A Note on the Nature of Ionic Hydrations and Hydrophobic Interactions in Aqueous Solutions

Kiyoshi ARAKAWA,* Kazuo TOKIWANO,** Norio OHTOMO,** and Hisashi UEDAIRA***
Research Institute of Applied Electricity, Hokkaido University, Kita-ku, Sapporo 060
***Faculty of Engineering, Hokkaido University, Kita-ku, Sapporo 060*
****Research Institute for Polymers and Textiles, Kanagawa-ku, Yokohama 221*

(Received January 16, 1979)

A theoretical consideration on the nature of solute-water and solute-solute interactions in aqueous solutions has been performed. Thermodynamic functions for the creation of cavities accommodating solute molecules were calculated by the use of the scaled particle theory, and the "negative hydration" effect of univalent ions such as Rb^+, Cs^+, Cl^-, I^- *etc.*, which was proposed first by Samoilov, Krestov and others, was interpreted and discussed. The nature of solute-water and solute-solute interactions in aqueous solutions of inert gases and hydrocarbons was elucidated in comparison with the interactions in nonaqueous solutions of those solutes.

Since the presentation of Frank and Evans' work,[1] the anomalously large and negative entropy of solution of nonpolar gases and liquids in water as well as the enormous partial molal heat capacity of those has generally been interpreted as the evidence that the solute molecules cause an increase of "ordering" around themselves within water, that is, the formation of "icebergs." Then, the cause of hydrophobic interactions between nonpolar groups or radicals in aqueous systems was ascribed to the disappearance of "icebergs" at the overlapped co-sphere region about those having direct contacts with each other.[2,3] The problems of the formation of "icebergs" and of the nature of hydrophobic interactions have become an object of increasing amount of debates since then.[4,5]

On the other hand, concerning the nature of ionic hydrations, Samoilov, Krestov and others proposed a dynamic model of ionic hydration and introduced the concept of "negative hydration" for univalent ions such as Cl^-, I^-, Cs^+ *et al.* from the consideration of diffusional behaviors of those within water.[6] The Samoilov model is a kind of the dynamical representation of ion-water interactions at the nearest neighbor of ions, while the Frank-Wen model[7] is a kind of the statical representation of those around ions.[5]

The formation of "icebergs" and the presence of "negative hydration" effect for comparatively large univalent ions are both closely related to the liquid structure of water, and many discussions have been made though no decisive conclusions are obtained at present.

The purpose of the present work is to give an explanation of those effects on the basis of a more sound theoretical ground.

While a number of new statistical mechanical approaches to treat fluids and fluid mixtures have been given for these two decades, the scaled particle theory[8] proposed by Reiss, Frisch, Lebowitz *et al.* has turned out to be one of the most useful approaches.[9] For hard-sphere fluids the theory gives an identical equation of state with that derived from the Percus-Yevick equation, and at the same time it is intuitive like a usual model theory. It gives a simple and useful method to calculate thermodynamic functions for the creation of cavities in fluids.[10] Then, the authors have applied the theory to aqueous solutions of ions as well as to those of nonpolar molecules such as inert gases and hydrocarbons *etc.*

With respect to the nature of the "negative hydration" an explanation of the effect has been given from theoretical viewpoint in the present paper. Concerning the hydrophobic interactions in aqueous systems a great deal of efforts have been devoted to the elucidation of the interactions until now, though many ambiguities are present among the results of those studies.[3–5,11] In the present paper the experimental data from various sources have been examined by the use of the scaled particle theory, and some detailed discussions have been given in combination with those results including the results of computer experiments.[12]

Calculation of Thermodynamic Functions for the Creation of Cavities

The Scaled Particle Theory. The theory is based on the consideration of the properties of a new distribution function $G(r)$ for a fluid composed of spherical molecules, where "$\rho G(r)$ is defined as the local concentration of molecular centers adjacent to a spherical cavity of radius r from which all molecular centers are excluded."[8] ρ is the number density of the fluid. The key relation of the theory is expressed as

$$G(a) = g(a), \tag{1}$$

where $g(r)$ is the ordinary radial distribution function at a separation r and a is a hard-sphere diameter of molecules. Noting that Eq. 1 is an exact relation for a hard-sphere fluid, Reiss *et al.* derived an approximate analytical expression for $G(r)$, and gave an equation of state for a hard-sphere fluid, which has turned out to be identical with the equation as an analytical solution of the Percus-Yevick equation for the fluid.[8]

