

# Solvation Free Energy of a Hard Sphere Solute in a Square Well Solvent as a Function of Solute Size

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The work required to couple a hard sphere solute into a solvent of molecules interacting through a square well potential is calculated by two methods. First a virial series approximation is used, and then an approximate integral equation is used. Both approximations show how the solvation work changes with the size of the solute particle. We find that the solvation work for a solute of size  $\sim R$  has the form  $W_s(R) \approx a + bR + cR^2 + dR^3$ .

## I. Introduction

A new measure of the *solvation free energy* was introduced almost 20 years ago<sup>1,2</sup> to quantify how equilibrium constants and the corresponding equilibrium concentrations and conformations of solutes depend upon the solute–solvent interactions. This measure is more general than, and has some significant advantages over, previously used measures. (A detailed review of the various measures of solvation free energies has been given in a recent monograph.<sup>3</sup>) This new measure of the solvation free energy is the reversible work  $W_s$  associated with this “solvation” process: A solute molecule,  $s$ , is transferred from a *fixed* position in a vacuum (or in an ideal gas) to a *fixed* position in the thermodynamically prescribed solution of interest. Although we only discuss a solute that has no internal degrees of freedom—a simple hard sphere—in this paper, this definition can be extended naturally to cover solutes with internal degrees of freedom.<sup>3</sup>

For a thermodynamic process a reversible work such as  $W_s$  depends only upon the initial and final thermodynamic states. The initial state is the solution of interest. The final state is this same solution, but in the “external field” associated with an additional solute molecule, i.e., in an “external field” which *looks* like a solute molecule. It is only the presence of this “external field” that distinguishes the initial and final thermodynamic states. If this external field is turned on in some *process*, the reversible work associated with the process will be the change in the fundamental free energy which thermodynamics associates with the independent thermodynamic variables used to prescribe the thermodynamic states of the system. If, for example, the thermodynamic state is fixed by prescribing the temperature  $T$ , pressure  $p$ , and the molecule numbers  $N_1, \dots, N_c$  of all components of the solution, the Gibbs free energy is the fundamental function and

$$W_s = \Delta G_s^* = G^*(T, p, N_1, \dots, N_c) - G(T, p, N_1, \dots, N_c) \quad (1.1)$$

with  $G^*$  the free energy of the solution in the presence of the field of the virtual solute molecule. If, to take another example,  $T$ , the volume  $V$ , and the chemical potentials  $\mu_1, \dots, \mu_c$  were prescribed, the fundamental function would be the grand potential  $\Omega$  and

$$W_s = \Delta \Omega_s^* = \Omega^*(T, V, \mu_1, \dots, \mu_c) - \Omega(T, V, \mu_1, \dots, \mu_c) \quad (1.2)$$

There is a formal argument that allows us to evaluate  $W_s$  from experimental data. If  $\mu_s$  is the absolute (third law) chemical potential of the solute in a solution of number density  $\rho_s = N_s/V$  and  $\Lambda_s = h/\sqrt{2\pi m_s k_B T}$  is the thermal deBroglie wavelength of the solute, let us *define* the quantity

$$\mu_s^* = \mu_s - k_B T \ln \rho_s \Lambda_s^3 \quad (1.3)$$

This  $\mu_s^*$ , just a part of the chemical potential of the solute, was called *the pseudochemical potential* of the solute in ref 3. For a solute  $s$  having no internal degrees of freedom,  $\mu_s^*$  is identical to the so-called *excess* chemical potential,

$$\mu_s^E = \mu_s - \mu_s^{\text{ideal}} = \mu_s - k_B T \ln \rho_s \Lambda_s^3 = \mu_s^* \quad (1.4)$$

where “ideal” refers to the ideal gas phase which would be realized if the solute did not interact with other molecules. The formal argument (the argument leading to (A5) in Appendix A) relates  $W_s$  to the solute chemical potential,

$$W_s = \Delta \Omega^* = \mu_s - k_B T \ln \rho_s \Lambda_s^3 = \mu_s^* \quad (1.5)$$

Thus it is only necessary to measure  $\mu_s^*$  to determine  $W_s$ .

As (1.4) indicates,  $\mu_s^*$  can be determined directly from an observation of the equilibrium between a gas and a liquid phase containing the structureless solute. For a sufficiently dilute gaseous phase ( $g$ ),

$$\mu_s^{*g} = \mu_s^g - k_B T \ln \rho_s^g \Lambda_s^3 = 0 \quad (1.6)$$

For a solution ( $l$ ) of composition  $\rho_1^l = N_1^l/V$  and  $\rho_s^l = N_s^l/V$ , (1.3) gives

$$\mu_s^{*l} = \mu_s^l - k_B T \ln \rho_s^l \Lambda_s^3 \quad (1.7)$$

Applying (1.5) to the  $l$  phase and using the equilibrium conditions,

$$\mu_s^l = \mu_s^g \quad (1.8)$$

(1.6), and (1.7), we find

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$$\begin{aligned}
W_s &= \mu_s^l - k_B T \ln \rho_s^l \Lambda_s^3 \\
&= \mu_s^g - k_B T \ln \rho_s^l \Lambda_s^3 \\
&= k_B T \ln [\rho_s^g / \rho_s^l]_{\text{eq}}
\end{aligned} \quad (1.9)$$

if the gaseous phase  $g$  in equilibrium with the solution  $l$  is ideal. It follows that for molecules such as proteins or nucleic acids, which have a negligible vapor pressure, the *differences* in solvation free energies between two liquid phases  $l_1$  and  $l_2$  will be given quite generally by

$$\Delta \mu_s^*(l_1 \rightarrow l_2) = W_s^{l_2} - W_s^{l_1} = k_B T \ln [\rho_s^{l_2} / \rho_s^{l_1}]_{\text{eq}} \quad (1.10)$$

All other thermodynamic quantities associated with the solvation of a structureless molecule can be deduced from  $W_s$  or  $\Delta \mu_s^*$  through standard thermodynamic manipulations. From (1.1), for example, the entropy and the volume of solvation are given by

$$\Delta S_s^* = - \frac{\partial}{\partial T} \Delta G_s^*(T, p, N_1, \dots, N_c) \quad (1.11)$$

$$\Delta V_s^* = \frac{\partial}{\partial p} \Delta G_s^*(T, p, N_1, \dots, N_c) \quad (1.12)$$

