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<th>Changes in thermodynamic quantities upon contact of two solutes in solvent under isochoric and isobaric conditions</th>
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Kyoto University
I. INTRODUCTION

The changes in thermodynamic quantities upon solute insertion into a solvent have been of considerable interest for decades, and a number of theoretical studies are found in literature.\(^1\,2\) As a notable example, the changes in energy, entropy, and free energy under the isochoric (constant volume) condition and those in energy, volume, enthalpy, entropy, and free energy under the isobaric (constant pressure) condition were extensively analyzed by Cann and Patey\(^3\) using the integral equation theory for molecular fluids. They considered solvophobic solutes simplified as hard spheres with a variety of sizes, which were inserted into three different model solvents. Their results provided us with a considerable amount of new information.

The changes in thermodynamic quantities upon contact of two solutes which have already been inserted into a solvent are also crucially important. Both the solute insertion into a solvent and the solute contact serve as fundamental subjects to be investigated as the first step. Nevertheless, relatively less is known about the latter. We note that a variety of processes such as protein folding and self-assembly by biomolecules correspond to the solute contact rather than to the solute insertion. In this article, we theoretically study statistical thermodynamics of the solute contact. It should be more successful to start with a much simpler process like the solute contact and to extend the study to the complex ones like protein folding step by step.

Suppose that large particles are immersed in small particles and the number density of the small particles is much higher than that of the large particles. The small and large particles are hard spheres with diameter \(d_S\) and those with diameter \(d_M\), respectively, and there are no soft (repulsive and attractive) interactions among the particles at all. In such a system, all allowed configurations share the same energy and the system behavior is purely entropic in origin. The presence of a large particle generates the volume from which the centers of the small particles are excluded. The excluded volume is spherical and its diameter is \(d_M+d_S\). When two large particles contact each other, the excluded volumes overlap, and the total volume available to the translational motion of the small particles increases by this amount. We note that the resultant free-energy change is the same regardless of the condition (isochoric or isobaric). If the microstructure of the small particles formed near the large ones is neglected, the free-energy change is approximately expressed as 

\[
\rho_S \Delta V k_B T \approx -3(\rho_M/\rho_S) \eta_S k_B T/2
\]

where \(\rho_S\) and \(\eta_S\) are the number density and the packing fraction of the small particles. However, the changes in enthalpy and entropy are strongly dependent on the temperature. However, the changes in enthalpy and entropy are largely cancelled out and the temperature dependency of the free-energy change is much weaker. The authors also discuss possible relevance to the enthalpy-entropy compensation experimentally known for a variety of physicochemical processes in aqueous solution such as protein folding. \(©\) 2006 American Institute of Physics.

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particles, respectively, $\Delta V$ the increase in the total volume available to the small particles defined above, and $k_B T$ the Boltzmann constant times the absolute temperature). This represents the same formulation as the Asakura-Oosawa (AO) theory. Under the isochoric condition, the entropy gain equals the free-energy change divided by $-T$. The following question arises: What if the contact occurs under the isobaric condition and/or the particle-particle potentials include attractive tails?

On the basis of the view that the large particles correspond to subunits of a protein immersed in solvent of the small particles, we suggested that the translational motion of water molecules is a major driving force in protein folding and aggregation, molecular recognition, and related processes. On the other hand, a large number of thermodynamic data have been collected by experiments for the folding or unfolding of various proteins. The experiments are usually performed under the isobaric condition. One of the notable features is the enthalpy-entropy compensation, which means that the changes in enthalpy and entropy upon the folding or unfolding are strongly dependent on the temperature, whereas the temperature dependency of the free-energy change is much weaker due to the cancellation of the enthalpy and entropy changes. (In this article, when an entropy change is compared to an enthalpy change in terms of their magnitudes, the former is multiplied by the absolute temperature $T$. This represents the same formulation as the Asakura-Oosawa (AO) theory.)