The dissolution process of a solute molecule into a solvent can be regarded as consisting of two steps: the first step is "the creation of a cavity in the solvent of a suitable size to accommodate the solute molecule" and the second step is "the introduction into the cavity of a solute molecule which interacts with the solvent," as Pierotti stated.[13] According to the scaled particle theory, the reversible work $W \equiv \overline{G}_c$ for the creation of cavities suitable for the accommodation of solute molecules of a diameter a_2 within a fluid composed of N molecules (diameter a_1) at temperature T and pressure p becomes

$$\overline{G}_c(a_{12}) \equiv W(a_{12}) = K_0 + K_1 a_{12} + K_2 a_{12}^2 + K_3 a_{12}^3, \tag{2}$$

$$K_0 = NkT\left[-\ln(1-\xi) + \frac{9}{2}\left(\frac{\xi}{1-\xi}\right)^2\right] - \frac{\pi}{6}Na_1^3 p,$$

$$K_1 = -\frac{NkT}{a_1}\left[\frac{6\xi}{1-\xi} + 18\left(\frac{\xi}{1-\xi}\right)^2\right] + \pi N a_1^2 p,$$

$$K_2 = \frac{NkT}{a_1^2}\left[\frac{12\xi}{1-\xi} + 18\left(\frac{\xi}{1-\xi}\right)^2\right] - 2\pi N a_1 p,$$

$$K_3 = \frac{NkT}{a_1^2}\frac{4}{3}\pi N p,$$

where k is the Boltzmann constant, $\xi = \pi a_1^3 \rho/6$ the packing fraction in the fluid and $a_{12} = (a_1 + a_2)/2$.[14)]

The enthalpy $\overline{H}_c(a_{12})$ for the creation of the cavities of the diameter a_2 becomes

$$\overline{H}_c = \alpha NkT^2\{\xi/(1-\xi)\}[\{6/(1-\xi)\}\{2(a_{12}/a_1)^2 - (a_{12}/a_1)\} + \{36\xi/(1-\xi)^2\}\{(a_{12}/a_1)^2 - (a_{12}/a_1) + 1/4\} + 1], \tag{3}$$

where α is the thermal expansion coefficient.

From Eqs. 2 and 3 we obtain the entropy for the creation of the cavities as

$$\overline{S}_c = (\overline{H}_c - \overline{G}_c)/T. \tag{4}$$

Equations 3 and 4 show that the magnitudes of $\overline{H}_c$ and $\bar{S}_c$ are determined by the parameters a_1, ξ, and α for the fluid as well as by the size a_2 of the cavities, and also show that the attractive molecular interactions in the fluid exert upon $\overline{H}_c$ and $\bar{S}_c$ through α and ξ implicitly.

Calculation of $\overline{H}_c$ and $\bar{S}_c$ for the Creation of Cavities in Water. As the basis for the discussions about the behaviors of solute molecules in water we have calculated $\overline{H}_c$ and $\bar{S}_c$ according to Eqs. 2—4 using the observed values for α and ρ. In Fig. 1 the values of $\bar{S}_c$ for the creation of a cavity are plotted against the diameter of the cavity a for several temperatures from 0 to 70 °C. In the application of the scaled particle theory the determination of molecular parameters, especially diameters of molecules, is important. The values given in Fig. 1 are those for $a_1 = 2.82$ Å, where a_1 is the effective hard-core diameter of water molecules.[15)] We have calculated those values for another assignment of $a_1 = 2.75$ Å for comparison, which are given in the tables in later sections. Some deviations are seen, though the deviations have turned out to bring no important influence upon the conclusions in the present paper. The values of $\overline{H}_c$ are also shown in the tables in later sections.

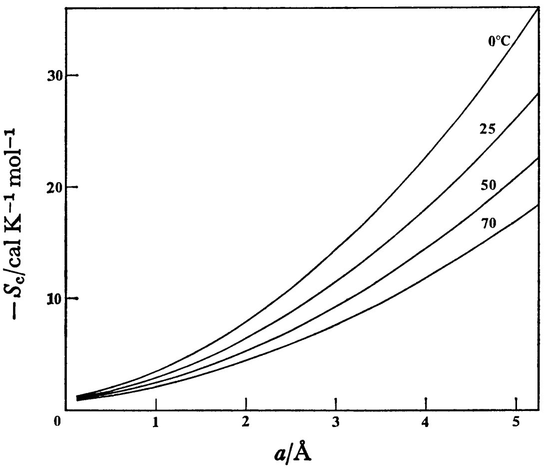

Fig. 1. The entropy for the creation of cavities in water. a: The diameter of the cavities.