A molecular scale interpretation for  $W_s$  can also be given. Let  $B_s$  represent the “external field” associated with a virtual solute molecule added at some (arbitrary, but fixed) point  $\mathbf{R}_s$  inside the solution. This is just the increase in the potential energy of the system when the “solute” molecule is introduced at  $\mathbf{R}_s$ . Then, for solute molecules with no internal degrees of freedom,

$$W_s = -k_B T \ln \langle \exp[-\beta B_s] \rangle_0 \quad (1.13)$$

with  $\langle \rangle_0$  denoting an equilibrium ensemble average in the field-free state.<sup>3</sup> An example of a derivation of (1.13) is given in Appendix A.

For a hard sphere solute of diameter  $\sigma_s$  which does not allow a nearest neighbor approach  $\leq R_{\text{cav}} = \frac{1}{2}(\sigma_s + \sigma_l)$ ,

$$\exp[-\beta B_s] = \begin{cases} 0, & \text{if the distance } R_{sl} \leq R_{\text{cav}} \\ 1, & \text{if not} \end{cases}$$

where  $R_{sl} = |\mathbf{R}_s - \mathbf{R}_l|$  is the distance between the center of  $s$  and the center of the closest solvent molecule. Here  $\sigma_l$  is the effective diameter of a solvent molecule. Thus the average  $\langle \exp[-\beta B_s] \rangle_0$  is the probability of finding a cavity of radius  $R_{\text{cav}}$  around  $\mathbf{R}_s$  in the solvent molecule. The probability of finding a cavity is a quantity which can be observed in a molecular simulation of a system, and (1.13) forms the basis of the most direct computer simulation evaluation of the (third-law) chemical potential of a hard sphere component in a fluid.<sup>4</sup> The “field turning on” process can be generalized to couple in any kind of particle into a system, and  $\mu_s$  can be simulated quite generally.<sup>5</sup> Since this probability is a monotonically decreasing function of  $R_{\text{cav}}$  or  $\sigma_s$ , the solvation free energy of a hard solute is a monotonically increasing function of  $R_{\text{cav}}$ . Reference 6 illustrates a Monte Carlo simulation of the free energy of cavity formation in a hard sphere fluid.

Recently we have examined the explicit size dependence of  $\Delta \mu_s^*$  for various solutes.<sup>7,8</sup> For linear solute molecules it can be shown that  $\Delta \mu_s^*$  is linear in the length of the molecule in concordance with the experimental data.<sup>3,9</sup> In section II we extend our examination of the size dependence of  $W_s$  for spherical solutes in a dilute gas solvent to higher order in the

solvent density  $\rho$ . The pair interactions between solvent molecules is taken to be a square well potential, and the solute is taken to be a simple hard sphere. In section III we make a similar calculation based on an approximate integral equation for the pair correlation function. With these results in hand we comment in section IV on some recent suggestions<sup>10–13</sup> to “correct” relation 1.10 to account for the size differences between the solute and the solvent molecules.

## II. Solvation Free Energy in a Dilute Gas

The leading terms in an expansion of  $W_s$  in the density of the solvent provide a good estimate for  $W_s$  when the solvent density is low. More importantly, the terms in this expansion clearly indicate how  $W_s$  depends upon the shape of the solute. We take the solvent to be a one-component fluid interacting through pairwise additive forces. The potential energy for  $N$  solvent molecules will thus be

$$\sum_{1 \leq i \leq j \leq N} \phi_{00}(r_{ij}) + \sum_{i=1}^N U(\mathbf{r}_{is})$$

with  $\phi_{00}(r)$  the solvent–solvent interaction potential and  $U(\mathbf{r})$  an “external field” seen by the solvent particles. The process of interest takes  $U(\mathbf{r}) = 0 \rightarrow U(\mathbf{r}) = \phi_{10}(r)$ , the actual solute–solvent interaction potential. The associated free energy change will be calculated through  $O(\rho^2)$  in the solvent density  $\rho$ .

It is simplest to calculate the free energy change for the fixed  $T, V, \mu$  process for which the fundamental free energy is the grand potential  $\Omega(T, V, \mu)$ . We seek  $W_s = \Delta \Omega_s^* = \Omega_s^*(T, V, \mu) - \Omega(T, V, \mu)$  with  $U(\mathbf{r}) = \phi_{10}(r)$  in the “\*” state. The Mayer expansion for  $\Omega(T, V, \mu)$  in the activity  $z = e^{\beta \mu} / \Lambda^3$  is given by<sup>14</sup>

$$-\beta \Omega(T, V, \mu) = \sum_{l=1}^{\infty} \frac{z^l}{l!} \int \dots \int d\mathbf{r}_1 \dots d\mathbf{r}_l e^{-\beta \sum_{i=1}^l U(\mathbf{r}_i)} C_l(\mathbf{r}_1, \dots, \mathbf{r}_l) \quad (2.1)$$

The  $C_l(\mathbf{r}_1 \dots \mathbf{r}_l)$  are the “sum of connected graphs of  $l$  points.” In terms of the Mayer  $f$  function

$$f_{00}(r) = e^{-\beta \phi_{00}(r)} - 1 \quad (2.2)$$

the lowest order terms in (2.1) are

$$\begin{aligned}
-\beta \Omega(T, V, \mu) &= z \int d\mathbf{r}_1 e^{-\beta U(\mathbf{r}_1)} + \\
&\quad \frac{1}{2} z^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 e^{-\beta [U(\mathbf{r}_1) + U(\mathbf{r}_2)]} f_{00}(r_{12}) + \dots
\end{aligned} \quad (2.3)$$

