), predicts a value of $\Delta C_P^* \approx 300$ J/(K mol) for the hydration of xenon at 298 K. This prediction is in remarkably good agreement with published experimental values, which range from 250 to 350 J/(K mole),[62,63] and is particularly striking when compared with the somewhat less satisfactory prediction of ~160 J/(K mole) obtained from recent simulations of xenon in SPC/E water.[59] However, the above approximation is also not completely satisfactory, because it implies that ΔC_P^* should increase with temperature, while the experimental values generally decrease with temperature.[3] In other words, the above approximation predicts the wrong sign for the *third* temperature derivative of $\mu_u^\times$. This discrepancy implies that either $\mu_u^\times$ and/or $\Delta\langle\Phi\rangle$ have negative *second* temperature derivatives of significant magnitude. Because $s_\mu^\times$ is a weak function of temperature,[18,19] it appears more likely that $\Delta\langle\Phi\rangle$ becomes increasingly negative with increasing temperature. However, testing this expectation and elucidating the detailed molecular mechanism underlying hydrophobic heat capacities[18,26,64−66] remain worthy topics for further investigation.

9. Appendix

9.1. Derivation of Equations. The following useful identity holds for any dynamical variable, M (such as energy), which is a function of another variable, τ (such as ξ)

$$d_\tau\langle M\rangle^{(\xi)} = \langle d_\tau M\rangle^{(\xi)} + \langle M\,d_\tau[-\beta\,\mathscr{U}(\xi)]\rangle^{(\xi)} - \langle M\rangle^{(\xi)}\langle d_\tau[-\beta\,\mathscr{U}(\xi)]\rangle^{(\xi)} \quad (75)$$

This equation follows by taking the derivative with respect to τ of the explicit expression of the expectation value

$$\langle M\rangle^{(\xi)} = \int dQ_u \int dQ_w\,e^{-\beta\,\mathscr{U}(\xi)}M / \int dQ_u \int dQ_w\,e^{-\beta\,\mathscr{U}(\xi)} \quad (76)$$

and considering that both M and $[-\beta\,\mathscr{U}(\xi)]$ might depend on τ.

Equation 6 may be concisely derived using the following sequence of relations

$$\mu_u^\times = -\frac{1}{\beta}\ln\{\mathscr{Z}(1)/\mathscr{Z}(0)\} = -\frac{1}{\beta}\int_0^1 d\xi\,d_\xi\ln\mathscr{Z}(\xi)$$

$$= -\frac{1}{\beta}\int_0^1 d\xi\,[d_\xi\mathscr{Z}(\xi)]/\mathscr{Z}(\xi)$$

$$= \int_0^1 d\xi \int dQ_u \int dQ_w\,e^{-\beta\,\mathscr{U}(\xi)}\,d_\xi\mathscr{U}(\xi)/\mathscr{Z}(\xi)$$

$$= \int_0^1 d\xi\,\langle d_\xi\mathscr{U}(\xi)\rangle^{(\xi)}$$

$$= \int_0^1 d\xi\langle\Psi\rangle^{(\xi)}$$

Equation 8 follows from eq 6 through a simple series of steps involving the identity in eq 75. Consider first the evaluation of $\langle\Psi\rangle^{(\xi)}$ in the integrand of of eq 6. Starting with eq 75, we identify M with $\xi\Psi$ and τ with ξ. Next, we solve eq 75 for $\langle d_\tau M\rangle^{(\xi)} = \langle\Psi\rangle^{(\xi)}$ and the result is

$$\langle\Psi\rangle^{(\xi)} = d_\xi\langle\xi\Psi\rangle^{(\xi)} + \beta\xi\{\langle\Psi^2\rangle^{(\xi)} - [\langle\Psi\rangle^{(\xi)}]^2\} \quad (77)$$

Replacing this expression for $\langle\Psi\rangle^{(\xi)}$ in the last line of eq 7 and carrying out the integral over the coupling parameter leads directly to eq 8.

Equation 33 can also be derived with the help of eq 75. The derivative $d_\xi\langle\Phi\rangle^{(\xi)}$ appearing in eq 32 easily follows from eq 75 with the choices $M = \Phi$ and $\tau = \xi$ and by noticing that Φ is independent of the coupling parameter. Thus, within the linear coupling scheme in eq 5, the derivative becomes

$$d_\xi\langle\Phi\rangle^{(\xi)} = -\beta[\langle\Phi\Psi\rangle^{(\xi)} - \langle\Phi\rangle^{(\xi)}\langle\Psi\rangle^{(\xi)}] \tag{78}$$

Equation 33 is obtained by substituting this expression into eq 32.