The Nature of Ionic Hydrations: A Consideration from the Entropy of Hydration of Ions

A great deal of efforts have been devoted to make clear the nature of ionic hydrations. However, the results are greatly diversified, as clearly seen in a comprehensive review by Hinton and Amis (1971),[16)] many problems being left unsolved for further studies.

Samoilov, Krestov and others proposed a kind of the dynamic model on ionic hydrations,[5,6,17)] where the concept of the negative hydration was introduced. However, from the view-point of the statistical theory of fluids no clear explanation of the concept has been given until today. Then, we have attempted here to give an explanation in this section.

The entropy of hydration ΔS_h of ions for the transfer from hypothetical 1 atm in the gas phase to hypothetical 1 M in the aqueous phase is expressed as

$$\Delta S_h = \Delta S_{\mathrm{ideal}} + \overline{S}_c + \delta S. \tag{5}$$

In Eq. 5 $\Delta S_{\mathrm{ideal}} = R\ln(\overline{V}_2/V_g)$ is the contribution of ions to the entropy of transfer from the state V_g at 1 atm to the state $\overline{V}_2$, where V_g is the molar volume of an ideal gas at the temperature T and $\overline{V}_2$ the volume of the aqueous solution containing 1 mol of ions. $\overline{V}_2$ is 1 dm^3 in this case. $\delta S = \Delta S_h - (\Delta S_{\mathrm{ideal}} + \bar{S}_c)$ is an excess entropy, which have been obtained by subtracting the calculated values of $(\Delta S_{\mathrm{ideal}} + \bar{S}_c)$ from the experimental values of ΔS_h. δS is ascribed to the contribution caused by the direct ion-water interactions.

The values of ΔS_h, $\Delta S_{\mathrm{ideal}}$, $\bar{S}_c$, and δS are given in Table 1. Those determined for $a_{H_2O} = 2.75$ Å are given together in the table for comparison, and a certain appreciable differences are seen between the values for $a_{H_2O} = 2.82$ Å and those for $a_{H_2O} = 2.75$ Å though it does not exert any influences upon the conclusions of the following discussions.

As clearly seen in the table the values of δS for alkali ions larger than K^+ and those for halide ions (Cl^-, Br^-, and I^-) are positive. This supports the idea that these ions exert a structure-breaking action upon the liquid structure of water[5,15)] on the whole, which is the so-called "negative hydration" effect of these ions. For alkali ions smaller than K^+ as well as for bivalent and trivalent ions the values of δS become minus, which corresponds to the usual "positive hydration" effect.

In the case of K^+ the values of δS becomes small

Table 1. The entropy of hydration of ions at 25 °C (cal K^{-1} mol^{-1})

	Radius[a)] (Å)	ΔS_h[b)]	ΔS_{ideal}	$a_{H_2O}=2.82$Å		$a_{H_2O}=2.75$Å	
				$\overline{S}_c$	δS	$\overline{S}_c$	δS
Li^+	0.59	−33.7	−6.4	−3.4	−23.9	−3.1	−24.2
Na^+	1.02	−26.2	−6.4	−6.5	−13.3	−5.9	−13.9
K^+	1.38	−17.7	−6.4	−10.0	−1.3	−9.0	−2.3
Rb^+	1.49	−14.8	−6.4	−11.3	2.9	−10.1	1.7
Cs^+	1.69	−14.1	−6.4	−13.7	6.0	−12.3	4.6
Cl^-	1.81	−18.2	−6.4	−15.3	3.5	−13.7	1.9
Br^-	1.96	−14.5	−6.4	−17.4	9.3	−15.6	7.5
I^-	2.20	−9.0	−6.4	−21.0	18.4	−18.9	16.3
Mg^{2+}	0.72	−74.3	−6.4	−4.2	−63.7	−3.8	−64.1
Ca^{2+}	1.00	−60.8	−6.4	−6.3	−48.1	−5.7	−48.7
Al^{3+}	0.53	−126.6	−6.4	−3.0	−117.2	−2.7	−117.5

a) R. D. Shannon and C. T. Prewitt, *Acta Crystallogr., Sect. B,* **25**, 925 (1969); L. H. Ahrens, *Geochim. Cosmochim, Acta,* **2**, 155 (1952). The ionic radii of polyvalent ions are those determined by taking the value of 6 for their solvation numbers. b) H. L. Friedman and C. V. Krishnan, "Water," ed by F. Franks, Plenum, New York (1973), Vol. 3, Chap. 1, Table V.

