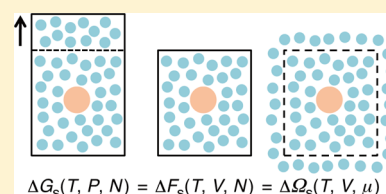


Thermodynamic-Ensemble Independence of Solvation Free Energy

Song-Ho Chong and Sihyun Ham*

Department of Chemistry, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Yongsan-Ku, Seoul 140-742, Korea

ABSTRACT: Solvation free energy is the fundamental thermodynamic quantity in solution chemistry. Recently, it has been suggested that the partial molar volume correction is necessary to convert the solvation free energy determined in different thermodynamic ensembles. Here, we demonstrate ensemble-independence of the solvation free energy on general thermodynamic grounds. Theoretical estimates of the solvation free energy based on the canonical or grand-canonical ensemble are pertinent to experiments carried out under constant pressure without any conversion.



Solvation free energy is the reversible work for transferring a solute molecule from a fixed position in an ideal gas phase into a fixed position in a liquid phase.¹ When the solute insertion is carried out under constant pressure, the reversible work is given by the Gibbs free energy. The Gibbs solvation free energy—to be denoted as $\Delta G_s(T, P, N)$ with T being the temperature, P the pressure, and N the number of solvent molecules—is therefore most closely related to experimental measurements.² (Here and in the following, we shall restrict ourselves to infinitely dilute solutions.) On the other hand, theoretical methods such as integral-equation and density-functional theories are usually formulated with canonical or grand-canonical ensemble in which system's volume V is fixed.^{3,4} Solvation free energy handled in the theoretical approaches is thus either the change in the Helmholtz free energy, $\Delta F_s(T, V, N)$, or the change in the grand potential, $\Delta \Omega_s(T, V, \mu)$, where μ refers to the chemical potential of the solvent. A natural question arises as to how $\Delta G_s(T, P, N)$, $\Delta F_s(T, V, N)$, and $\Delta \Omega_s(T, V, \mu)$ determined in different thermodynamic ensembles are related. In this regard, it has been demonstrated that for a macroscopic system where the fluctuations in N and V are negligible relative to the average values $\langle N \rangle$ and $\langle V \rangle$ ⁵

$$\Delta G_s(T, P, N) = \Delta F_s(T, V, N) = \Delta \Omega_s(T, V, \mu) \quad (1)$$

This equivalence stems from the facts that (i) the solvation free energy is given by an ensemble average of the quantity $\exp(-\beta B_s)$, where $\beta^{-1} = k_B T$ with k_B being Boltzmann's constant and B_s the solute–solvent interaction energy, (ii) the average is taken with respect to the system before the addition of the solute, i.e., pure solvent, and (iii) macroscopic systems characterized by the same temperature T and density $\rho (= N/V, \langle N \rangle/V, \text{ or } N/\langle V \rangle$ depending on the ensembles) are thermodynamically identical.

Recently, an interesting question regarding the possible ensemble-dependence has been posed based on the thermodynamic scheme depicted in Figure 1.⁶ The density-functional theory (DFT) of fluids is conventionally formulated with the grand-canonical ensemble. The DFT solvation free energy is therefore $\Delta \Omega_s(T, V, \mu)$ corresponding to the constant- V transition between state 1 and state 2 in Figure 1, during which

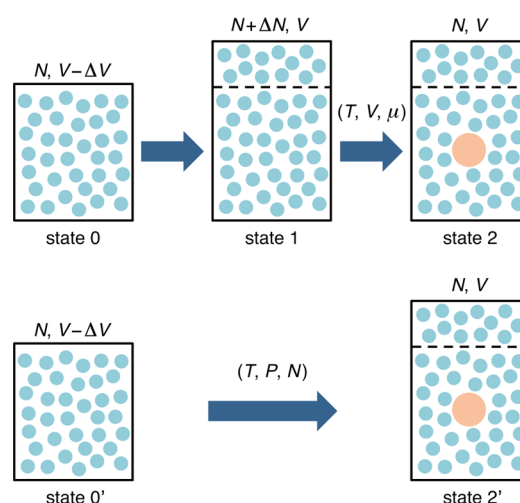


Figure 1. Thermodynamic scheme considered in ref 6 for the computation of the solvation free energy in the grand-canonical ensemble (top) or in the isothermal–isobaric ensemble (bottom). Solvent particles are colored with cyan, and a solute with orange.