The corresponding expansion for the spatially varying density is<sup>15</sup>

$$\begin{aligned}
\rho(\mathbf{r}_1) &= \frac{\delta(-\beta \Omega)}{\delta(-\beta U(\mathbf{r}_1))} \\
&= \sum_{l=1}^{\infty} \frac{z^l}{(l-1)!} \int \dots \int d\mathbf{r}_2 \dots d\mathbf{r}_l e^{-\beta \sum_{i=1}^l U(\mathbf{r}_i)} C_l(\mathbf{r}_1, \dots, \mathbf{r}_l) \\
&= z e^{-\beta U(\mathbf{r}_1)} + z^2 e^{-\beta U(\mathbf{r}_1)} \int d\mathbf{r}_2 e^{-\beta U(\mathbf{r}_2)} f_{00}(r_{12}) + \dots
\end{aligned} \quad (2.4)$$

Now  $\rho(\mathbf{r}_1)$  differs from the bulk density  $\rho$  only in the region around the virtual particle where  $U(\mathbf{r}) \neq 0$ . If we take the position of the solute  $\mathbf{R}_s$  as the origin of our coordinate system, this will be a small volume  $v_M \ll V$  around  $\mathbf{r} = 0$ . Outside this volume  $\rho(\mathbf{r}) \rightarrow \rho$  and (2.4) reduces to

$$\begin{aligned}\rho &= \sum_{l=1}^{\infty} \frac{z^l}{(l-1)!} \int \dots \int d\mathbf{r}_2 \dots \mathbf{r}_l C_l(\mathbf{r}_1, \dots, \mathbf{r}_l) \\ &= z + z^2 \int d\mathbf{r}_2 f_{00}(r_{12}) + \dots \\ &= z + z^2 \int d\mathbf{r}_2 f_{00}(r_{02}) + \dots\end{aligned}\quad (2.5)$$

which shows no actual  $\mathbf{r}_1$  dependence. In the last line of (2.5) the dummy variable  $\mathbf{r}_1$  has been moved to  $\mathbf{R}_s$  for convenience in what follows. When  $U(\mathbf{r}) = 0$ ,  $\Omega = -pV$  and (2.3) gives

$$\beta p(T, \mu, V) = z + \frac{1}{2} z^2 \int d\mathbf{r} f_{00}(r) + \dots \quad (2.6)$$

for the pressure of the solution.

The centerpiece of the Mayer analysis is the fact that (2.5) can be inverted, giving  $z$  as a series in  $\rho$ ,<sup>14</sup>

$$\ln z = \ln \rho - \sum_{k=2}^{\infty} \frac{\rho^{k-1}}{(k-1)!} \int \dots \int d\mathbf{r}_2 \dots d\mathbf{r}_k S_k(\mathbf{r}_1, \dots, \mathbf{r}_k) \quad (2.7)$$

with  $S_k(\mathbf{r}_1, \dots, \mathbf{r}_k)$  the sum of irreducible graphs of  $k$  points. The leading terms are

$$\begin{aligned}\ln z &= \ln \rho - \rho \int d\mathbf{r}_2 f_{00}(r_{12}) + \dots \\ z &= \rho - \rho^2 \int d\mathbf{r}_2 f_{00}(r_{02}) + \dots\end{aligned}\quad (2.8)$$

With this expansion of  $z$  in  $\rho$ , the free energy (2.3) and the pressure (2.6) may be rewritten as expansions in  $\rho$ ,

$$\begin{aligned}-\beta\Omega &= \rho \int d\mathbf{r}_1 e^{-\beta U(\mathbf{r}_1)} + \\ &\frac{1}{2} \rho^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 e^{-\beta U(\mathbf{r}_1)} [e^{-\beta U(\mathbf{r}_2)} f_{00}(r_{12}) - 2f_{00}(r_{02})] + \dots\end{aligned}\quad (2.9)$$

$$\beta p = \rho - \frac{1}{2} \rho^2 \int d\mathbf{r} f_{00}(r) + \dots \quad (2.10)$$

Thus

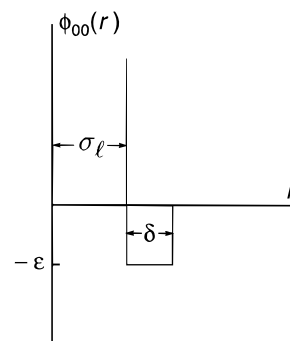
$$\begin{aligned}-\beta\Delta\Omega_s^* &= -\beta\{\Omega[U(\mathbf{r})] - \Omega[0]\} \\ &= \rho \int d\mathbf{r}_1 [e^{-\beta U(\mathbf{r}_1)} - 1] + \\ &\frac{1}{2} \rho^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 \{ [e^{-\beta[U(\mathbf{r}_1)+U(\mathbf{r}_2)]} - \\ &1] f_{00}(r_{12}) - 2[e^{-\beta U(\mathbf{r}_1)} - 1] f_{00}(r_{02}) \} + \dots\end{aligned}\quad (2.11)$$

If  $\mathbf{R}_s = \mathbf{r}_0$  locates the virtual solute particle, then

$$e^{-\beta U(\mathbf{r}_1)} = e^{-\beta\phi_{10}(r_{10})} = f_{10}(r_{10}) + 1 \quad (2.12)$$

with  $f_{01}(r)$  the Mayer  $f$  function associated with the solvent-solute pair potential, and (2.11) becomes

$$\begin{aligned}-\beta\Delta\Omega_s^* &= \rho \int d\mathbf{r}_1 f_{10}(r_{10}) + \frac{1}{2} \rho^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 \{ [(1 + \\ &f_{10}(r_{10}))(1 + f_{10}(r_{20})) - 1] f_{00}(r_{12}) - \\ &2f_{10}(r_{10})f_{00}(r_{20}) \} + \dots \\ &= \rho \int d\mathbf{r}_1 f_{10}(r_{10}) + \\ &\frac{1}{2} \rho^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 f_{10}(r_{10}) f_{10}(r_{20}) f_{00}(r_{12}) + \dots\end{aligned}\quad (2.13)$$