and minus, while Samoilov and others proposed that it behaves as a structure breaker (at 25 °C).[6)] This contradiction can not be explained successfully at present. At any rate $|\delta S|$ for K^+ is clearly small. As seen in the table, the transition from the positive to negative hydration behavior for univalent ions occurs at about 1.4 Å of ionic radius, which is nearly identical with the effective hard-sphere radius for water molecules, while Samoilov and others proposed it to occur at about 1.1 Å.[6)] The presence of negative hydration effect for univalent ions at room temperature is explained here by the application of the scaled particle theory to the calculation of the entropy for the creation of cavities, with the exception of the case of K^+ which is left to further investigations.

A Consideration on Hydrophobic Interactions in Aqueous Solutions

Solubilities of Nonpolar Gases. Determination of Molecular Parameters: The determination of molecular diameters for nonpolar gases has been performed according to the procedures proposed by Bienkowski and Chao by the application of the Percus-Yevick equation in combination with critical data for those.[18)]

The diameter a is calculated from the following equation,

$$\frac{a}{\left(\dfrac{6}{\pi}\dfrac{\tilde{V}_c}{\tilde{N}}\right)^{1/3}} = 0.544046 - 0.010218T_r, \qquad (6)$$

where $\tilde{V}_c$ is the critical molar volume and T_r the reduced temperature. This equation was derived by applying the Percus-Yevick (PY) equation. The formula derived from Carnahan-Starling (CS) equation also was used by Bienkowski and Chao. The values determined by the use of the PY equation as well as those by the CS equation are given together in Table 2. The differences between these two are clearly small. Then we have used the values of the second column (PY), because the CS equation is essentially a conventional one.

Table 2. Effective hard-sphere diameters (Å)

	a (PY)	a (CS)
CH_4	3.59	3.62
C_2H_6	4.15	4.18
C_3H_8	4.63	4.67
n-C_4H_{10}	5.00	5.04
C_2H_4	3.94	3.99
C_2H_2	3.79	3.83
Ne	2.42	2.43
Ar	3.24	3.26
Kr	3.50	3.53
Xe	3.85	3.88
N_2	3.42	3.44
O_2	3.23	3.25
CO	3.47	3.49

A Consideration on Solute-Water Interactions in Comparison with Solute-CCl_4 Interactions: An investigation on the behaviors of nonpolar solute molecules (Table 3) in aqueous environments has been performed by the examination of solubility data from various sources.

The molar entropy and enthalpy of transfer of a solute species from an ideal gas phase at 1 atm to an aqueous solution at an equilibrium concentration x_2, $\overline{S}_2(x_2) - S_2^g$, and ΔH_s, are expressed as

$$\overline{S}_2(x_2) - S_2^g = \Delta S_{\text{ideal}} + \overline{S}_c + \delta S, \qquad (7)$$

and

$$\Delta H_s = \overline{H}_c + \delta H + (\alpha RT^2 - RT), \qquad (8)^{9)}$$

respectively. ΔS_{ideal} is determined according to the similar procedure to the case of ionic solutions in the preceding section, where the magnitude of $\overline{V}_2(x_2)$, the molar volume of the solution containing 1 mole of solute species at an equilibrium concentration x_2, becomes a function of x_2 in this case, and its magnitude varies in different species being in contrast to the case of ionic hydration as in Table 1. The experimental values of $\bar{S}_2(x_2)$, ΔH_s, and x_2 have been taken from various sources cited in the footnote of Table 3. The calculated values of the enthalpy and entropy of the creation of cavities, $\overline{H}_c$ and $\bar{S}_c$, are shown in the seventh and ninth columns of the table, respectively, and the excess enthalpy $\delta H=\Delta H_s-(\overline{H}_c+\alpha RT^2-RT)$ and the excess entropy $\delta S=(\bar{S}_2(x_2)-S_2{}^g)-(\Delta S_{\text{ideal}}+\bar{S}_c)$ are given in the eighth and tenth colums. In the table the values of $\Delta C_{p,c}$ which are determined from the temperature dependence of $\overline{H}_c$ are given in the eleventh column.