9.2. Chemical Potential at Finite Concentration. The following results pertain to a solution of finite, rather than infinitely dilute, solute concentration. These are required to reproduce certain intermediate results obtained by Yu–Karplus.[13] Consider a solution comprising the solute species, u, at finite concentration in a solvent, w. We write the coupling-parameter-dependent potential energy of interaction $\mathscr{U}(\xi)$ of this solution in the form

$$\mathscr{U}(\xi) = \Phi + \Lambda(\xi) \tag{79}$$

where, as in eq 5, Φ is the potential energy of interaction among the solvent molecules. However, the ξ-dependent term

$$\Lambda(\xi) \equiv \Theta(\xi) + \Psi_N(\xi) \tag{80}$$

now comprises the potential energy of interaction $\Theta(\xi)$ between the solute molecules as well as the corresponding solute–solvent portion $\Psi_N(\xi)$. The coupling-parameter dependence of the functions is such that $\Lambda(0) = 0$ and $\Lambda(1) = \Theta + \Psi_N \equiv \Lambda$. The variable $\Lambda(\xi)$ is thus the same as the Yu–Karplus variable $U_{u,v}(\{\bar{R}\};\lambda)$ (as defined by the Yu–Karplus eq 2).[13]

To derive eq 7 of Yu–Karplus, we choose $M = \Lambda(\xi)$ and $\tau = \xi$ in eq 75 to obtain

$$\langle d_\xi\Lambda(\xi)\rangle^{(\xi)} = d_\xi\langle\Lambda(\xi)\rangle^{(\xi)} + \beta[\langle\Lambda(\xi) d_\xi\Lambda(\xi)\rangle^{(\xi)} - \langle\Lambda(\xi)\rangle^{(\xi)}\langle d_\xi\Lambda(\xi)\rangle^{(\xi)}] \tag{81}$$

The Yu and Karplus result emerges when replacing the above expression into the coupling-parameter expression for the chemical potential[13]

$$\mu_u^\times = \int_0^1 d\xi\langle d_\xi\Lambda(\xi)\rangle^{(\xi)} \tag{82}$$

to obtain

$$\mu_u^\times = \langle\Lambda\rangle^{(1)} + \beta \int_0^1 d\xi[\langle\Lambda(\xi) d_\xi\Lambda(\xi)\rangle^{(\xi)} - \langle\Lambda(\xi)\rangle^{(\xi)} \langle d_\xi\Lambda(\xi)\rangle^{(\xi)}] \tag{83}$$

Note that this reduces to eq 8 in the dilute solute (linear-coupling) limit in which $\Lambda(\xi) = \xi\Psi$.

9.3. Average Energy Integrals. In fluids with pairwise additive intermolecular interaction potentials, the average solute–solvent interaction energy $\langle\Psi\rangle^{(1)}$ can be expressed as

$$\langle\Psi\rangle^{(1)} =$$

$$\rho \int d^3\mathbf{r} \int \frac{d\Omega_u}{\Omega_u} \int \frac{d\Omega_w}{\Omega_w} u_{uw}(r, \Omega_u, \Omega_w) g_{uw}^{(1)}(r, \Omega_u, \Omega_w) \tag{84}$$

In this equation, $\int d\Omega_u \cdots$ and $\int d\Omega_w \cdots$ indicate integration over the orientations of the solute and solvent molecules,

respectively, with $1/\Omega_u$ and $1/\Omega_w$ as the probability densities that a solute or solvent molecule has a particular orientation in the solution. Moreover, $g_{uw}(r, \Omega_u, \Omega_w)$ is the solute–solvent molecular pair correlation function for a solute at infinite solute dilution, and $\rho \equiv N_w/V$ is the number density of the pure solvent.

