Bull. Chem. Soc. Jpn., *58*, *3068—3072 (1985)* [Vol. 58, No. 11

The Theoretical Study of the Solvophobic Interaction

Masaharu OHBA and Kiyoshi ARAKAWA*
Research Institute of Applied Electricity, Hokkaido University, Sapporo 060
(Received February 2, 1985)

The relation between a solvophobic interaction (SI) and a solute–solute radial distribution function is discussed. The SI is defined as the difference between the indirect part of the solute–solute potential of the mean force in a solvent and that in a "homomorphic" solvent. It was calculated using the RHNC-like integral equation of RISM-1 for a dilute solution of hard spheres in a solvent composed of polar hard dumb-bells. The existence of a SI was comfirmed in a simple system. The SI in this system proved to have originated from the effect of a dipole–dipole interaction between solvent molecules making the excluded volume of the solute molecules small. It was found that the strength of a SI decreases with increasing temperature. It was also shown that Ben-Naim's measure [*J. Chem. Phys.*, **54**, 1387 (1971)] gives an incorrect conclusion with respect to the temperature dependence of the SI of this system because it includes an excess factor irrelevant to a SI.

Hydrophobic interactions have been investigated by many authors,1–5) but from a microscopic point of view, their essential character is still not clear. Recently, molecular dynamical calculations were performed6,7) and semiphenomenological theories were proposed on the basis of an integral equation for liquids.8,9) However, no clear conclusions have been reached. Statistical mechanical studies from first principles are required in order to clarify the microscopic properties of the hydrophobic interactions, and then, an investigation on solvophobic interactions (SI) is expected to be fruitful as the first step for a thorough understanding of hydrophobic interactions.

There are two problems regarding a study of the SI. The first is how the SI is defined on the basis of statistical mechanics. Ben-Naim10) related the SI to the potential of the mean force between two solute molecules. However, the potential of the mean force includes a contribution which has no direct connection with the SI, and in the definition of the SI it must be subtracted from the potential of the mean force. The second is to calculate the SI defined by statistical mechanics from first principles. To understand the fundamental aspects of the SI, we investigated the SI of a dilute solution of hard spheres in a polar solvent composed of dipolar hard dumb-bells using the RHNC-like integral equation of RISM-1.11,12)

The Solvophobic Interaction and the Potential of the Mean Force

In this section, we consider the SI induced in a solution including nonpolar molecules in a solvent. For simplicity, consider the solute molecules to be spherical, and the interaction potential between two solute molecules $U_{\mathrm{AA}}(r)$ to have no angular dependence. Hereafter, subscripts A and S denote the solute and the solvent species, respectively.

The potential of mean force between two solute molecules $W_{\mathrm{AA}}(r)$ is defined by

$$W_{\mathrm{AA}}(r) = -k_{\mathrm{B}}T\ln g_{\mathrm{AA}}(r), \tag{1}$$

where k_{B} is the Boltzmann constant, T the absolute temperature and $g_{\mathrm{AA}}(r)$ the radial distribution function between two solute molecules. The physical meaning of $W_{\mathrm{AA}}(r)$ is "the free energy change which is caused when two solute molecules move each other from an infinite separation to a distance r in a given solvent." The indirect part of $W_{\mathrm{AA}}(r)$ is given by

$$w_{\mathrm{AA}}(r) = W_{\mathrm{AA}}(r) - U_{\mathrm{AA}}(r) = -k_{\mathrm{B}}T\ln y_{\mathrm{AA}}(r), \tag{2}$$

where $y_{\mathrm{AA}}(r)$ is the indirect pair correlation function between two solute molecules. $w_{\mathrm{AA}}(r)$ is the effective potential between the two solute molecules induced by all the other molecules, and it is identical with Ben-Naim's $\delta A^{\mathrm{HI}}(r)$.10)

Here, we consider that the solvent–solvent interaction $U_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}})$ can be divided into two parts,13)

$$U_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}}) = U^{(0)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}}) + U^{(1)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}}). \tag{3}$$