**Figure 1.** Square well potential for the interaction of a pair of solvent molecules.

It has been explicitly assumed in (2.13) that  $\phi_{00}(r)$  and  $\phi_{10}(r)$  are radially symmetric. In this case the integration can be simplified to

$$\begin{aligned}-\beta\Delta\Omega_s^* &= 4\pi\rho \int dr r^2 f_{10}(r) + \\ &(2\pi\rho)^2 \int_0^\infty dr r f_{00}(r) \int_0^\infty ds s f_{10}(s) \int_{|r-s|}^{r+s} dt t f_{10}(t) + \\ &\mathcal{O}(\rho^3)\end{aligned}\quad (2.14)$$

We now evaluate  $\Delta\Omega_s^*$  for a simple model. First we take the solute to be a simple “hard sphere” of diameter  $\sigma_s$ . If  $\sigma_l$  is the diameter of the solvent,

$$f_{10}(r) = \begin{cases} -1, & r \leq R_{\text{cav}} = \frac{1}{2}(\sigma_s + \sigma_l) \\ 0, & r > R_{\text{cav}} \end{cases} \quad (2.15)$$

Using (2.15) in (2.14) gives

$$-\beta W_s = -\beta\Delta\Omega_s^* = -\frac{4\pi}{3} \rho R_{\text{cav}}^3 + 8\pi^2 \rho^2 /_3(R_{\text{cav}}) + \mathcal{O}(\rho^3) \quad (2.16)$$

with

$$/_3(R) = \int_0^{2R} dr f_{00}(r) \left( \frac{2}{3} r^2 R^3 - \frac{1}{2} r^3 R^2 + \frac{r^5}{24} \right) \quad (2.17)$$

The range of  $r$  over which  $f_{00}(r) \neq 0$  is the range of the force between two solvent molecules. Once  $2R$  exceeds this range, the upper limit in the integral in (2.17) can be extended to infinity. For  $R$  sufficiently large that the  $R^3$  term is the dominant term in (2.17),

$$8\pi^2 /_3(R) \approx \frac{4\pi}{3} R^3 \int_0^\infty f_{00}(r) 4\pi r^2 dr = V_{\text{cav}} \int d\mathbf{r} f_{00}(r) \quad (2.18)$$

with  $V_{\text{cav}}$  the volume of the cavity. In this limit (2.16) gives

$$\beta W_s \approx V_{\text{cav}} \left[ \rho - \frac{1}{2} \rho^2 \int d\mathbf{r} f_{00}(r) + \dots \right] = \beta p V_{\text{cav}} \quad (2.19)$$

using (2.10) to identify the expression in brackets as  $\beta p$ . That  $W_s \approx p V_{\text{cav}}$  for cavities with diameters much greater than the range of the interactions between solvent molecules is the physically expected result for mesoscopic cavities. Just where this behavior is realized in practice depends upon the size of the other two terms in (2.17).

To give an explicit numerical example, we now evaluate (2.17), taking the interaction  $\phi_{00}(r)$  between two solvent molecules to be the square well potential shown in Figure 1. For this potential

$$f_{00}(r) = \begin{cases} -1, & r < \sigma_l \\ e^{\beta\epsilon} - 1, & \sigma_l \leq r \leq \sigma_l + \delta \\ 0, & r > \sigma_l + \delta \end{cases} \quad (2.20)$$

and the integral in (2.17) can be evaluated analytically. The result is

$$\begin{aligned} \mathcal{I}_3(R) = & \begin{cases} -(2/9)R^6 & \text{for } R \leq \sigma_l/2 \\ [-32R^6 + e^{\beta\epsilon}(32R^6 - 32R^3\sigma_l^3 + 18R^2\sigma_l^4 - \sigma_l^6)]/144 & \text{for } \sigma_l/2 \leq R \leq (\sigma_l + \delta)/2 \\ -[e^{\beta\epsilon}\sigma_l^6 - (e^{\beta\epsilon} - 1)(\sigma_l + \delta)^6]/144 + \\ [e^{\beta\epsilon}\sigma_l^4 - (e^{\beta\epsilon} - 1)(\sigma_l + \delta)^4]R^2/8 - \\ 2[e^{\beta\epsilon}\sigma_l^3 - (e^{\beta\epsilon} - 1)(\sigma_l + \delta)^3]R^3/9 & \text{for } (\sigma_l + \delta)/2 \leq R \end{cases} \quad (2.21) \end{aligned}$$

$\mathcal{I}_3(R)$  is negative for small  $R$ , only becoming positive for  $R > (\sigma_l + \delta)/2$ .

How does  $W_s$  depend upon the size of the solute? The term linear in  $\rho$  in (2.17) depends only upon  $R^3$ , i.e., upon the volume of the solute. Inclusion of the  $\rho^2$  terms leads to a complex behavior at small  $R$ , but for  $R > (\sigma_l + \delta)/2$  there are contributions proportional to  $R^3$  and  $R^2$ , i.e., to the area of the solute. A  $R^1$  contribution appears when  $\rho^3$  terms are included. A representative plot of  $\mathcal{I}_3(R)$  is given in Figure 2. An asymptotic (in  $R$  as  $R \rightarrow \infty$ ) representation for  $W_s$  would identify the coefficient of  $4\pi R^3/3$  as the pressure, the coefficient of  $4\pi R^2$  as the surface tension of the solvent in contact with a hard wall,<sup>16</sup> etc.

The sum of the first two terms in (2.14) for  $W_s$  remains positive for all  $\rho < 1/(4\pi\sigma_l^3/3)$  and rises monotonically with  $R_{\text{cav}}$ . We show this sum is a function of  $R_{\text{cav}}$  in Figure 3 at a solvent density  $\rho = 0.1/\sigma_l^3$ , along with the corresponding probability of finding a cavity of diameter  $R_{\text{cav}}$ ,  $e^{-\beta W_s(R_{\text{cav}})}$ . Since the probability of finding a cavity of diameter  $R_{\text{cav}} = \sigma_l$  is  $\sim 0.7$ , this density is much lower than that of a typical liquid. At higher densities  $W_s(R)$  will shift in the qualitative direction of  $\mathcal{I}_3(R)$ , but a quantitative prediction cannot be made from (2.17) since the first two terms in the series cease to give a good estimate of this function at higher densities. The calculation in section IV shows that Figure 3 is qualitatively correct at liquid densities, however. Under the conditions assumed in Figure 3, (2.10) gives a pressure of 1.40 atm at 300 K.