the number of solvent molecules decreases from $N + \Delta N$ to N due to the imposed constant solvent chemical potential μ . On the other hand, the Gibbs solvation free energy $\Delta G_s(T, P, N)$ refers to the isobaric transition between state 0' and state 2' in Figure 1, in which the system volume increases from $V - \Delta V$ to V by an amount given by the solute partial molar volume ΔV . The final states 2 and 2' in these transitions are chosen so that they are characterized by the same T , V , and N , and the presence of one solute molecule, and hence, they are equivalent in the thermodynamic limit. Here comes the proposition of ref 6: the DFT solvation free energy should be evaluated using the same reference state 0 characterized by T , $V - \Delta V$, and N (see Figure 1). By taking into account the “missing” transition between state 0 and state 1, the following relation (using our notation) was suggested:

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$$\Delta G_s(T, P, N) = \Delta \Omega_s(T, V, \mu) - \left[\rho k_B T - \frac{k_B T}{2} \rho^2 c(k=0) \right] \Delta V \quad (2)$$

Here the quantity in square brackets corresponds to an approximate expression for the pressure P in terms of the solvent direct correlation function $c(k)$. In previous computational studies,^{7–9} it has been observed for an extensive number of organic solute molecules that theoretical estimates of the solvation free energy agree well with the experimental data after empirical partial molar volume corrections. It has therefore been claimed that the thermodynamic consideration leading to eq 2 provides a theoretical justification to such empirical corrections. However, eq 2 is obviously in contradiction with eq 1.

In this Letter, we demonstrate that the thermodynamic scheme in Figure 1 actually serves as a good model to confirm the ensemble-independence of the solvation free energy. To simplify the demonstration, we shall consider an infinitely dilute solution comprising spherical solute and solvent particles. In addition, we remove the constraint imposed in defining the solvation free energy: we do not fix the position of the solute in the liquid phase, and the solution is considered homogeneous. For the system under consideration, this leads to the solvation free energies that differ from those appearing in eq 1 just by a common term (the so-called libration free energy, $k_B T \log(\rho_s \lambda_s^3)$, with the solute density ρ_s and the thermal de Broglie wavelength λ_s), and therefore does not affect the argument on the ensemble independence/dependence. For this reason, we shall use the same notation for the solvation free energies. Furthermore, we do not resort to any approximation in liquid theories such as the hypernetted-chain (HNC) approximation in the integral-equation theory or the equivalent homogeneous reference fluid (HRF) approximation in DFT.³ All that is necessary here is the standard statistical mechanical expression for the free energy such as $F(T, V, N, N_s) = -k_B T \log Q(T, V, N, N_s)$ with the partition function $Q(T, V, N, N_s)$ for a homogeneous solution consisting of N solvent particles and N_s solute particles. The solvation free energies to be handled are defined by $\Delta G_s(T, P, N) = G(T, P, N, 1) - G(T, P, N, 0)$, $\Delta F_s(T, V, N) = F(T, V, N, 1) - F(T, V, N, 0)$, and $\Delta \Omega_s(T, V, \mu) = \Omega(T, V, \mu, 1) - \Omega(T, V, \mu, 0)$ under the thermodynamic limit ($N, V \rightarrow \infty$ but with N/V constant).