$U^{(0)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}})$ is the hard-core potential including the dispersion force. $U^{(1)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}})$ is the interaction other than $U^{(0)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}})$, including the contribution of the dipole–dipole interaction, the hydrogen bond and others. i_{S} and j_{S} denote the positions and orientations of the i-th and the j-th solvent molecules, respectively. Then, we define $w^{(0)}_{\mathrm{AA}}(r)$ as the indirect part of the potential of the mean force between two solute molecules in a homomorphic solvent in the same state as the solution, where a "homomorphic solvent" denotes a solvent composed of molecules whose intermolecular interaction is expressed as $U^{(0)}_{\mathrm{SS}}(i_{\mathrm{S}}, j_{\mathrm{S}})$. Since $w^{(0)}_{\mathrm{AA}}(r)$ is the effective potential caused by the packing effect of molecules with a hard core in nonpolar solvents, it has no direct relation to the SI. It is equivalent to the indirect part of the potential of the mean force in liquids composed of nonpolar molecules. It must be subtracted from $w_{\mathrm{AA}}(r)$. Here, we define $\delta w_{\mathrm{AA}}(r)$ as follows,

$$\delta w_{\mathrm{AA}}(r) = w_{\mathrm{AA}}(r) - w^{(0)}_{\mathrm{AA}}(r). \tag{4}$$

$\delta w_{AA}(r)$ is the effective potential between two solute molecules. This is the quantity which expresses the SI of a solution.

When the solute molecules are hard spheres, $w_{AA}(0) = -\Delta\mu_A$.[8,14] Here, $\Delta\mu_A$ is the chemical potential of solute molecules in a solution with respect to an ideal gas. Thus, we have

$$\delta w_{AA}(0) = \Delta\mu_A{}^{(0)} - \Delta\mu_A, \tag{5}$$

where $\Delta\mu_A^{(0)}$ is the chemical potential of the solute molecules in a homomorphic solvent. Equation 5 shows that $\delta w_{AA}(0)$ is the chemical potential change with respect to a transfer of the solute molecules from the solvent to the homomorphic solvent. Thus, Eq. 5 gives grounds for the fact that the chemical potential change with respect to the transfer of solutes from water to a hydrocarbon solvent is a good measure for the strength of the hydrophobic interaction.

In the following sections, we calculate $\delta w_{AA}(r)$ of the dilute solutions of hard spheres in a solvent composed of polar hard dumb-bells.[15]

The Application to the Dilute Solutions of Hard Spheres in Polar Solvents

The system considered is a dilute solution of nonpolar molecules in a polar solvent. Solute molecules are hard spheres with a diameter σ_{AA}. Solvent molecules are two fused hard spheres with the same diameter σ_{SS}, on whose center the charges $+q_S$ and $-q_S$ are sited. The bond length of a solvent molecule is l. An illustration of a molecule is shown in Fig. 1.

The total potential energy of the solution is assumed to be the sum of all pairs of intermolecular potentials. The intermolecular potential between the i-th molecule of type M and the j-th molecule of type M′ is given by

$$U_{MM'}(i_M, j_{M'}) = \sum_{\alpha}\sum_{\gamma} u_{\alpha M \gamma M'}(|\boldsymbol{r}^{\alpha}_{iM} - \boldsymbol{r}^{\gamma}_{jM'}|), \tag{6}$$

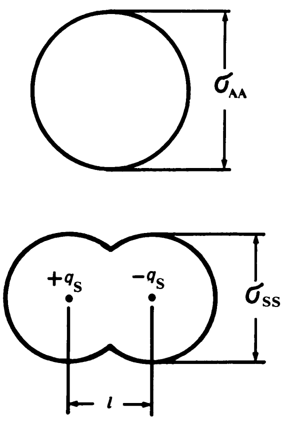

Fig. 1. The shapes of the solute molecule and the solvent molecule.