The entropy change upon the folding is positive at sufficiently low temperatures but negative at higher temperatures. Qualitatively the same characteristics were observed for aggregation of proteins as well. Moreover, the enthalpy-entropy compensation is known for a variety of physicochemical processes in aqueous solution. The physical origins of these observations have not been clarified yet. It is interesting to ask the following question: How is the effect of the translational motion of water molecules related to these thermodynamic data?

Here, we analyze the changes in excess thermodynamic quantities upon solute contact in a solvent using the radial-symmetric and three-dimensional (3D) versions of the integral equation theory. Our concern is to extract the physical basis or to draw qualitatively correct conclusions rather than to give quantitatively reliable results. To this end, we employ simple models for the solvent and the solute. A wide range of the solute-solvent affinity is examined to cover highly solvophobic and highly solvophilic solutes. The solute contact is considered under the isochoric and isobaric conditions. Possible relevance to the experimental data mentioned above, which should further be examined in future studies, is also briefly discussed.

II. MODEL AND THEORY

A. Model

We consider a single solute and a pair of solutes in contact with each other immersed in solvent at infinite dilution. Spheres with diameter $d_S$ interacting through strongly attractive pair potential form the solvent. The solvent-solute potential $u_{SS}(r)$ is given by

$$u_{SS}(r) = -\varepsilon_{SS}(d_S/r)^6 \quad \text{for } r \geq d_S. \quad (1b)$$

The value of $\varepsilon_{SS}/(k_B T)$ adopted is 1.5 for $T=298$ K. This type of solvent roughly mimics water. Unless otherwise specified, $T=298$ K and the solvent density $\rho_S = \rho_S d_S^3$ is set at 0.7.

The solute is a sphere with diameter $d_M$. The solute-solvent potential is given by

$$u_{MS}(r) = \varepsilon_{MS}(d_M/r) \exp[-\kappa_{MS}(r/d_M - 1)] \quad \text{for } r \geq d_M. \quad (2b)$$

where $d_{MS} = (d_M + d_S)/2$ and the solute size $d_M$ is set to 3$d_S$. The values of $\varepsilon_{MS}/(k_B T)$ tested are in the range of 0.0–3.0 for $T=298$ K, and $\kappa_{MS}$ is set to 5.0. The larger the parameter $\lambda_{MS}$ is, the higher the solute-solvent affinity is: The solute with $\lambda_{MS}/(k_B T)=0.0$ is highly solvophobic, while that with 3.0 is highly solvophilic.

B. Theory

We employ the Ornstein-Zernike integral equation coupled with the hypernetted-chain closure. After the solvent-solvent correlation functions are calculated. For a single solute, the solvation free energy $\mu$ is calculated from

$$\frac{\mu}{k_B T} = 4\pi \rho_S \int_0^\infty \left\{ \frac{h_{MS}(r/2)}{2} - c_{MS}(r) - \frac{h_{MS}(r)c_{MS}(r/2)}{2} \right\} r^2 dr. \quad (3)$$

Here, we define $\Delta X$ as

$$\Delta X = (X \text{ for the contact pair of solutes}) - (X \text{ for a single solute}) \times 2. \quad (4)$$

The potential of mean force between solutes $\Phi(r)$ is calculated and $\Delta \mu$ is obtained as $\Phi(r=d_S)$. Equivalently, $\mu$ for the contact of solutes is obtained as $\Phi(r=d_M) + (\mu \text{ for a single solute}) \times 2$. In the numerical treatment, the grid width and the number of grid points are set to $\delta r = 0.01 d_S$ and 8192, respectively.