The density dependence of  $W_s$  makes it difficult to compare the relative contributions of the  $R^3$  and  $R^2$  terms, because the  $R^2$  terms in (2.16) are always small at densities for which (2.16) provides an accurate assessment. One can, nevertheless, compare the magnitude of the various terms in  $\mathcal{I}_3(R)$ , i.e., in (2.21), when  $R > (\sigma_l + \delta)/2$ . This provides a qualitative guide to the relative importance of these terms. The constant,  $R_{\text{cav}}$ -independent term in (2.21) is the largest of the three terms in (2.21) only when  $R/\sigma_l \leq 0.504$ . The magnitude of the  $R^2$  term is the largest for  $0.504 < R/\sigma_l < 1.387$ , while the  $R^3$  term is the largest when  $R/\sigma_l \geq 1.387$ . At  $R/\sigma_l = 1.387$  the  $R^2$  and  $R^3$  terms actually sum to zero since they have opposite signs. Clearly the assumption that  $W_s$  behaves as either  $R^2$  or  $R^3$  for  $R \approx \sigma_l$  is unreasonable.

### III. An Integral Equation Approximation

The Helmholtz free energy of a solvent in an "external field"  $U(\mathbf{r})$ ,  $A(T, V, N, [U])$ , is a function of the thermodynamic parameters  $T$ ,  $V$ ,  $N$  and a functional of the potential  $U(\mathbf{r})$ . The

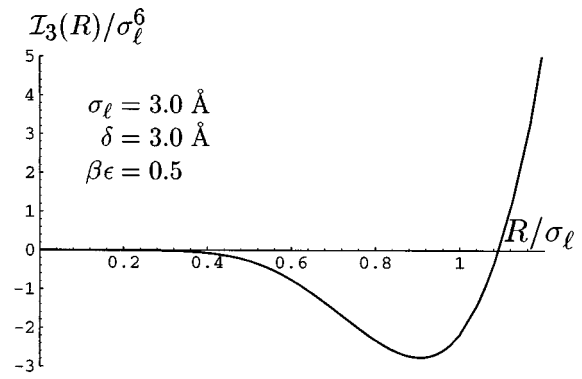


Figure 2. Plot of the function  $\mathcal{I}_3(R)$  given in (2.17) for  $\sigma = \delta = 3.0 \text{ \AA}$  and  $\epsilon = 0.5 k_B T$ .

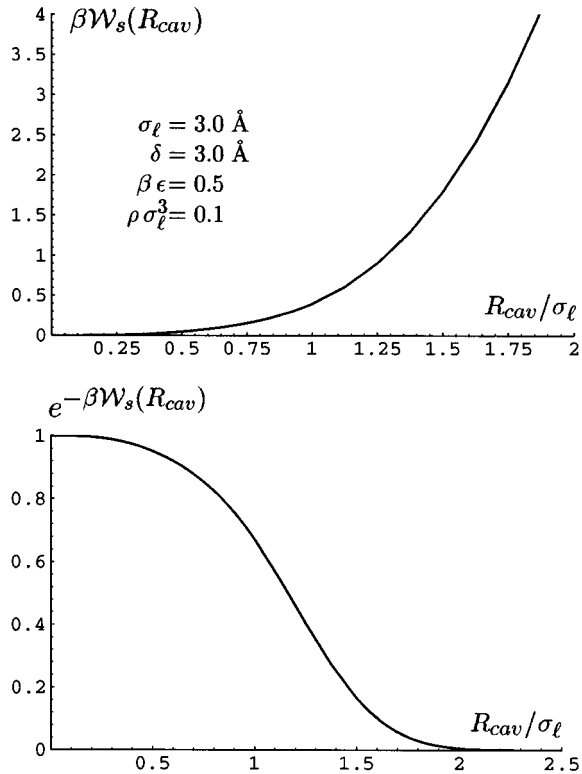
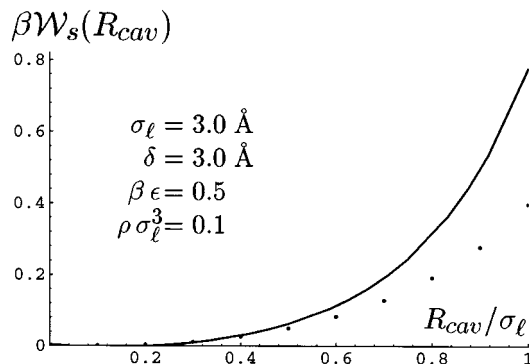


Figure 3.  $R_{\text{cav}}$  dependence of  $W_s/k_B T$  calculated from the first two terms in the density expansion (2.14).

solvation free energy is  $W_s = A(T, V, N, [\phi_{10}]) - A(T, V, N, [0])$ . We can calculate an approximate value for  $W_s$  by making a functional expansion of  $A(T, V, N, [U])$  in  $U(\mathbf{r})$  about  $U(\mathbf{r}) = 0$ . Since the hard core repulsion makes  $\phi_{10}(\mathbf{r})$  singular at small  $r$ , we will actually make the expansion in  $\exp[-\beta U(\mathbf{r})]$ . The leading terms in such an expansion are

$$\begin{aligned} A[U] = & A[0] + \int d\mathbf{r}_1 \left. \frac{\delta A[U]}{\delta e^{-\beta U(\mathbf{r}_1)}} \right|_{U(\mathbf{r})=0} [e^{-\beta U(\mathbf{r}_1)} - 1] + \\ & \frac{1}{2} \int \int d\mathbf{r}_1 d\mathbf{r}_2 \left. \frac{\delta^2 A[U]}{\delta e^{-\beta U(\mathbf{r}_1)} \delta e^{-\beta U(\mathbf{r}_2)}} \right|_{U(\mathbf{r})=0} [e^{-\beta U(\mathbf{r}_1)} - 1] \\ & [e^{-\beta U(\mathbf{r}_2)} - 1] + \dots \\ = & A[0] - k_B T \rho \int d\mathbf{r}_1 [e^{-\beta U(\mathbf{r}_1)} - 1] - \\ & \frac{1}{2} k_B T \int \int d\mathbf{r}_1 d\mathbf{r}_2 [\rho^{(2)}(\mathbf{r}_{12}) - \rho^2] [e^{-\beta U(\mathbf{r}_1)} - 1] \\ & [e^{-\beta U(\mathbf{r}_2)} - 1] - \dots \quad (3.1) \end{aligned}$$

with  $\rho$  and  $\rho^{(2)}(\mathbf{r}_{12})$  the density and the pair number density of