where $u_{\alpha M\gamma M'}(|r^{\alpha}_{iM} - r^{\gamma}_{jM'}|)$ is the interaction potential between the α-th atom of the i-th molecule of type M (A or S) and the γ-th atom of the j-th molecule of type M′. r^{α}_{iM} is the position of the α-th atom of the i-th molecule of type M. The atom–atom interactions are given as

$$u_{\alpha S\gamma S}(r) = u^{(0)}_{SS}(r) + q_{\alpha S} q_{\gamma S}/4\pi\varepsilon_0 r, \tag{7}$$

$$u_{\alpha SA}(r) = u^{(0)}_{SA}(r), \tag{8}$$

$$u_{AA}(r) = u^{(0)}_{AA}(r), \tag{9}$$

$$u^{(0)}_{MM'}(r) = \begin{cases} \infty, & r < \sigma_{MM'} \\ 0, & r > \sigma_{MM'} \end{cases} \tag{10}$$

where we assume that $\sigma_{AS} = (\sigma_{AA} + \sigma_{SS})/2$. ε_0 is the dielectric constant of the vacuum. In this system, $U^{(0)}_{SS}(i_S, j_S)$ and $U^{(1)}_{SS}(i_S, j_S)$ in the previous section are given as

$$U^{(0)}_{SS}(i_S, j_S) = \sum_{\alpha}\sum_{\gamma} u^{(0)}_{SS}(|\boldsymbol{r}^{\alpha}_{iS} - \boldsymbol{r}^{\gamma}_{jS}|)$$

and

$$U^{(1)}_{SS}(i_S, j_S) = \sum_{\alpha}\sum_{\gamma} q_{\alpha S} q_{\gamma S}/4\pi\varepsilon_0 |\boldsymbol{r}^{\alpha}_{iS} - \boldsymbol{r}^{\gamma}_{jS}|,$$

respectively.

Radial distribution functions and $\delta w_{AA}(r)$ were obtained by solving the RHNC-like integral equation of RISM-1,[11,12] and the procedures of the calculation are quite identical with those described in reference 12.

Results and Discussion

The present system is characterized by five parameters, as follows: the reduced number densities of solute molecules and solvent molecules $\rho^*_A = \rho_A \sigma^3_{AA}$ and $\rho^*_S = \rho_S d^3$, the reduced dipole moment of solvent molecules $\mu^*_S = (\mu^2_S/4\pi\varepsilon_0 k_B T d^3)^{1/2}$, the reduced bond length of solvent molecules $L^* = l/\sigma_{SS}$, and the ratio of σ_{AA} to σ_{SS} $\sigma^*_{AA} = \sigma_{AA}/\sigma_{SS}$. Here, ρ_A and ρ_S are the number densities of solute molecules and solvent molecules, respectively, $\mu_S = q_S l$ the magnitude of the dipole moment of solvent molecules, and d the diameter of a hard sphere whose volume is the same as a solvent molecule. It is given by the following equation

$$d^3 = \sigma^3_{SS}(1 + 3L^*/2 - L^{*3}/2).$$

Because of symmetry, we have four types of atom–atom radial distribution functions, as follows; $g_{AA}(r)$, $g_{AS+}(r) = g_{S+A}(r) = g_{AS-}(r) = g_{S-A}(r) \equiv g_{AS}(r)$, $g_{S+S+}(r) = g_{S-S-}(r)$ and $g_{S+S-}(r) = g_{S-S+}(r)$.

The Structure of the Solution. The atom–atom radial distribution functions of the solution are shown in Figs. 2a—c. The broken curves indicate atom–atom radial distribution functions of the solution in a homomorphic solvent. Figure 2a shows that an orientational correlation between two solvent molecules exists over a considerably long-range region.[11] As seen in Fig. 2b, $g_{AA}(r)$ is larger than that in a homomorphic solvent at $r<2\sigma_{SS}$, and in Fig. 2c the contact value of $g_{AS}(r)$ is smaller than that in a homomorphic solvent. This result shows that the solvent molecules are atracted to each other by dipole-dipole interactions. Thus, the probability that solute molecules approach each other is enlarged. This confirms the presence of a solvophobic interaction in this system.