For the purpose of comparing the values of various thermodynamic functions given in Table 3 with those for a nonpolar solvent we have carried out a calculation for the CCl_4 solutions of the same species according to the quite identical procedures described above. The results are given in Table 4.

The features on the whole, which are seen in Tables 3 and 4, are summarized in Table 5 and the temperature dependence of the thermodynamic functions for the creation of cavities is shown in Table 6.

In CCl_4 solutions the negligibly small values of $\bar{S}_c$ suggest that no appreciable perturbation on the liquid structure occurs by the creation of cavities. The enthalpic terms are supposed to be dominant in the solute-solvent interactions in CCl_4 solutions of nonpolar gases. On the contrary the dominant features in aqueous solutions are large minus values of $\bar{S}_c$ and small positive values of $\overline{H}_c$. The greater part of large minus values of $(\bar{S}_2(x_2)-S_2{}^g)_{\text{obsd}}$ is attributed to $\bar{S}_c$, and further the small values of $\overline{H}_c$ in sharp contrast to those in CCl_4 solutions are the cause of large minus values of ΔH_s observed. As clearly seen in Table 3, the small values of $\overline{H}_c$ in aqueous solutions comes from

TABLE 3. THE ENTHALPY (cal mol^{-1}) AND ENTROPY (cal K^{-1} mol^{-1}) OF TRANSFER OF NONPOLAR SOLUTES FROM AN IDEAL GAS PHASE AT 1 atm TO WATER (25 °C)

	a (Å)	ΔH_s	$\overline{S_2}(x_2)-S_2{}^g$	10^5x_2	$\overline{G}_c$	$\overline{H}_c$	δH	$\overline{S}_c$	δS	$\Delta C_{p,c}$
CH_4	3.59	−3050a)	−10.5b)	2.48b)	5390	900	−3400	−15.1	−2.1	38
C_2H_6	4.15	−3980a)	−13.4b)	3.10b)	6840	1150	−4580	−19.1	−0.6	49
C_3H_8	4.63	−5700a)	−19.1a)	2.73b)	8220	1400	−6550	−22.9	−2.8	60
n-C_4H_{10}	5.00	−6000a)	−20.3b)	2.17b)	9380	1610	−7060	−26.1	−1.2	69
C_2H_4	3.94	−3790c)	−12.7d)	8.74b)	6270	1050	−4290	−17.5	0.6	45
C_2H_2	3.79	−3360c)	−11.2d)	75.3e)	5890	980	−3790	−16.4	5.2	42
Ne	2.42	−1090f)	−3.6f)	0.82f)	2930	460	−1000	−8.3	−4.2	20
Ar	3.24	−2730g)	−9.1b)	2.54b)	4570	750	−2930	−12.8	−3.0	32
Kr	3.50	−3470f)	−11.6f)	4.28f)	5170	860	−3780	−14.5	−2.7	37
Xe	3.85	−4360f)	−14.6f)	7.83f)	6040	1010	−4820	−16.9	−2.1	43
N_2	3.42	−2590h)	−8.7h)	1.18h)	4980	820	−2860	−14.0	−2.9	35
O_2	3.23	−2830h)	−9.5h)	2.30h)	4550	750	−3030	−14.8	−3.6	32

a) W. F. Claussen and M. F. Polglase, *J. Am. Chem. Soc.*, **74**, 4817 (1952). b) K. W. Miller and J. H. Hildebrand, *J. Am. Chem. Soc.*, **90**, 3001 (1969), Table 1. c) See Table IV in Ref. 1. Frank and Evans obtained these values from the data of J. A. V. Butler, *Trans. Faraday Soc.*, **33**, 229 (1937), Table VI. d) See footnote c. The standard state of Frank and Evans is $x_2=1$ for the solution, and we have subtsrcted the term of $R \ln x_2$ from their values. e) Calculated from the values given in Table 2 of W. Hayduk and H. Laudie, *AIChE J.*, **19**, 1233 (1973). f) T. J. Morrison and N. B. Johnstone, *J. Chem. Soc.*, **1954**, 3441. g) See Table IV in Ref. 1. Frank and Evans obtained these values from the data of D. D. Eley, *Trans. Faraday Soc.*, **35**, 1281 (1939). h) E. Douglas, *J. Phys. Chem.*, **68**, 169 (1964); T. J. Morrison and F. Billett, *J. Chem. Soc.*, **1952**, 3819.