**Figure 4.**  $W_s/k_B T$  as a function of  $R_{cav}$  calculated from the integral equations (3.6)–(3.7) [solid curve] and from the density expansion (2.14) [dots].

the pure, field-free solvent. The general form for such functional expansions and the evaluation of the functional derivatives which lead from the first line in (3.1) to the second are described in ref 15. If  $U(\mathbf{r}) = \phi_{10}(r)$ , assumed to be radially symmetric, then (3.1) gives

$$\beta W_s = -\rho \int d\mathbf{r}_1 f_{10}(r_1) - \frac{1}{2} \int \int d\mathbf{r}_1 d\mathbf{r}_2 [\rho^{(2)}(r_{12}) - \rho^2] f_{10}(r_1) f_{10}(r_2) - \dots \quad (3.2)$$

The analogous expansion of  $\rho(\mathbf{r}_1, [U])$  about  $U(\mathbf{r}) = 0$  is

$$\begin{aligned} \rho(\mathbf{r}_1, [U]) &= \rho(\mathbf{r}_1, [0]) + \int d\mathbf{r}_2 \frac{\delta \rho(\mathbf{r}_1, [U])}{\delta e^{-\beta U(\mathbf{r}_2)}} \bigg|_{U(\mathbf{r})=0} [e^{-\beta U(\mathbf{r}_2)} - 1] + \dots \\ &= \rho + \rho \int d\mathbf{r}_2 [\rho^{(2)}(r_{12}) - \rho^2 + \rho \delta(\mathbf{r}_2 - \mathbf{r}_1)] [e^{-\beta U(\mathbf{r}_2)} - 1] + \dots \end{aligned} \quad (3.3)$$

If we set  $U(\mathbf{r}) = \phi_{00}(r)$  in (3.3), i.e., if we take the “external field” to be that of a *solvent* molecule, the left-hand side of (3.3) will be<sup>15</sup>  $\rho(\mathbf{r}_1, [U]) = \rho^{(2)}(r_1)/\rho$ . Thus

$$\rho^{(2)}(r_1)/\rho = \rho + \rho f_{00}(r_1) + \int d\mathbf{r}_2 [\rho^{(2)}(r_{12}) - \rho^2] f_{00}(r_2) + \dots \quad (3.4)$$

The “...” in (3.2) and (3.4) represent contributions from  $n$ -body correlations in the system with  $n \geq 3$ . We will approximate  $W_s$  by neglecting these. Let

$$h(r_{12}) = [\rho^{(2)}(r_{12}) - \rho^2]/\rho^2 \quad (3.5)$$

Then neglecting these higher order correlations makes (3.4) an integral equation that determines  $h(r)$ ,

$$h(r_1) = f_{00}(r_1) + \rho \int d\mathbf{r}_2 h(r_{12}) f_{00}(r_2) \quad (3.6)$$

and (3.2) expresses the solvation free energy in terms of  $h(r)$ ,

$$\beta W_s = -\rho \int d\mathbf{r}_1 f_{10}(r_1) - \frac{1}{2} \rho^2 \int \int d\mathbf{r}_1 d\mathbf{r}_2 h(r_{12}) f_{10}(r_1) f_{10}(r_2) \quad (3.7)$$

Since (3.6) gives  $h(r) = f_{00}(r) + O(\rho)$ , (3.7) has a low density limit which agrees with the evaluation of  $W_s$  in section 2. The details of a numerical solution for  $h(r)$  and the subsequent evaluation of  $W_s$  for the model system considered in section 2 are presented in Appendix B. The solid curve in Figure 4 represents the prediction of (3.6)–(3.7), while the dotted curve reproduces the results of the density expansion in (2.14). At

low solvent density the results of section 2 are recovered, but the integral equation includes (approximately, of course) work done against  $n > 2$  particles in the formation of a cavity, contributions ignored in the  $\rho$  expansion. The free energy  $W_s$  is correspondingly higher, as shown in Figure 4.

#### IV. Discussion

A qualitative understanding of how the solvation free energy depends upon the size and shape of a solute molecule is a central biochemical question. A simple model such as treating a large globular protein as a hard sphere of radius  $R_{cav}$  is a reasonable first approximation. Hence our quantitative study of how  $W_s$  depends upon  $R_{cav}$  provides insight into how the solvation free energy will depend upon the size and shape of the solute. In section II we showed that, at low solvent densities and for  $R_{cav} \geq (\sigma_l + \delta)/2$ ,

$$W_s(R_{cav}) \underset{R_{cav} \rightarrow \infty}{\approx} c_0 + c_2 R_{cav}^2 + c_3 R_{cav}^3 \quad (4.1)$$

This is just the form of the  $R_{cav}$  dependence that macroscopic thermodynamics predicts [with  $c_3 = (4\pi/3) \times$  the solution pressure and  $c_2 = 4\pi \times$  the solution–wall surface free energy]. A qualitatively similar behavior is shown in section III for a dense liquid. Both these results are consistent with the scaled-particle-theory result that  $W_s$  is a cubic polynomial in  $R_{cav}$ .<sup>16</sup> [A term in (4.1) proportional to  $R_{cav}$ , as found in the scaled-particle theory, appears when the  $O(\rho^3)$  term is included.]