The Solvophobic Interaction. The potential of the mean force between two solute molecules and the solvophobic interaction $\delta w_{AA}(r)$ are shown in Fig. 3. These are calculated from the solute-solute radial distribution functions shown in Fig. 2b. $w_{AA}(r)$ and $w^{(0)}_{AA}(r)$ have maxima at $r\approx 1.6\sigma_{AA}$ and have an oscilltory structure around the asymptotic value zero. $\delta w_{AA}(r)$ has a maximum at $r\approx 2.1\sigma_{AA}$, but the maximum is very small. The value of $\delta w_{AA}(r)$ is negative at $r<r_{max}$ and nearly equal to zero at $r<r_{max}$, where r_{max} denotes the position of the first maximum of $\delta w_{AA}(r)$. This shows that the dipole-dipole

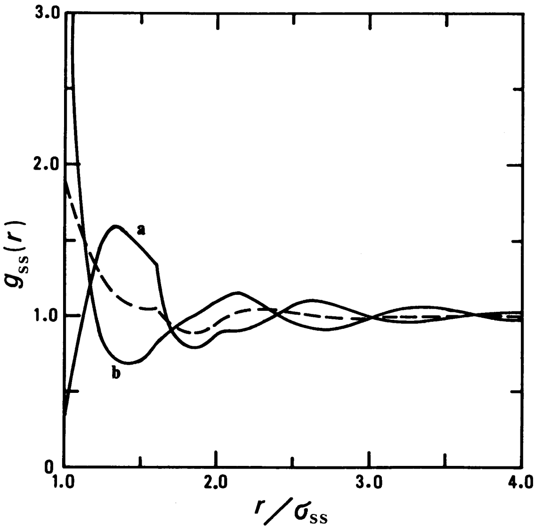

Fig. 2a. The solvent-solvent radial distribution functions for the solution at $\rho^*_A=0.001$, $\rho^*_S=0.8$, $\mu^*_S=3.0$, $L^*=0.6$ and $\sigma^*_{AA}=1.0$. a; $g_{S+S+}(r)$, b; $g_{S+S-}(r)$, ----; $g^{(0)}_{SS}(r)$.

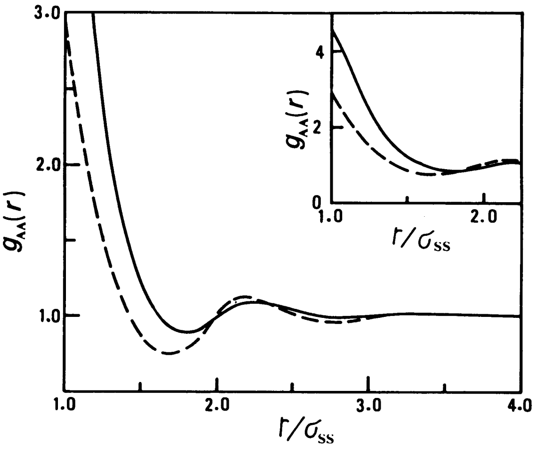

Fig. 2b. The solute-solute radial distribution functions for the same solution as Fig. 2a. ——; $g_{AA}(r)$, ----; $g^{(0)}_{AA}(r)$.

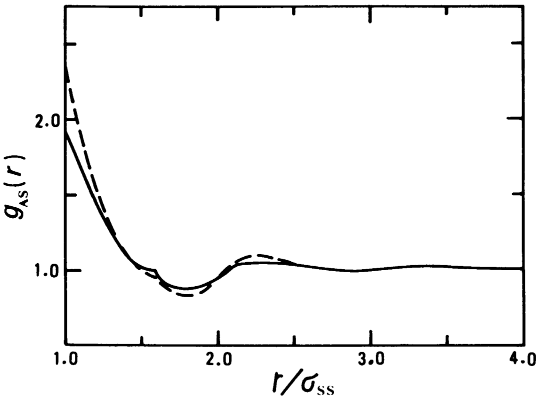

Fig. 2c. The solute-solvent radial distribution functions for the same solution as Fig. 2a. ——; $g_{AS}(r)$, ----; $g^{(0)}_{AS}(r)$.