Gibbs free energy difference between state 0' and state 2' in Figure 1 corresponds to $\Delta G_s(T, P, N)$, and it can be expressed in terms of the partition functions as

$$\Delta G_s(T, P, N) = \Delta G_{0'2'} = -k_B T \log \left[\frac{\int dV' e^{-\beta P V'} Q(T, V', N, 1)}{\int dV' e^{-\beta P V'} Q(T, V', N, 0)} \right] \quad (3)$$

Since the fluctuations in V' are negligible in the thermodynamic limit, the numerator (for state 2') is dominated by the term with $V' = V$ whereas the denominator (state 0') by the term with $V' = V - \Delta V$. We therefore obtain

$$\begin{aligned} \Delta G_s(T, P, N) &= -k_B T \log \left[\frac{e^{-\beta P V} Q(T, V, N, 1)}{e^{-\beta P (V - \Delta V)} Q(T, V - \Delta V, N, 0)} \right] \\ &= P \Delta V + F(T, V, N, 1) - F(T, V - \Delta V, N, 0) \\ &= P \Delta V + \Delta F_{0'2'} \end{aligned} \quad (4)$$

in terms of the Helmholtz free energy difference, $\Delta F_{0'2'}$, between state 0' and state 2'. This quantity can be rewritten as

$$\begin{aligned} \Delta F_{0'2'} &= [F(T, V, N, 1) - F(T, V, N, 0)] \\ &\quad + [F(T, V, N, 0) - F(T, V - \Delta V, N, 0)] \\ &= \Delta F_s(T, V, N) + [F(T, V, N, 0) \\ &\quad - F(T, V - \Delta V, N, 0)] \end{aligned} \quad (5)$$

with the Helmholtz solvation free energy $\Delta F_s(T, V, N)$. The second term on the right-hand side can be handled using the fact that ΔV is negligibly small relative to V : we obtain from the Taylor expansion truncated at the first order

$$\begin{aligned} F(T, V, N, 0) &= F(T, V - \Delta V, N, 0) \\ &\quad + \Delta V \left(\frac{\partial F(T, V - \Delta V, N, 0)}{\partial (V - \Delta V)} \right)_{T,N} \\ &= F(T, V - \Delta V, N, 0) - P \Delta V \end{aligned} \quad (6)$$

since the pressure of the pure solvent, $-(\partial F(T, V', N, 0)/\partial V')_{T,N}$, evaluated for $V' = V - \Delta V$ (state 0') is P . It then follows from eqs 5 and 6 that

$$\Delta F_{0'2'} = \Delta F_s(T, V, N) - P \Delta V \quad (7)$$

and substituting this into eq 4 yields the relation

$$\Delta G_s(T, P, N) = \Delta F_s(T, V, N) \quad (8)$$

Now let us compute ΔF_{01} and ΔF_{12} and examine the consequence of the equivalence of the transitions $0 \rightarrow 1 \rightarrow 2$ and $0' \rightarrow 2'$, i.e., $\Delta F_{01} + \Delta F_{12} = \Delta F_{0'2'}$. Helmholtz free energy difference between state 0 and state 1 can be written as

$$\begin{aligned} \Delta F_{01} &= F(T, V, N + \Delta N, 0) - F(T, V - \Delta V, N, 0) \\ &= -[F(T, V, N, 0) - F(T, V, N + \Delta N, 0)] \\ &\quad + [F(T, V, N, 0) - F(T, V - \Delta V, N, 0)] \end{aligned} \quad (9)$$

The second term on the right-hand side can be handled with eq 6. Similarly, the first term can be dealt with using the fact that ΔN is negligibly small relative to N , and the first-order Taylor expansion yields

$$\begin{aligned} F(T, V, N, 0) &= F(T, V, N + \Delta N, 0) \\ &\quad - \Delta N \left(\frac{\partial F(T, V, N + \Delta N, 0)}{\partial (N + \Delta N)} \right)_{T,V} \\ &= F(T, V, N + \Delta N, 0) - \mu \Delta N \end{aligned} \quad (10)$$