The partial molar volume $V_p$ (i.e., the change in system volume under the isobaric condition) of the contact pair of solutes cannot be calculated by the radial-symmetric version of the integral equation theory. Hence, the 3D version is employed. To make everything consistent, the 3D version is used for $V_p$ of a single solute as well. $V_p$ is given by

$$V_p = \int \int \left\{ 1 - g_{MS}(x,y,z) \right\} dxdydz, \quad (5)$$

where the ideal term is neglected and $g_{MS}(x,y,z)$ is the reduced-density profile for the solvent. The grid spacing ($\delta x$, $\delta y$, and $\delta z$) is set to 0.05 $d_S$ and the grid resolution ($N_x \times N_y \times N_z$) is $256 \times 256 \times 256$ for a single solute and $512 \times 256 \times 256$ for the contact pair of solutes. It has been
verified that the spacing is sufficiently small and the box size ($N_i\Delta x$, $N_i\Delta y$, and $N_i\Delta z$) is large enough.

C. Analysis under isochoric condition

The solvation free energy (excess chemical potential) is the same irrespective of the solute insertion condition (isochoric or isobaric), but the changes in energy and entropy are not. The solvation entropy under the isochoric condition $S_V$ is calculated through

$$S_V = -\langle \partial \mu / \partial T \rangle_V,$$

where the temperature derivative is numerically evaluated from

$$\langle \partial \mu / \partial T \rangle_V = \{\mu(T + \delta T) - \mu(T - \delta T)\}/(2\delta T),$$

$$\delta T = 5 \text{ K}.$$ (7)

The solvation energy under the isochoric condition $U_V$ is then obtained from

$$U_V/(k_B T) = \mu/(k_B T) + S_V/k_B.$$ (8)

In order to calculate the changes in energy and entropy upon solute contact under the isochoric condition ($\Delta U_V$ and $\Delta S_V$, respectively), the above equations are applied both to a single solute and to the contact pair of solutes. It is obvious that the following equations hold: $\Delta S_V = -\langle \partial \mu / \partial T \rangle_V$ and $\Delta U_V/(k_B T) = \Delta \mu/(k_B T) + \Delta S_V/k_B$.

D. Analysis under isobaric condition

The solvation energy under the isobaric condition $U_P$ is calculated using the thermodynamic relation

$$U_P/(k_B T) = U_V/(k_B T) + (\alpha^*/\kappa_T - P^*)V_P/d_S^3,$$ (9)

where $U_V$ is calculated in the manner described in Sec. II C, $(\alpha^*/\kappa_T - P^*)$ is calculated from the bulk-solvent properties:

$$\alpha^* = \alpha T,$$ (10a)

$$\kappa_T = \kappa_T k_B T d_S^3,$$ (10b)

$$P^* = P d_S^3/(k_B T).$$ (10c)

Here, $\alpha$ is the isobaric thermal expansion coefficient, $\kappa_T$ the isothermal compressibility, and $P$ the pressure. The solvation enthalpy $H$ and the solvation entropy under the isobaric condition $S_P$ are then obtained from

$$H/(k_B T) = P^* V_P / d_S^3 + U_P/(k_B T)$$ (11)

and

$$S_P/k_B = H/(k_B T) - \mu/(k_B T),$$ (12)

respectively. By applying the above equations both to a single solute and to the contact pair of solutes, we obtain $\Delta H$ and $\Delta S_P$ (the changes in enthalpy and entropy upon contact of two solutes under the isobaric condition, respectively). For example, the following equation holds:

$$\Delta U_P/(k_B T) = \Delta U_V/(k_B T) + (\alpha^*/\kappa_T - P^*)\Delta V_P/d_S^3.$$ (13)

$\Delta H/(k_B T) = \Delta U_V/(k_B T) + (\alpha^*/\kappa_T)\Delta V_P/d_S^3,$ (14)

and

$$\Delta S_P/k_B = \Delta S_V/k_B + (\alpha^*/\kappa_T)\Delta V_P/d_S^3.$$ (15)

The second terms in the right hand side of Eqs. (14) and (15) can be quite large but cancel out when the enthalpy and entropy changes are summed up to obtain the free-energy change.