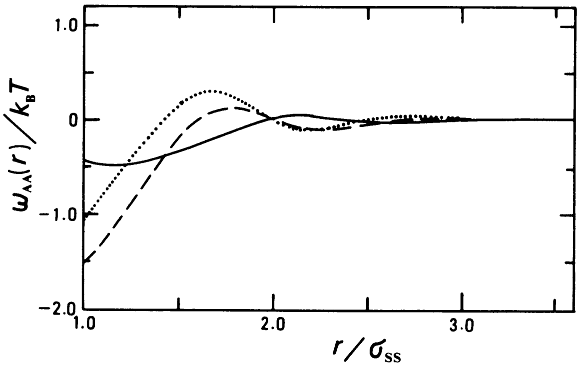

Fig. 3. The potential of mean force between two solute molecules for the same solution as Fig. 2. ——; $\delta w_{AA}(r)$, ----; $w_{AA}(r)$, ····; $w^{(0)}_{AA}(r)$.

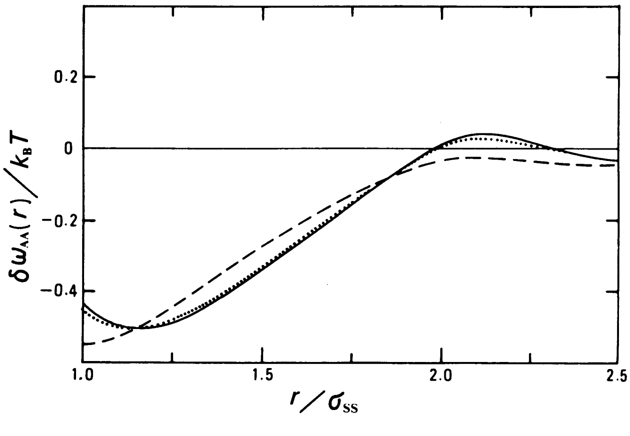

Fig. 4. The solvophobic interactions at $\rho^*_S=0.8$, $\mu^*_A=3.0$, $L^*=0.6$ and $\sigma^*_{AA}=1.0$. ——; $\rho^*_A=0.001$, ····; $\rho^*_A=0.01$, ----; $\rho^*_A=0.04$.

interaction between solvent molecules induces an apparent and effective attraction between the two solute molecules, that is, a solvophobic interaction. It is also shown that the SI is short ranged. $\delta w_{\mathrm{AA}}(r)$ has a small minimum at $r \approx 1.2\sigma_{\mathrm{AA}}$. The minimum is probably an artifact due to the approximation of the RHNC-like integral equation. $\delta w_{\mathrm{AA}}(r)$ decreases with decreasing r near the contact distance.

The concentration dependence of $\delta w_{\mathrm{AA}}(r)$ is shown in Fig. 4. $\delta w_{\mathrm{AA}}(r)$ for $\rho_{\mathrm{A}}^*=0.01$ is practically the same as that for $\rho_{\mathrm{A}}^*=0.001$ and no appreciable difference between $\delta w_{\mathrm{AA}}(r)$ for $\rho_{\mathrm{A}}^*=0.001$ and that for more dilute solutions was found. This shows that $\rho w_{\mathrm{AA}}(r)$ at $\rho_{\mathrm{A}}^*=0.001$ can be safely regarded as that for a solution at infinite dilution. Figure 5 shows that the strength of the SI increases with increasing μ_{S}^* and the position of the maximum is unchanged. It is found from Fig. 6 that the bond length of solvent molecules has little effect on the SI when the dipole moment of solvent molecules is held constant.