since the solvent chemical potential, $(\partial F(T, V, N', 0)/\partial N')_{T,V}$, evaluated for $N' = N + \Delta N$ (state 1) is μ . We therefore obtain $\Delta F_{01} = \mu \Delta N - P \Delta V$. We next evaluate ΔF_{12} through the consideration of the change in the grand potential between

state 1 and state 2, which is nothing but the solvation free energy $\Omega_s(T, V, \mu)$:

$$\begin{aligned}\Omega_s(T, V, \mu) &= \Delta\Omega_{12} \\ &= -k_B T \log \left[\frac{\sum_{N'=0}^{\infty} e^{\beta N' \mu} Q(T, V, N', 1)}{\sum_{N'=0}^{\infty} e^{\beta N' \mu} Q(T, V, N', 0)} \right]\end{aligned}\quad (11)$$

Again, since the fluctuations in N' are negligible in the thermodynamic limit, the numerator (for state 2) is dominated by the term with $N' = N$ whereas the denominator (state 1) by the term with $N' = N + \Delta N$. Hence, there holds

$$\begin{aligned}\Omega_s(T, V, \mu) &= -k_B T \log \left[\frac{e^{\beta N \mu} Q(T, V, N, 1)}{e^{\beta(N+\Delta N) \mu} Q(T, V, N + \Delta N, 0)} \right] \\ &= \mu \Delta N + F(T, V, N, 1) - F(T, V, N + \Delta N, 0) \\ &= \mu \Delta N + \Delta F_{12}\end{aligned}\quad (12)$$

yielding $\Delta F_{12} = \Omega_s(T, V, \mu) - \mu \Delta N$. Taken together, we have $\Delta F_{01} + \Delta F_{12} = \Omega_s(T, V, \mu) - P \Delta V$. Therefore, the thermodynamic equivalence $\Delta F_{01} + \Delta F_{12} = \Delta F_{0'2'}$ leads to

$$\Delta F_s(T, V, N) = \Delta\Omega_s(T, V, \mu) \quad (13)$$

Equations 8 and 13 demonstrate that the ensemble-independence of the solvation free energy (eq 1) also follows from the thermodynamic consideration of the scheme shown in Figure 1. Since our derivation does not rely on any approximation in liquid theories, the partial molar volume correction in eq 2 cannot be justified on general thermodynamic grounds. From the comparison of our equations with those presented in ref 6, we find that the first term on the right-hand side of eq 4 (the pressure mechanical work, $P \Delta V$) is discarded in deriving eq 2 (see eq 7 and subsequent discussion of ref 6).

Solvation free energy is intimately connected with the equilibrium solute–solvent distribution function through the Kirkwood charging formula.¹⁰ Therefore, the improvement in the theoretical estimate of the solvation free energy that does not result from the improvement in the distribution-function theory is not sensible nor consistent. For example, it is well-known that the three-dimensional reference interaction site model (3D-RISM) theory,^{11–14} an integral-equation theory capable of handling molecular solutions, tends to overestimate the solvation free energy of hydrophobic solutes, but adding a repulsive bridge correction to the 3D-RISM theory turned out to improve both the solvation structure and the solvation free energy.¹⁵ More recently, an integral-equation theory for aqueous solutions has been developed based on the density-functional formalism that exactly takes into account the intramolecular structural correlations of solvent water,¹⁶ a feature missing in the 3D-RISM theory. By further adding an approximate intermolecular bridge function taken from a reference hard-sphere system,¹⁷ it has been demonstrated that the resulting theory predicts the solvation free energies of 500 small neutral molecules in good agreement with the experimental data.¹⁸ While there remains much work to be done since the effective hard-sphere radius is empirically determined and the possible orientation dependence of the bridge function is not taken into account, we believe that these are examples in the right direction toward better estimates of

the solvation free energy, and one needs not worry about the thermodynamic ensemble in such theoretical developments.

AUTHOR INFORMATION

Corresponding Author

*Phone: 82 2 710 9410. Fax: 82 2 2077 7321. E-mail: sihyun@sookmyung.ac.kr.

Notes

The authors declare no competing financial interest.

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