$\alpha^*/\kappa_T$ is positive regardless of the solvent species. The problem is that it is difficult to evaluate $\alpha$, $\kappa_T$, and $P$ using the integral equation theory. The values are rather inaccurate and dependent on the routes via which they are calculated due to the well-known thermodynamic inconsistency. The objective of the present study is not to calculate quantitatively accurate values of the solvation-thermodynamic quantities but to extract the essential physics and draw qualitatively reliable conclusions. Therefore, we use the experimental values of $\alpha$ and $\kappa_T$ for real water at $P=1 \text{ atm}$. This treatment allows us to account for the unique characteristic of water that $\alpha$ is extremely small at low temperatures ($\sim 278 \text{ K}$) while it is much larger at higher temperatures. As a result, for example, $\alpha^*/\kappa_T=0.048$ at $T=278 \text{ K}$, 0.84 at 298 K, and 1.8 at 338 K. $\alpha^*/\kappa_T$ for water is strongly dependent on the temperature and quite large except at low temperatures. We note that $\alpha^*/\kappa_T \gg P^*$ at $P=1 \text{ atm}$.

III. RESULTS AND DISCUSSION

A. Solvent-density profile near a solvophobic or solvophilic solute

In this section, the discussion is limited to an insertion of a single solute. The insertion generates the excluded volume of $V_{ex}=33.51 d_S^3$ for the solvent. The partial molar volume $V_P$ ($T=298 \text{ K}$) of a highly solvophobic solute with $\lambda_{MS}/(k_B T)$ $=0.0$ is 38.66$d_S^3$ and that of a highly solvophilic solute with 3.0 is 6.65$d_S^3$. (For the hard-sphere solvent with no attractive tails in the solvent-solvent and solute-solvent potentials, $\varepsilon_{SS}/(k_B T)=0.0$ and $\lambda_{MS}/(k_B T)=0.0$, $V_P=19.69 d_S^3$.) In the solvophobic-solute case, the system volume expands by more than the excluded volume, which is consistent with the report by Cann and Patey. In the solvophilic-solute case, the expansion is only $\sim 20\%$ of the excluded volume. The solvent-density profile formed near each solute is shown in Fig. 1. The average solvent density within the solute-induced layer near a highly solvophilic solute is much higher than the bulk solvent density, whereas that near a highly solvophobic solute is significantly lower. The above results for $V_P$ are ascribed to the formation of the solute-induced layer.

B. Change in system volume upon contact of two solvophobic or solvophilic solutes

The contact of two solutes is illustrated in Fig. 2. When the contact occurs under the isochoric condition, the excluded volume for the solvent decreases and the total volume available to the translational motion of solvent mol-
ecules (i.e., the volume of the configurational phase space which can be explored by solvent molecules) increases by $-\Delta V_{ex} = 2.88 \, d_5^2$. We note that the solvent-density profiles are formed near the solutes. The region shown in black in the figure represents the solute-induced layer. When the solute is highly solvophilic, the layer is much denser than the bulk solvent. Under the isochoric condition, the decrease in volume of the denser layer gives rise to the increase in system pressure because some of the solvent molecules that were forming the layer are released to the bulk. In other words, under the isobaric condition, the system volume expands upon solute contact ($\Delta V_p > 0$). For a highly solvophobic solute, on the other hand, the layer shown in black is significantly more depleted than the bulk solvent, leading to the volume compression upon solute contact under the isochoric condition ($\Delta V_p < 0$). The volume of the configurational phase space which can be explored by solvent molecules changes by $-\Delta V_{ex} + \Delta V_p$ under the isobaric condition. $-\Delta V_{ex} + \Delta V_p$ can be negative for solvophilic solutes. $\Delta V_p$ is revisited in Sec. III D.