Figures 7 and 8 show the effect of the size of solute molecules on the SI. Shapes of $g_{\mathrm{AS}}(r)$ at $\sigma_{\mathrm{AA}}^*=0.8$ and 1.6 are very similar (Fig. 7). This indicates that a change in the size of solute molecules has little effect on the solvent structure around the solute molecules. The magnitude of $|\delta w_{\mathrm{AA}}(r)|$ at $r<r_{\mathrm{max}}$ increases remarkably with an enlargement of the size of the solute molecules (Fig. 8), and the position of the maximum coincides with each other when the curves are plotted on the abscissa $(r-\sigma_{\mathrm{AA}})/\sigma_{\mathrm{SS}}$. It is found that the positions of the maximum of $\delta w_{\mathrm{AA}}(r)$ of all systems shown in Figs. 3—6 and 8 are approximately expressed as $r_{\mathrm{max}}=\sigma_{\mathrm{AA}}+1.1\sigma_{\mathrm{SS}}$, which is nearly equal to the diameter of the excluded volume of solute molecules $(\sigma_{\mathrm{AA}}+\sigma_{\mathrm{SS}})$. Thus, it is said that the SI is negligible when excluded volumes of two solute molecules do not overlap with each other and is attractive when the excluded volumes do overlap. Namely, the SI acts to make the total excluded volume of solute molecules small when the excluded volumes overlap. Then, taking account of the size dependence of $\delta w_{\mathrm{AA}}(r)$ at $r<r_{\mathrm{max}}$ (Fig. 8) together, it is concluded that the origin of the SI is the effect of the attractive dipole-dipole interaction between solvent molecules to make the excluded volume of solute

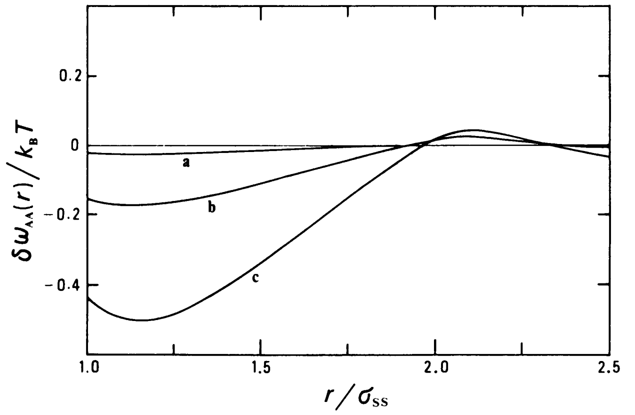

Fig. 5. The solvophobic interactions at $\rho_{\mathrm{A}}^*=0.001$, $\rho_{\mathrm{S}}^*=0.8$, $L^*=0.6$, and $\sigma_{\mathrm{AA}}^*=1.0$. a; $\mu_{\mathrm{S}}^*=1.0$, b; $\mu_{\mathrm{S}}^*=2.0$, c; $\mu_{\mathrm{S}}^*=3.0$.

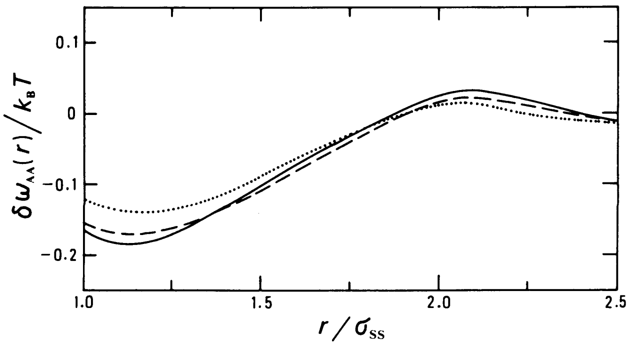

Fig. 6. The solvophobic interactions at $\rho_{\mathrm{A}}^*=0.001$, $\rho_{\mathrm{S}}^*=0.8$, $\mu_{\mathrm{S}}^*=3.0$, and $\sigma_{\mathrm{AA}}^*=1.0$. ——; $L^*=0.4$, ----; $L^*=0.6$, ;···· $L^*=0.8$.