Given this conclusion that (4.1) represents the expected  $R_{cav}$  dependence of  $W_s$ , it follows that (see refs 10, 11), if  $W_s$  is fit to

$$W_s = 4\pi R_{cav}^2 \sigma \quad (4.2)$$

then the “ $\sigma$ ” found cannot be interpreted as the solute–solvent interfacial free energy. It is also important to note that the formal definition of  $W_s$  leading to (4.1) makes no assumption about the relative size of the solvent and solute molecules. Assumptions (see refs 10, 11) that  $W_s$  depends upon this relative size are inconsistent with the definition of  $W_s$ <sup>9</sup> and attempts (see refs 12, 13 to provide a “derivation” of such a size dependence can only represent a *distinct* (and at the moment, unclear) redefinition of what solvation free energy means. Similarly, the conclusion<sup>17</sup> that the Flory–Huggins theory of mixtures requires that the solvation free energy  $W_s$  is missing a size dependence can only be interpreted as proposing some other (again, unclear) definition of the solvation free energy.

In conclusion, our explicit calculation of the solvation free energy  $W_s$  for the simple model used in sections II and III exhibits explicitly the complex dependence of  $W_s$  upon the size of the solute particle. The value of  $W_s$  naturally takes into account the relative sizes of the solvent and solute particles without further adjustment of the definition.

#### Appendix A: The Formal Evaluation of the Solvation Free Energy

Let us evaluate  $\Delta\Omega_s^*$  formally for a two-component system.  $\Omega(T, V, \mu_1, \mu_2)$  can be calculated from the grand canonical partition function,

$$\begin{aligned} e^{-\beta\Omega(T, V, \mu_1, \mu_2)} &= \sum_{N_1, N_2 \geq 0} \frac{z_1^{N_1} z_2^{N_2}}{N_1! N_2!} \int \dots \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \dots \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2} \times \\ &\quad e^{-\beta U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} \end{aligned} \quad (A1)$$

with  $\beta = 1/k_B T$  and  $z_i = e^{\beta\mu_i}/\Lambda_i^3$ , the activity of species  $i$ .  $U_{N_1, N_2}$  is the interaction potential for a system of composition  $N_1, N_2$ .

In the presence of an “external field” which looks like a molecule of species 2 located at  $\mathbf{R}^*$ , the potential energy is changed,

$$U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}) \rightarrow U_{N_1, N_2+1}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}, \mathbf{R}^*)$$

whence

$$e^{-\beta\Omega^*(T, V, \mu_1, \mu_2)} = \sum_{N_1, N_2 \geq 0} \frac{z_1^{N_1} z_2^{N_2}}{N_1! N_2!} \int \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2} \times e^{-\beta U_{N_1, N_2+1}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}, \mathbf{R}^*)} \quad (\text{A2})$$

We assume that  $\mathbf{R}^*$  is located inside  $V$  (away from the walls) so that  $\Omega^*(T, V, \mu_1, \mu_2)$  does not actually depend upon the location  $\mathbf{R}^*$ .

Two interpretations can be given for this result. First, since the right-hand side of (A2) does not depend upon  $\mathbf{R}^*$ , (A2) will be unaltered by adding a  $(1/V) \int d\mathbf{R}^*$  on the right-hand side. This gives

$$\begin{aligned} e^{-\beta\Omega^*(T, V, \mu_1, \mu_2)} &= \frac{1}{V} \sum_{N_1, N_2 \geq 0} \frac{z_1^{N_1} z_2^{N_2}}{N_1! N_2!} \int \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2+1} \times e^{-\beta U_{N_1, N_2+1}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2+1})} \\ &= \frac{1}{V} \sum_{N_1 \geq 0, N_2 \geq 1} \frac{z_1^{N_1} z_2^{N_2-1} N_2}{N_1! N_2!} \int \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2} \times e^{-\beta U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} \\ &= \sum_{N_1, N_2 \geq 0} \frac{N_2 z_1^{N_1} z_2^{N_2}}{z_2 V N_1! N_2!} \int \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2} \times e^{-\beta U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} \\ &= e^{-\beta\Omega(T, V, \mu_1, \mu_2)} \left\langle \frac{N_2}{V z_2} \right\rangle_0 \end{aligned} \quad (\text{A3})$$

where  $\langle \rangle_0$  represents the ensemble average over the states of the field-free system. For this system, however,  $\langle N_2/V \rangle_0 = \rho_2$ . Thus

$$-\beta\Omega^*(T, V, \mu_1, \mu_2) = \ln \rho_2 \Lambda_2^3 - \beta\mu_2 - \beta\Omega(T, V, \mu_1, \mu_2) \quad (\text{A4})$$

or the free energy change is given by

$$\begin{aligned} \Delta\Omega^* &= \Omega^* - \Omega \\ &= \mu_2 - k_B T \ln \rho_2 \Lambda_2^3 \end{aligned} \quad (\text{A5})$$

For the second interpretation, set

$$B_s(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}) = U_{N_1, N_2+1}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}, \mathbf{R}^*) - U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2}) \quad (\text{A6})$$

the contribution to the potential energy arising from the insertion of a particle of species 2 at  $\mathbf{R}^*$ . In terms of  $B_s$ , (A2) can be rewritten

$$e^{-\beta\Delta\Omega^*} = e^{-\beta(\Omega^*(T, V, \mu) - \Omega(T, V, \mu))}$$

$$\begin{aligned} &= e^{\beta\Omega^*(T, V, \mu)} \sum_{N_1, N_2 \geq 0} \frac{z_1^{N_1} z_2^{N_2}}{N_1! N_2!} \int \int d\mathbf{r}_1 \dots d\mathbf{r}_{N_1} \int \int d\mathbf{R}_1 \dots d\mathbf{R}_{N_2+1} \times e^{-\beta U_{N_1, N_2}(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} e^{-\beta B_s(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} \\ &= \langle e^{-\beta B_s(\mathbf{r}_1, \dots, \mathbf{r}_{N_1}, \mathbf{R}_1, \dots, \mathbf{R}_{N_2})} \rangle_0 \end{aligned} \quad (\text{A7})$$

The free energy increment associated with turning on the field  $B_s$  is just the expectation of  $\exp[-\beta B_s]$  in the system *before* the field is turned on. An elementary derivation of this result is also discussed in ref 3 and 18.