C. Energy, entropy, and free-energy changes under isochoric condition: Effects of solute-solute affinity

$\Delta U_V$, $\Delta S_V$, and $\Delta \mu$ calculated as functions of $\lambda_{MS}/(k_B T)$ are collected in Table I. The solute-solute interaction energy, which alters $\Delta U_V$ and $\Delta \mu$, is not considered in the discussion. For the hard-sphere solvent with no attractive tails in the solvent-solvent and solute-solvent potentials, $e_{SS}/(k_B T) = 0.0$ and $\lambda_{MS}/(k_B T) = 0.0$. $\Delta S_V/k_B = 2.67$. As shown in the table, $\Delta S_V$ is always positive, indicating that the solute contact leads to a significant entropy gain. The entropy gain estimated by the AO-type theory is $(\Delta S_V/k_B)_{AO} = -\Delta S_{AO} = 2.02$ (the subscript “AO” denotes the value estimated using the AO-type theory), giving a good approximation except in the cases of $\lambda_{MS}/(k_B T) = 0.0$ and $\lambda_{MS}/(k_B T) = 3.0$. In particular, the AO-type theory gives the best estimation when $\lambda_{MS}/(k_B T)$ is almost zero. These results suggest that the entropy gain under the isochoric condition, which is not strongly dependent on the solvent-solvent and solute-solvent attractive interactions, can be discussed in terms of the increase in the total volume available to the translational motion of solvent molecules, unless the solute solvophobicity or solvophilicity is extremely high.

When the solute is highly solvophobic, an energy gain (i.e., a negative energy change) occurs. This arises from the decrease in the solvent-accessible surface area upon solute contact. In the case of solvophilic solutes, by contrast, the energy change is positive. The solute contact results in a free-energy gain (i.e., a negative free-energy change) only for solvophobic solutes ($\lambda_{MS}/(k_B T) < 1.4$). For moderately solvophobic solutes [$1.0 < \lambda_{MS}/(k_B T) < 1.4$], the contact is unfavorable from the energetic viewpoint but driven by the entropic effect.

D. Enthalpy and entropy changes under isobaric condition: Effects of solute-solvent affinity

$\Delta V_p$, $\Delta H$, $\Delta S_p$, and $\Delta \mu$ calculated as functions of $\lambda_{MS}/(k_B T)$ are collected in Table II. The first term in the right

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<th>$\lambda_{MS}/(k_B T)$</th>
<th>$\Delta V_p/d_5$</th>
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<th>$\Delta S_p/k_B$</th>
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<td>3.0</td>
<td>6.92</td>
<td>12.51</td>
<td>6.31</td>
<td>6.20</td>
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FIG. 1. Solvent-density profile formed near a single solute. Case 1: Hard spheres forming the solvent and a hard-sphere solute; $e_{SS}/(k_B T) = 0.0$ in Eq. (1) and $\lambda_{MS}/(k_B T) = 0.0$ in Eq. (2). Case 2: Spheres interacting through the attractive potential, which form the solvent, and a highly solvophobic solute; $e_{SS}/(k_B T) = 1.5$ and $\lambda_{MS}/(k_B T) = 0.0$. Case 3: Spheres interacting through the attractive potential, which form the solvent, and a highly solvophilic solute; $e_{SS}/(k_B T) = 1.5$ and $\lambda_{MS}/(k_B T) = 3.0$.

FIG. 2. Contact of two solutes immersed in solvent. The solvent molecules are not shown here. The region shown in black represents the solute-induced layer within which the solvent density is different from that in the bulk.
TABLE III. Energy, entropy, and free-energy changes upon solute contact under the isochoric conditions, and volume, enthalpy, and entropy changes under the isobaric condition \( \lambda_{B} / S_{0}(k_{B}T)=0.5 \) at \( T=298 \) K.