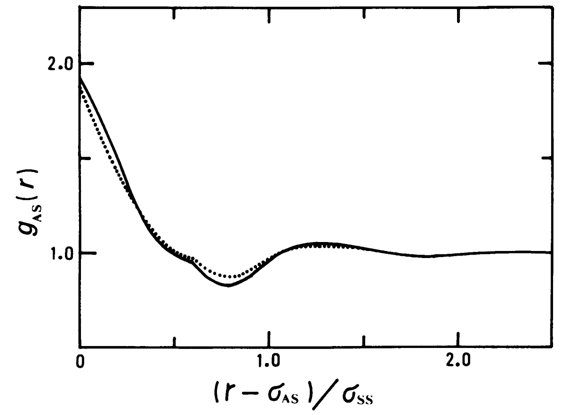

Fig. 7. The solute-solvent radial distribution functions at $\rho_{\mathrm{A}}^*=0.001$, $\rho_{\mathrm{S}}^*=0.8$, $\mu_{\mathrm{S}}^*=3.0$, and $L^*=0.6$. ——; $\sigma_{\mathrm{AA}}^*=1.6$, ----; $\sigma_{\mathrm{AA}}^*=0.8$.

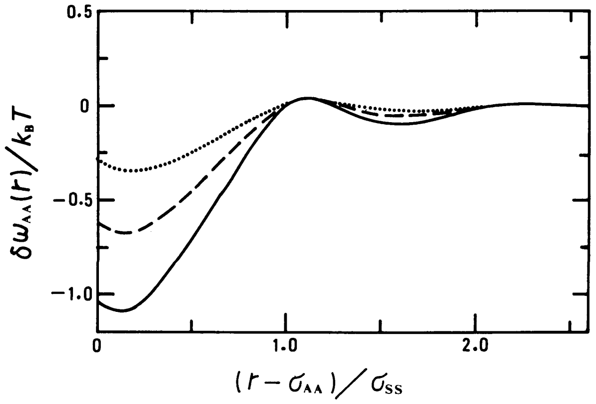

Fig. 8. The solvophobic interactions at $\rho_{\mathrm{A}}^*=0.001$, $\rho_{\mathrm{S}}^*=0.8$, $\mu_{\mathrm{S}}^*=3.0$, and $L^*=0.6$. ——; $\sigma_{\mathrm{AA}}^*=1.6$, ----; $\sigma_{\mathrm{AA}}^*=1.2$, ····; $\sigma_{\mathrm{AA}}^*=0.8$.

TABLE 1. THE TEMPERATURE DEPENDENCE OF THE SOLVOPHOBIC INTERACTION AT $\rho^*_A=0.001$, $\rho^*_S=0.8$, $L^*=0.6$, AND $\sigma^*_{AA}=1.0$

$1/ck_BT$[a]	$cw_{AA}(\sigma_{AA})$	$cw^{(0)}_{AA}(\sigma_{AA})$	$c\delta w_{AA}(\sigma_{AA})$
9.00	−0.168	−0.119	−0.049
6.25	−0.216	−0.172	−0.044
4.00	−0.307	−0.269	−0.038
2.25	−0.509	−0.478	−0.031
1.00	−1.097	−1.077	−0.020
0.25	−4.316	−4.308	−0.008
0	—	—	0

a) $c=4\pi\varepsilon_0 d^3/\mu^2_S$.

molecules small. In this respect, the SI of this system is an energetic effect. A solvophobic solvation like the ice-berg as stated by Némethy and Sheraga[3] does not exist, or hardly contributes to the SI even if the solvophobic solvation exists. If the solvophobic solvation is the main source of the SI, the range of the SI must be longer than $(\sigma_{AA}+2\sigma_{SS})$ which is the shortest distance when the solvation cells of two solute molecules contact each other.