Similarly, $\langle\Phi\rangle^{(0)}$ can be expressed as

$$\langle\Phi\rangle^{(0)} =$$

$$\frac{V\rho^2}{2} \int d^3\mathbf{r} \int \frac{d\Omega_a}{\Omega_w} \int \frac{d\Omega_b}{\Omega_w} u_{ww}(r, \Omega_a, \Omega_b) g_{ww}^{(0)}(r, \Omega_a, \Omega_b) \tag{85}$$

which only involves the pair correlation function of the pure solvent, because the solute molecule fully decoupled from the (0)-system. The corresponding equation for $\langle\Phi\rangle^{(1)}$ is

$$\langle\Phi\rangle^{(1)} =$$

$$\frac{V\rho^2}{2} \int d^3\mathbf{r} \int \frac{d\Omega_a}{\Omega_w} \int \frac{d\Omega_b}{\Omega_w} u_{ww}(r, \Omega_a, \Omega_b) g_{ww}^{(1)}(r, \Omega_a, \Omega_b) \tag{86}$$

In this case, however, it is the solvent–solvent molecular pair correlation function $g_{ww}^{(1)}(r, \Omega_a, \Omega_b)$ in the presence of the fully coupled solute that is required.

We may further re-express the above average solvent energy integrals in terms of the solvent–solvent *generic* two-particle molecular distribution function, $\rho_{ww}(a, b)$

$$V\rho^2 \int d^3 \int \mathbf{r} \int \frac{d\Omega_a}{\Omega_w} \int \frac{d\Omega_b}{\Omega_w} \cdots g_{ww}(r, \Omega_a, \Omega_b) =$$

$$\int da \int db \cdots \rho_{ww}(a, b) \tag{87}$$

where a and b represent generalized solvent molecule position orientation variables.

9.4. The GvdW Approximations. The GvdW0 approximation applies to a class of fluids whose solute–solvent and solvent–solvent repulsive core potentials are sufficiently steep that they may be approximated as hard spheres of diameter σ_i and whose attractive interactions are sufficiently slowly varying that they give rise to a uniform (van der Waals) cohesive mean field. It may be shown that, in this limit, the resulting first-order perturbation-theory predictions are, in fact, identical to the corresponding exact thermodynamic quantities (as demonstrated by Kac, Hemmer, and Uhlembeck for 1-D fluids[67] and by Lebowitz and Penrose for 3-D fluids[68]).

Any fluid composed of hard-body particles lacks a natural temperature scale, other than kT. Thus, the pressure and the Helmholtz free energy in any such fluid must be linear functions of T with constant ρ. This implies that $\beta\mu_u^R$ for a dilute solute in a reference fluid composed of hard-body solvent and solute particles is a temperature-independent function, $\gamma(\rho, \sigma_u, \sigma_w)$. The van der Waals mean-field approximation applies to any cohesive potential whose range extends sufficiently beyond the first solvation shell that one may accurately predict average solute–solvent interaction energies by assuming $g_{uw}^R(r) \cong 1$ when $r > \sigma_{uw} = (\sigma_u + \sigma_w)/2$, and 0 otherwise. In other words, the van der Waals mean-field approximation implies that a, which represents the integral in eq 58, is a T- and ρ-independent constant.

In a hard-sphere (or hard-body) fluid (with no solvent–solvent cohesion) the compressibility factor, $Z = P/\rho kT$, must be a T-independent function of ρ. This implies the following interrelationship between such a fluid's thermal expansion and compressibility coefficients.[20]

$$T\alpha_P = P\kappa_T = \frac{Z}{Z + \eta(\partial Z/\partial \eta)} \quad (88)$$

Thus, in a hard-sphere fluid, $T\alpha_P - P\kappa_T = 0$. However, in a more realistic ambient fluid (with both repulsive and cohesive interactions), the above relation no longer holds. Moreover, under ambient conditions, P is sufficiently small that $P\kappa_T$ is typically on the order of 1000 times smaller in magnitude than $T\alpha_P$, and thus to a very good approximation, $T\alpha_P - P\kappa_T \cong T\alpha_P$.

When the GvdW0 model is applied to a pure solvent, the following Carnahan−Starling−van der Waals (CSvdW) equation expresses the dependence of the pressure, P, on T, ρ, σ_w, and the cohesive mean-field parameter $\tau_w = a_w/[(4\pi/3)\sigma_w^3 R]$ (where σ_w and a_w are the molecules' effective hard-sphere diameter and cohesive mean-field coefficients, respectively, $R = N_A k$ is the gas constant, N_A is Avogadro's number, and k is Boltzmann's constant).[37,69]

$$Z = \frac{(1 + \eta + \eta^2 - \eta^3)}{(1 - \eta)^3} - 4\left(\frac{\tau_w}{T}\right)\eta \quad (89)$$

The parameter η represent the fluid packing fraction, $\eta = (\pi/6)\rho\sigma_w^3$ (where ρ is the solvent number density).