<table>
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<th>( T (\text{K}) )</th>
<th>( \Delta U_{V}/(k_{B}T) )</th>
<th>( \Delta S_{V}/k_{B} )</th>
<th>( \Delta U_{P}/d_{V}^{2} )</th>
<th>( \Delta H/(k_{B}T) )</th>
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hand side of Eq. (11), the so-called \( PV \) work, can be neglected \( \Delta H \sim \Delta U_{P} \). Again, the solute-solute interaction energy is not considered in the discussion. Under the isobaric condition, the system volume decreases upon solute contact for solvophobic solutes \( \Delta V_{P}<0 \), while it increases for solvophilic solutes \( \Delta V_{P}>0 \). The system volume remains unchanged only when the solute is neither solvophobic nor solvophilic. \( \Delta S_{G} \) is lower than corresponding \( \Delta S_{P} \) for solvophobic solutes [see Eq. (15)], while the opposite is true for solvophilic solutes. When the solute is highly solvophilic, \( \Delta S_{P} \) becomes negative. The total volume available to the translational motion of solvent molecules decreases \( \Delta V_{G} \) upon solute contact because the volume compression, leading to a corresponding entropy loss. It is interesting to apply the AO-type theory to the isochoric case: \( \Delta S_{P} / k_{B} \) is also given in Table II. Though there is significant discrepancy between \( \Delta S_{P} / k_{B} \) and \( \Delta S_{P} / k_{B} \) in Table II, the general trend of their dependence on the solute-solute affinity is the same. The AO-type theory gives a quantitatively good estimate of the entropy gain when \( \Delta H / (k_{B}T) \) is sufficiently small, which is similar to the behavior observed under the isochoric condition. However, \( \Delta S_{P} / k_{B} \) is considerably different from \( \Delta S_{P} / k_{B} \) when \( \Delta H / (k_{B}T) \) takes a large, negative value.

In the case of solvophobic solutes \( \Delta V_{P}<0 \), \( \Delta U_{P} \) is lower (more negative) than corresponding \( \Delta U_{V} \) because the average volume occupied by a solvent molecule decreases, which originates from the decrease in the volume of the configurational phase space which can be explored by solvent molecules. For a solvent interacting through strongly attractive potential, the reduction leads to a lower energy. This result is consistent with the report by Cann and Patey. When the solute is highly solvophilic \( \Delta V_{P}>0 \), \( \Delta S_{P} \) and \( \Delta U_{P} \) are higher (more positive) than corresponding \( \Delta S_{V} \) and \( \Delta U_{V} \), respectively.

E. Energy, entropy, enthalpy, and free-energy changes under isochoric and isobaric conditions for solvophobic solutes: Effects of temperature

Choosing \( \lambda_{B} / S_{0}(k_{B}T)=0.5 \) (at \( T=298 \) K), we calculate the changes in thermodynamic quantities for two more temperatures, 278 and 338 K. The solvent densities \( \rho_{S}=\rho_{S} d_{S}^{2} \) are set to 0.7021 and 0.6884 (these values are determined in analogy to the temperature dependency of water density), respectively. The results are collected in Table III. Under the isochoric condition, \( \Delta U_{V} / (k_{B}T) \) decreases while \( \Delta S_{V} / k_{B} \) increases as \( T \) becomes higher (they are somewhat compensating). These changes are reasonable because the increase in thermal energy leads to a smaller effect of the interaction potential but to a larger entropic effect. Under the isobaric condition, \( \Delta H / (k_{B}T) \) increases but \( \Delta S_{P} / k_{B} \) decreases with increasing \( T \). In Table IV, \( \Delta H, \Delta T \Delta S_{P}, \) and \( \Delta \mu \) are given in units of kcal/mol. \( \Delta H \) and \( T \Delta S_{P} \) are strongly dependent on \( T \), whereas the dependency of \( \Delta \mu \) on \( T \) is much weaker.