The temperature dependence of the SI is shown in the Table 1. It is noted that $w_{AA}(\sigma_{AA})$ is identical with $\delta A^{SI}(\sigma_{AA})=\Delta\mu_D-2\Delta\mu_M$, Ben-Naim's measure of the SI,[4,10] where $\Delta\mu_D$ and $\Delta\mu_M$ are the chemical potentials of the dimer and the monomer of the solute molecules in the solution, respectively. $|\delta w_{AA}(\sigma_{AA})|$ decreases with increasing temperature, which means that the strength of the SI of this system decreases as the temperature increases. On the other hand, $|w_{AA}(\sigma_{AA})|$ increases with increasing temperature. This is because $\ln y^{(0)}_{AA}(r)=-w^{(0)}_{AA}(r)/k_BT$ of this system does not depend on the temperature. $|w^{(0)}_{AA}(\sigma_{AA})|$ becomes larger in propotion to the temperature, and resultantly the increment of $|w^{(0)}_{AA}(\sigma_{AA})|$ exceeds the decrement of $|\delta w_{AA}(\sigma_{AA})|$. Thus, Ben-Naim's measure, $w_{AA}(\sigma_{AA})$, gives an incorrect conclusion with respect to the temperature dependence of the SI of this system, because its temperature dependence is dominated by that of $w^{(0)}_{AA}(r)$ which is essentially irrelevant to the SI.

Concluding Remarks

It was shown that the SI can be expressed by $\delta w_{AA}(r)=w_{AA}(r)-w^{(0)}_{AA}(r)$, and that Ben-Naim's measure of the SI, which is identical with $w_{AA}(r)$, gives an incorrect temperature dependence because it includes an excess term, like $w^{(0)}_{AA}(r)$ which is irrelevant to the SI.

$\delta w_{AA}(r)$ of dilute solutions of hard spheres in a polar hard dumb-bell solvent was calculated by means of an RHNC-like integral equation of RISM-1 in order to clarify the microscopic properties of the SI. It was shown from this calculation that (1) the dipole–dipole interaction between solvent molecules can cause the SI, (2) the SI in this system mainly originates from the effect of a dipole–dipole interaction between solvent molecules to make the excluded volume of solute molecules small, and (3) a solvophobic solvation like the ice-berg does not exist or hardly contributes to the SI of this system.

References

1) W. Kauzman, *Adv. Protein Chem.*, **14**, 1 (1959).

2) H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).

3) G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3382, 3401 (1962); *J. Phys. Chem.*, **66**, 1773 (1962).

4) A. Ben-Naim, "Hydrophobic Interactions," Plenum Press, New York (1980).

5) K. Arakawa, K. Tokiwano, N. Ohtomo, and H. Uedaira, *Bull. Chem. Soc. Jpn.*, **52**, 2483 (1979).

6) A. Geiger, A. Rahman, and F. H. Stillinger, *J. Chem. Phys.*, **70**, 263 (1979).

7) D. C. Rapaport and H. A. Scheraga, *J. Phys. Chem.*, **86**, 873 (1982).

8) L. R. Pratt and D. Chandler, *J. Chem. Phys.*, **67**, 3683 (1977); **73**, 3430 (1980).

9) A. Tani, *Mol. Phys.*, **48**, 1229 (1983); **51**, 161 (1984).

10) A. Ben-Naim, *J. Chem. Phys.*, **54**, 1387, 3696 (1971); **57**, 5257, 5266 (1972).

11) M. Ohba and K. Arakawa, *Bull. Chem. Soc. Jpn.*, **55**, 1387 (1982).

12) M. Ohba and K. Arakawa, *Bull. Chem. Soc. Jpn.*, **58**, 9 (1985).

13) In general, the intermolecular interaction is expressed as the sum of potentials of hard core repulsions, dispersion forces, dipole–dipole interactions and others. The interaction between nonpolar molecules consists of the first two factors. The occurrence of the SI is thus ascribed to the presence of the other facters ($U^{(1)}_{SS}(i_S, j_S)$ in Eq. 3).

14) E. Meeron and A. J. F. Siegert, *J. Chem. Phys.*, **48**, 3139 (1968).

15) In the following sections, calculations are carried out without dispersion forces in $U^{(0)}_{SS}(i_S, j_S)$. Inclusion of dispersion forces is supposed to cause no important changes to the conclusions of the present calculations.