The GvdW0 approximation furthermore implies that the dilute solution of interest may be represented as a hard-sphere reference solution plus solvent−solvent and solute−solvent van der Waals mean-field cohesive interactions. The following expression for the solute cavity formation chemical potential is obtained from the Boublik−Mansoori−Carnahan−Starling−Leland (BMCSL) mixed hard-sphere fluid equation of state[70−73] in which parameter $d = \sigma_u/\sigma_w$ is the solute−solvent diameter ratio.

$$\gamma = \beta\mu_u^R$$

$$= \left[\frac{3\eta d(1 + d - d^2)}{1 - \eta} + \frac{3\eta d^2}{(1 - \eta)^2} + \frac{2\eta d^3}{(1 - \eta)^3} - (1 - 3d^2 + 2d^3)\ln(1 - \eta)\right] \quad (90)$$

The derivative of γ with respect to η yields the required factor appearing in eqs 64−66.

$$\rho\left(\frac{\partial\gamma}{\partial\rho}\right) = \eta\left(\frac{\partial\gamma}{\partial\eta}\right) \quad (91)$$

The above expressions are used to approximate the cavity formation contribution to the solvation of xenon in *n*-hexane.

The hard-sphere diameter of xenon, $\sigma_{xe} = 0.392$ nm,[37] is obtained by fitting eq 89 to the equation of state of pure fluid xenon (at 298 K). The hard-sphere diameter of *n*-hexane obtained using the same procedure is $\sigma_{hex} = 0.595$ nm.[37] However, comparisons with simulation results for the cavity formation energies in *n*-hexane suggest that a slightly smaller diameter of 0.587 mm is more appropriate when using eq 90 to represent the free energy required to produce a cavity the size of xenon in *n*-hexane. More specifically, simulated cavity formation energies in *n*-hexane[36,57] were first adjusted to account for the fact that the diameter of methyl and methylene groups used in the simulations are about 0.033 nm larger than the hard-sphere diameter of methane obtained by fitting the equation of state of fluid methane to eq 89.[37] Thus, to correct for this difference, the reported cavity hard-sphere diameters were increased by 0.033 nm. The resulting cavity formation chemical

potentials were then fit to eq 90 to obtain an effective hard-sphere diameter of *n*-hexane of $\sigma_{hex} = 0.587$ nm, and this value was used in subsequent GvdW0 calculations of xenon in *n*-hexane. Although the solvation thermodynamic results obtained when using the two values of σ_{hex} differ by less than kT, the partial molar volume of xenon is quite sensitive to σ_{hex}. More specifically, $V^* = 58$ cm³/mol is obtained using the GvdW0 model with $\sigma_{hex} = 0.595$ nm, while a significantly more realistic value of $V^* = 47$ cm³/mol is obtained when using $\sigma_{hex} = 0.587$ nm. The latter diameter also yields somewhat better agreement between the predicted and experimental values of the remaining thermodynamic functions.

A number of previous studies have represented cavity formation free energies in water using hard-sphere reference fluids with diameters ranging from 0.25 nm $< \sigma_w <$ 0.32 nm.[43,56,74−76] However, careful comparisons with simulation results in TIP4P water reveal that hard-sphere solvation free energies[36,56] and partial molar volumes[58] cannot be satisfactorily represented using a hard-sphere reference fluid, regardless of the value of σ_w. Thus, in the present work, we have chosen to derive cavity formation free energies directly from water simulation results. Because the simulation results were obtained in terms of the cavity radius, which excludes the centers of the water oxygen atoms, $R_c = (\sigma_w + \sigma_c)/2$, one must choose a reasonable value of σ_w in order to convert the R_c values to solute cavity diameters, σ_c. However, the selected value for σ_w is no longer a critical parameter, because the cavity distribution function in water is now accurately represented regardless of the value of σ_w (as further discussed below).

In describing the interaction of xenon and water, an appropriate value of σ_w is one that represents the size of water in the absence of electrostatic interactions. Because the Lennard-Jones diameter of TIP4P water is 0.316 nm and the hard-sphere diameters of argon and methane are about 0.016 nm smaller than their Lennard-Jones diameters,[37,55] we have chosen a value of $\sigma_w = 0.316 - 0.016$ nm $= 0.300$ nm as a reasonable water hard-sphere diameter for describing the xenon−water interaction.