## Appendix B: Solving the Integral Equation

Equation 3.6 is easily solved by Fourier transformation. Since

$$\tilde{h}(k) = \int d\mathbf{r} e^{i\mathbf{k} \cdot \mathbf{r}} h(r) = \tilde{f}_{00}(k) + \rho \tilde{h}(k) \tilde{f}_{00}(k) \quad (\text{B1})$$

we have<sup>16</sup>

$$\tilde{h}(k) = \frac{\tilde{f}_{00}(k)}{1 - \rho \tilde{f}_{00}(k)} \quad (\text{B2})$$

Thus

$$\begin{aligned} \beta W_s &= -\rho \tilde{f}_{10}(0) - \frac{\rho^2}{16\pi^3} \int d\mathbf{k} \tilde{h}(k) |\tilde{f}_{10}(k)|^2 \\ &= -\rho \tilde{f}_{10}(0) - \frac{\rho^2}{4\pi^2} \int_0^\infty dk k^2 \frac{\tilde{f}_{00}(k)}{1 - \rho \tilde{f}_{00}(k)} |\tilde{f}_{10}(k)|^2 \end{aligned} \quad (\text{B3})$$

Evaluating  $\tilde{f}_{10}(k)$  with the hard sphere model (2.13) gives

$$\tilde{f}_{10}(k) = \frac{4\pi}{k^3} [k R_{\text{cav}} \cos(k R_{\text{cav}}) - \sin(k R_{\text{cav}})] \quad (\text{B4})$$

whence

$$\tilde{f}_{10}(0) = -\frac{4\pi}{3} R_{\text{cav}}^3 \quad (\text{B5})$$

and

$$\begin{aligned} \beta W_s &= \frac{4\pi}{3} \rho R_{\text{cav}}^3 - 4\rho^2 \int_0^\infty dk \frac{\tilde{f}_{00}(k)}{1 - \rho \tilde{f}_{00}(k)} \left[ \frac{k R_{\text{cav}} \cos(k R_{\text{cav}}) - \sin(k R_{\text{cav}})}{k^2} \right]^2 \end{aligned} \quad (\text{B6})$$

It is possible to make an asymptotic expansion of the integral in (B6) in  $1/R$ . The leading term in this expansion gives

$$\begin{aligned} \beta W_s &= \frac{4\pi}{3} \rho R_{\text{cav}}^3 - 4\rho R_{\text{cav}}^3 \frac{\rho \tilde{f}_{00}(0)}{1 - \rho \tilde{f}_{00}(0)} \int_0^\infty dx \left[ \frac{x \cos x - \sin x}{x^2} \right]^2 + O(R_{\text{cav}}^{-2}) \\ &= \frac{4\pi}{3} \rho R_{\text{cav}}^3 - \frac{2\pi}{3} \rho R_{\text{cav}}^3 \frac{\rho \tilde{f}_{00}(0)}{1 - \rho \tilde{f}_{00}(0)} + O(R_{\text{cav}}^{-2}) \end{aligned} \quad (\text{B7})$$

Only one particle can make contact with a small- $R$  cavity, but as  $R$  is increased, the number of particles that can make contact grows. At each change in the number of possible contacts there is a change in the form of the  $R$  dependence of  $W_s$ .<sup>16</sup> For this

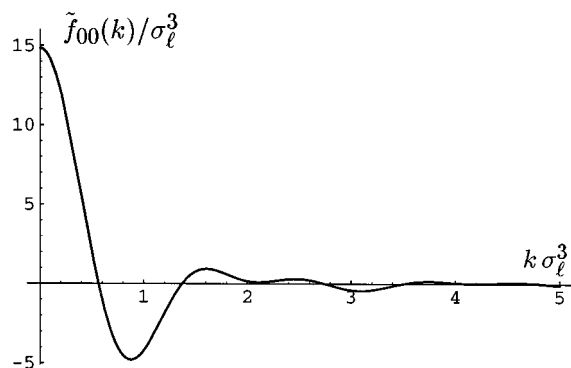


Figure 5.  $\tilde{f}_{00}(k)$  for the potential shown in Figure 1.

reason there is no convergent power series about  $R = 0$  and the integral involved in the  $O(R)$  term in (B7) diverges.

It is also obvious from (B7) that the  $\rho$  dependence of  $W_s$  is singular. Using the potential (2.16) shown in Figure 1,

$$1 - \rho \tilde{f}_{00}(0) = 1 - \rho \frac{4\pi}{3} (\delta + \sigma_l)^3 (e^{\beta\epsilon} - 1) \\ = 1 - 21.7389 \rho \sigma_l^3$$

so the second term in (B7) becomes infinite when  $\rho$  reaches  $\sim 0.046/\sigma_l^3$ . That is, the solution to (3.6) by Fourier transformation is restricted to sufficiently low densities that  $1 - \rho \tilde{f}_{00}(k)$  remains  $> 0$  at all  $k$ . For  $k > 0$ ,

$$\tilde{f}_{00}(k) = \frac{4\pi}{k^3} \{ e^{\beta\epsilon} [k\sigma_l \cos k\sigma_l - \sin k\sigma_l - \\ k(\sigma_l + \delta) \cos k(\sigma_l + \delta) + \sin k(\sigma_l + \delta)] + \\ [k(\sigma_l + \delta) \cos k(\sigma_l + \delta) - \sin k(\sigma_l + \delta)] \} \quad (\text{B8})$$

which is plotted in Figure 5. Since  $-4.779 \leq \tilde{f}_{00}(k)/\sigma_l^3 \leq 14.833$ , the integrand in (B3) will only be nonsingular if  $\rho < 0.046/\sigma_l^3$ . This singularity is a feature of the solution method, however. If a sensible interpretation to the integral in (B3) can

be provided for all  $\rho$ , we will have a practical solution for  $W_s$ . Such an interpretation is provided by taking the *principle part* of the integral in (B3).<sup>19</sup> We have evaluated the integral in (B3) *numerically* in this way. At  $\rho = 0.1/\sigma_l^3$  there is only one pole at  $k \approx 0.8175 \sigma_l^{-1}$  on the integration path. The curve shown in Figure 4 is the result of separating out the pole, integrating over the pole analytically, and then integrating the remainder numerically.

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