We consider the solute contact under the isobaric condition by decomposing it into two processes (see Fig. 3): the solute contact under the isochoric condition (process 1) and the system-volume change for returning the pressure to the initial value (process 2). In process 2, the volume is compressed for solvophobic solutes while it is expanded for solvophilic solutes. Due to this volume change, the second term in the right hand side of Eq. (15) is added to the entropy change which already occurred in process 1. We note that the same term appears in the right hand side of Eq. (14). When the solute is solvophobic \( \Delta V_{P}<0 \), we can take the view that in process 2 part of or more than the entropy gain is converted to a corresponding enthalpy gain. As a result, the entropy change under the isobaric condition can be negative except at low temperatures. The quantity converted becomes considerably larger with rising temperature because \( \alpha_{L} / k_{B} \) is an increasing function of \( T \), making the entropy and enthalpy changes strongly dependent on \( T \) (the dependency is even stronger than in the case of the entropy and energy changes under the isochoric condition). The free-energy change, by contrast, remains roughly constant. An important point is that the conversion arises from the volume compression. The translational motion of solvent molecules, whose effect is

![FIG. 3. Contact of two solutes under the isochoric condition. It can be decomposed into process 1, contact of two solutes under the isochoric condition, and process 2 where the pressure is returned to the initial value. V and P denote the volume and the pressure, respectively. \( \Delta V_{P}=V_{F}-V_{I} \). For solvophobic solutes: \( P_{I}<P_{V} \) and \( \Delta V_{P}<0 \). For solvophilic solutes: \( P_{I}>P_{V} \) and \( \Delta V_{P}>0 \). Let \( S_{I} \) be the entropy in state \( I \). It can be shown that \( \Delta S_{I}=S_{F}-S_{I} \) and \( (S_{F}-S_{I}) / k_{B}=(\alpha_{L} / k_{B}) \Delta V_{P} / d_{V}^{2} \) [see Eq. (15)]. In process 2, the entropy change scaled by \( k_{B} \) is given by \( (\alpha_{L} / k_{B}) \Delta V_{P} / d_{V}^{2} \).]}
entropic in origin, is a major driving force in the solute contact even under the isobaric condition. It always drives the free energy to decrease during the solute-contact process. A negative entropy change in the higher-temperature region never implies that the effect is unimportant for the contact. A negative enthalpy change is not necessarily attributable to the gain in solute-solute interaction energy.

For solvophilic solutes ($\Delta V_P > 0$) process 2 is accompanied by an entropy gain and a corresponding enthalpy loss. $\Delta S_P/k_B$ and $\Delta H/k_B$ take large, positive values and increase with rising temperature. Like in the case of solvophobic solutes, the changes in enthalpy and entropy are both strongly dependent on $T$, while the dependence of $\Delta \mu$ on $T$ is much weaker. Thus, the enthalpy-entropy compensation occurs regardless of the solute solvophobicity or solvophilicity.

**F. Relevance to changes in thermodynamic quantities observed for protein folding in experiments**

The experiments are usually performed for protein unfolding under the isobaric condition. When the numerical data are simply multiplied by $-1$, the resultant value represents the data for protein folding discussed here. The data are decomposed into hydration terms and protein intramolecular terms in a conventional manner, and we are interested in the hydration terms. A protein is heterogeneous in the sense that it comprises both nonpolar and polar groups. In the folding process the intramolecular contacts occur not only for nonpolar groups but also for polar groups and nonpolar-polar groups. The folding is more complicated than the contact of simple solutes analyzed in the present study. Nevertheless, some qualitative aspects of the hydration-thermodynamic data can be understood. Since the enthalpy-entropy compensation occurs in the contacts of all groups, it is observed for protein folding through the hydration terms. Makhatazde and Privalov showed for the folding that the contribution to the entropy change from hydration of nonpolar groups decreases with rising temperature, whereas that from hydration of polar groups increases. Their results are also in qualitatively good accord with our theoretical calculations.