Simulation data for cavity formation free energies[36,56] spanning a cavity size range of 0.15 nm $\leq R_c \leq$ 0.5 nm (corresponding to 0 nm $\leq \sigma_c \leq$ 0.7 nm) were fit to polynomials in σ_c (nm) to obtain the following accurate interpolation formula for γ in water.

$$\gamma_w = 0.4 + 9.5\sigma_c + 42.0\sigma_c^2 + 21.6\sigma_c^3 \quad (92)$$

A similar fit of the partial molar volumes of hard spheres in TIP4P water[58] was performed to obtain the density derivative of γ_w. More specifically, the simulated partial molar volumes, $V^* = N_A\upsilon_u - RT\kappa_T$, were converted to $\rho(\partial\gamma_w/\partial\rho)_T = V^*/RT\kappa_T$ using the isothermal compressibility of TIP4P water ($\kappa_T = 48.6$ atm⁻¹) at 298 K.[58]

$$\rho\left(\frac{\partial\gamma_w}{\partial\rho}\right)_T = 0.0 + 15.6\sigma_c + 129.0\sigma_c^2 + 380.6\sigma_c^3 \quad (93)$$

Although the above expressions pertain to a water hard-sphere diameter of $\sigma_w = 0.30$ nm, results corresponding to different choices for the value of σ_w may be obtained simply by shifting the value of σ_c. For example, to accurately represent simulation results pertaining to $\sigma_w = 0.26$ nm and $\sigma_c = 0.39$ nm, one may use the above equations with σ_c replaced by 0.39 nm − (0.3 nm − 0.26 nm) = 0.32 nm. Although the choice of σ_w is in some respects arbitrary, the value of 0.30 nm was chosen so as to be self-consistent with tabulated effective hard-sphere

diameters derived from the equations of state of a large number of compounds.[37,69] Thus, with $\sigma_w = 0.30$ nm, these tabulated effective hard-sphere diameters may be used directly in eqs 92 and 93 to obtain realistic estimates of the coresponding hard-sphere cavity formation free energies and partial molar volumes in water.

In both GvdW0 and GvdW1 fluids, the van der Waals mean-field coefficient, a, is a temperature- and density-independent constant. The value of this constant may be approximately related to the geometric mean of the corresponding pure solvent and pure solute fluid mean-field parameters,[37,69] $a = \sqrt{a_u a_w} = (4\pi/3)R\sigma_w^3\sqrt{\tau_u\tau_w}d^3$. However, although this approximation often provides a reasonable rough estimate, it is not, in general, expected to realistically represent the true solute−solvent cohesive interaction (particularly when applied to solute and solvent molecules of very different sizes, shapes, and/or polarities). Thus, in the present work, we have treated a as an empirically adjustable parameter whose value is determined by combining the predicted value of γ with the experimental solvation free energy.

$$a\rho = \mu_u^R - \mu_u^{\times}$$

$$= RT\gamma - \Delta G_u^{\times}|_P \tag{94}$$

Having thus obtained values of $a\rho$, γ, and $\rho(\partial\gamma/\partial\rho)_T$, the resulting GvdW0 solvation thermodynamic predictions are derived using eqs 60−66. The corresponding GvdW1 predictions are obtained by introducing an additional variable representing the value of $\Delta\langle\Phi\rangle = (\partial\gamma/\partial\beta)_\rho$ in eqs 67−69. However, comparisons of GvdW1 predictions with experimental xenon solvation results suggest that the value of $\Delta\langle\Phi\rangle$ is small (at most, on the order of $\pm kT$). Thus, both GvdW0 and GvdW1 predictions are equally satisfactory, as long as the solvent cavity distribution function is faithfully represented.

References and Notes

(1) Chandler, D. *Introduction to Modern Statistical Mechanics*; Oxford University Press: New York, 1987.

(2) Hill, T. L. *An Introduction to Statistical Thermodynamics*; Dover: New York, 1960.

(3) Ben-Naim, A. *Solvation thermodynamics*; Plenum Press: New York, 1987.

(4) Reichardt, C. *Solvents and solvent effects in organic chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.

(5) Hirata, F. Understand chemical reactivity. In *Molecular theory of solvation*; Kluwer Academic Publishers: Dordrecht, 2003; Vol. 24.

(6) Hansen, J. P.; McDonald, I. R. *Theory of Simple Liquids*, 2nd ed.; Academic Press: New York, 1986.

(7) Ben-Naim, A. *Statistical Thermodynamics for Chemists and Biochemists*; Plenum Press: New York, 1992.

(8) Frenkel, D.; Smit, B. *Understanding Molecular Simulation. From Algorithms to Applications*; Academic Press: San Diego, 2002.

(9) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Oxford University Press: Oxford, 1987.

(10) Widom, B. *J. Chem. Phys.* **1963**, *39*, 2802.

(11) Widom, B. *J. Phys. Chem.* **1982**, *86*, 869.

(12) Ben-Naim, A. *J. Phys. Chem.* **1978**, *82*, 874.

(13) Yu, H. A.; Karplus, M. *J. Chem. Phys.* **1988**, *89*, 2366.

(14) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1977**, *67*, 3683.

(15) Guillot, B.; Guissani, Y. *J. Chem. Phys.* **1993**, *99*, 8075.

(16) Qian, H.; Hopfield, J. J. *J. Chem. Phys.* **1996**, *105*, 9292.

(17) Gallicchio, E.; Kubo, M. M.; Levy, R. M. *J. Phys. Chem. B* **2000**, *104*, 6271.

(18) Lazaridis, T. *J. Phys. Chem. B* **2000**, *104*, 4964.

(19) Stone, M. T.; In't Veld, P. J.; Lu, Y.; Sanchez, I. C. *Mol. Phys.* **2002**, *100*, 2773.

(20) Ben-Amotz, D.; Omelyan, I. P. *J. Chem. Phys.* **2001**, *115*, 9401.

(21) Kubo, M. M.; Gallicchio, E.; Levy, R. M. *J. Phys. Chem. B* **1997**, *101*, 10527.

(22) Chandler, D.; Singh, Y.; Richardson, D. M. *J. Chem. Phys.* **1984**, *81*, 1975.

(23) Pratt, L. R.; Chandler, D. *Methods Enzymol.* **1986**, *127*, 48.

(24) Sanchez, I. C.; Truskett, T. M.; in't Veld, P. J. *J. Phys. Chem. B* **1999**, *103*, 5106.

(25) Gardiner, C. W. *Handbook of Stochastic Methods for Physics, Chemistry, and Natural Sciences*, 2nd ed.; Springer-Verlag: Berlin, 1994.

(26) Garde, S.; Garcia, A. E.; Pratt, L. R.; Hummer, G. *Biophys. Chem.* **1999**, *78*, 21.

(27) TenWolde, P. R.; Chandler, D. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 6539.

(28) Ayton, G. S.; Tepper, H. L.; Mirijanian, D. T.; Voth, G. A. *J. Chem. Phys.* **2004**, *120*, 4074.

(29) Ben-Amotz, D.; Stell, G. *J. Chem. Phys.* **2003**, *119*, 10777.

(30) Ben-Amotz, D.; Stell, G. *J. Chem. Phys.* **2004**, *120*, 4994.

(31) Weeks, J. D.; Chandler, D.; Andersen, H. C. *J. Chem. Phys.* **1971**, *54*, 5237.

(32) Ben-Amotz, D.; Stell, G. *J. Phys. Chem. B* **2004**, *108*, 6877.

(33) Lide, D. R. *Handbook of Chemistry and Physics*, 77th ed.; CRC Press: Boca Raton, 1996.

(34) Bonifacio, R. P.; Costa Gomesb, M. F.; Filipe, E. J. M. *Fluid Phase Equilib.* **2002**, *193*, 41.

(35) Kennan, R. P.; Pollack, G. L. *J. Chem. Phys.* **1990**, *93*, 2724.

(36) Pohorille, A.; Pratt, L. R. *J. Am. Chem. Soc.* **1990**, *112*, 5066.

(37) Ben-Amotz, D.; Herschbach, D. R. *J. Phys. Chem.* **1990**, *94*, 1038.

(38) Matubayasi, N.; Nakahara, M. *J. Chem. Phys.* **2000**, *112*, 8089.

(39) Pratt, L. R.; Pohorille, A. *Proc. Nat. Acad. Sci. U.S.A.* **1992**, *89*, 2995.

(40) Graziano, G. *Chem. Phys. Lett.* **2004**, *396*, 226.