In protein folding the intramolecular contacts of nonpolar groups occur more than those of polar ones, leading to the volume compression: $\Delta V_P < 0$. However, the system-volume decrease arising from the compression is much smaller than the decrease in the excluded volume upon the folding: $|\Delta V_P| \ll |\Delta V_{\text{ex}}|$. As a result, the change in hydration entropy certainly decreases with rising temperature but remains positive. When the conformational-entropy loss is added to the hydration-entropy gain, the resulting total entropy is positive at sufficiently low temperatures but negative at higher temperatures. As for the entropy change in hydration enthalpy, it is a decreasing function of the temperature. Thus, the experimental results are quite consistent with our theoretical ones. We have recently suggested that the translational motion of water molecules, whose effect is entropic in origin, is a major driving force in protein folding. However, this suggestion is never consistent with the negative total-entropy change at high temperatures upon the folding. Part of the entropy gain is simply converted to a corresponding enthalpy gain due to the compression which occurs during the folding process, and the translational motion of water molecules always drives the free energy of water to decrease.

**IV. SUMMARY AND CONCLUSIONS**

The changes in excess thermodynamic quantities upon contact of two solutes in a solvent are analyzed using the radial-symmetric and three-dimensional integral equation theories. A simple model mimicking a solute in water is employed. A wide range of the solute-solvent affinity is considered under the isochoric and isobaric conditions. The solute-solute interaction energy is not included in the calculations.

When the solute is highly solvophobic, the solute contact under the isochoric condition leads to large gains in energy, entropy, and free energy. Under the isobaric condition, the system volume is greatly compressed with the result of a negative entropy change except at low temperature and a larger, negative enthalpy change upon solute contact. As for highly solvophilic solutes, the solute contact under the isobaric condition leads to an entropy gain but causes a larger energy loss and a free-energy loss. Under the isobaric condition, the system volume expands to a large extent with the result of a large, positive entropy change and an even larger, positive enthalpy change upon solute contact. The effects of compression or expansion become greater with rising temperature. If the solute is neither solvophobic nor solvophilic, the entropy and energy changes under the isobaric condition are not significantly different from those under the isochoric condition (i.e., the solute contact occurs at almost constant volume and pressure).

When the solvent molecules interact through strongly attractive potential and the pressure is low (1 atm), the so-called $PV$ work in the solute contact under the isobaric condition is quite small. However, the energy changes under the isochoric and isobaric conditions can be large and remarkably different from each other. In the case of solvophobic solutes, for example, the energy change under the isobaric condition is much more negative. This important factor is not taken into account in the recently reported argument that the excluded volume effect is unimportant in protein folding and aggregation, which clearly conflicts with our view.

The temperature effect for a solvophobic solute can be summarized as follows. Under the isochoric condition, the entropy gain upon solute contact increases but the energy gain decreases with rising temperature. The entropy and energy changes are somewhat compensating. Under the isobaric condition, the enthalpy gain increases as the temperature becomes higher. The entropy change, which is a decreasing function of the temperature, is positive at low temperatures but can be negative at higher temperatures. The dependence of the free-energy change on the temperature is much weaker than that of the entropy, energy, and enthalpy changes. This trend is stronger under the isobaric condition, and a remarkable cancellation of the enthalpy and entropy changes occur. This enthalpy-entropy compensation is also true for a solvophilic solute though the entropy change is positive and an increasing function of the temperature. It is
no wonder that the compensation is experimentally known for a variety of physicochemical processes in aqueous solution.

An important finding is that the change in the total volume available to the translational motion of water molecules within the system (i.e., the volume of the configurational phase space which can be explored by water molecules), which is caused by the solute contact, makes a large contribution to the changes in entropy and energy or enthalpy. In particular, the volume change governs the entropy change when the changes in energy or enthalpy are sufficiently small.

One should be careful about interpreting the thermodynamic data measured under the isobaric condition for the solute contact and related processes. A negative enthalpy change upon solute contact is not necessarily attributable to the gain in solute-solute interaction energy. The decrease in the amount of water exhibiting local ordering near the solutes does not always lead to a positive entropy change.\textsuperscript{3,42,43}

In the next stage, the effect of the solute size is to be examined. Further, the analysis should be extended to conformational changes of a protein by accounting for its complex polyatomic structure. Works in these directions are in progress.

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