(41) Huang, D. M.; Geissler, P. L.; Chandler, D. *J. Phys. Chem. B* **2001**, *105*, 6704.

(42) Hummer, G.; Garde, S.; Garcia, A. E.; Pohorille, A. E.; Pratt, L. R. *Proc. Nat. Acad. Sci. U.S.A.* **1996**, *93*, 8951.

(43) de Souza, L. E. S.; Ben-Amotz, D. *J. Chem. Phys.* **1994**, *101*, 9858.

(44) de Souza, L. E. S.; Stamatopoulou, A.; Ben-Amotz, D. *J. Chem. Phys.* **1994**, *100*, 1456.

(45) Lum, K.; Chandler, D.; Weeks, J. D. *J. Phys. Chem. B* **1999**, *103*, 4570.

(46) Stillinger, F. H. *J. Solution Chem.* **1973**, *2*, 141.

(47) Stillinger, F. H. *Science* **1980**, *209*, 451.

(48) Wallqvist, A.; Gallicchio, E.; Levy, R. M. *J. Phys. Chem. B* **2001**, *105*, 6745.

(49) Huang, X.; Margulis, C. J.; Berne, B. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 11953.

(50) Zhou, R.; Huang, X.; Margulis, C. J.; Berne, B. J. *Science* **2004**, *305*, 1605.

(51) Mamatkulov, S. I.; Khabibullaev, P. K.; Netz, R. R. *Langmuir* **2004**, *20*, 4756.

(52) Jensen, T. R.; Jensen, M. O.; Reitzel, N.; Balashev, K.; Peters, G. H.; Kjaer, K.; Bjornholm, T. *Phys. Rev. Lett.* **2003**, *90*, 86101.

(53) Huang, X.; Margulis, C. J.; Berne, B. J. *J. Phys. Chem. B* **2003**, *107*, 11742.

(54) Graziano, G. *J. Phys. Chem. B* **2004**, *108*, 9371.

(55) Ben-Amotz, D.; Gift, A. D.; Levine, R. D. *J. Chem. Phys.* **2002**, *117*, 4632.

(56) Floris, F. M.; Selmi, M.; Tani, A.; Tomasi. *J. Chem. Phys.* **1997**, *107*, 6353.

(57) Tomas-Oliveira, I.; Wodak, S. J. *J. Chem. Phys.* **1999**, *111*, 8576.

(58) Floris, F. M. *J. Phys. Chem. B* **2004**, *108*, 16244.

(59) Paschek, D. *J. Chem. Phys.* **2004**, *120*, 10605.

(60) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, 2nd ed.; Wiley: New York, 1980.

(61) Ikeguchi, M.; Shimizu, S.; Nakamura, S.; Shimizu, K. *J. Phys. Chem. B* **1998**, *102*, 5891.

(62) Plyasunova, N. V.; Plyasunov, A. V.; Shock, E. L. *Int. J. Thermophys.* **2004**, *25*, 351.

(63) Crovetto, R.; Fernandez-Prini, R.; Japas, M. L. *J. Chem. Phys.* **1982**, *76*, 1077.

(64) Gallagher, K. R.; Sharp, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 9853.

(65) Chandler, D. *Nature* **2002**, *417*, 491.

(66) Lee, B. *Biophys. Chem.* **1994**, *51*, 271.

(67) Kac, M.; Hemmer, P. C.; Uhlenbeck, G. E. *J. Math. Phys.* **1963**, *4*, 216.

(68) Lebowitz, J. L.; Penrose, O. *J. Math. Phys.* **1966**, *7*, 98.

(69) Ben-Amotz, D.; Willis, K. G. *J. Phys. Chem.* **1993**, *97*, 7736.

(70) Boublik, T. *J. Chem. Phys.* **1970**, *53*, 471.

(71) Mansoori, G. A.; Carnahan, N. F.; Starling, K. E.; Leland, T. W. *J. Chem. Phys.* **1971**, *54*, 1523.

(72) Ben-Amotz, D. *J. Phys. Chem.* **1993**, *97*, 2314.

(73) Gift, A. D.; Ben-Amotz, D. *J. Chem. Phys.* **2003**, *118*, 6427.

(74) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717.

(75) Madan, B.; Lee, B. *Biophys. Chem.* **1994**, *51*, 279.

(76) Graziano, G.; Lee, B. *Biophys. Chem.* **2003**, *105*, 241.