TABLE 4. THE ENTHALPY (cal mol^{-1}) AND ENTROPY (cal K^{-1} mol^{-1}) OF TRANSFER OF NONPOLAR SOLUTES FROM AN IDEAL GAS PHASE AT 1 atm TO CCl_4 (25 °C)

	a (Å)	ΔH_sa)	$\overline{S_2}(x_2)-S_2{}^g$b)	10^3x_2b)	$\overline{G}_c$	$\overline{H}_c$	δH	$\overline{S}_c$	δS	$\Delta C_{p,c}$
CH_4	3.59	−700	−2.4	2.84	3780	3710	−4030	−0.2	−2.9	13
C_2H_6	4.15	−2620b)	−8.8	20.8	4680	4710	−6050	0.1	−5.6	15
C_2H_4	3·94	−2340	−7.7	14.5	4330	4320	−6280	0.0	−5.1	14
C_2H_2	3.79	−2330	−7.8	11.5	4090	4050	−6000	−0.1	−5.1	14
Ar	3.24	−140c)	−0.5c)	1.35c)	3260	3150	−2910	−0.4	−2.2	11
N_2	3.42	+590	2.1	0.64	3520	3430	−2460	−0.3	−1.2	12
O_2	3.23	+10	0.0	1.20	3250	3130	−2740	−0.4	−2.0	11
CO	3.47	+340	1.0	0.86	3600	3510	−2790	−0.3	−1.8	12

a) See Ref. 1. Frank and Evans obtained these values from the data of J. Horiuti, *Sientific Papers Inst. Phys. Chem. Res.*, Tokyo, **17**, 125 (1931). b) J. E. Jolley and J. H. Hildebrand, *J. Am. Chem. Soc.*, **80**, 1050 (1958), Table II. These authors obtained their values from the data of J. Horiuti (footnote a). c) L. W. Reeves and J. H. Hildebrand, *J. Am. Chem. Soc.*, **79**, 1313 (1957).

TABLE 5. $\bar{S}_c$, $\bar{H}_c$, AND $\Delta C_{p,c}$ FOR WATER AND CCl_4

Solvent	$\bar{S}_c$	$\bar{H}_c$	$\Delta C_{p,c}$	
CCl_4	0	large plus	small	$\lvert\Delta H_s\rvert < \bar{H}_c$
Water	large minus	small plus	large	$\bar{H}_c \ll \lvert\Delta H_s\rvert \sim \lvert\delta H\rvert$

TABLE 6. TEMPERATURE DEPENDENCE OF THERMODYNAMIC FUNCTIONS FOR THE CREATION OF CAVITIES

Solvent	T (°C)	CH_4				Ar			
		$\bar{G}_c$ (cal mol^{-1})	$\bar{H}_c$ (cal mol^{-1})	$\bar{S}_c$ (cal K^{-1} mol^{-1})	$\Delta C_{p,c}$ (cal K^{-1} mol^{-1})	$\bar{G}_c$ (cal mol^{-1})	$\bar{H}_c$ (cal mol^{-1})	$\bar{S}_c$ (cal K^{-1} mol^{-1})	$\Delta C_{p,c}$ (cal K^{-1} mol^{-1})
H_2O	0	4970	−200	−18.9	50	4210	−170	−16.0	42
	25	5390	900	−15.1	38	4570	750	−12.8	32
	50	5730	1820	−12.1	36	4860	1530	−10.3	30
	70	5950	2540	−9.9	36	5050	2130	−8.5	30
CCl_4	25	3780	3710	−0.2	13	3260	3150	−0.4	11
	35	3770	3830	0.2	13	3260	3250	0.0	11

the small values of α for water, which is the direct evidence of the presence of some "bulky structure" decreasing with temperature. This is supposed to be closely related to the behavior of $(\partial U/\partial V)_T$ for water in comparison with that for carbon tetrachloride, which is calculated using the following thermodynamical formula

$$\left(\frac{\partial U}{\partial V}\right)_T = \frac{\alpha T}{\beta} - p, \tag{9}$$

where U is the internal energy. The magnitude of $(\partial U/\partial V)_T$ for water at 25 °C is 1500 atm which is smaller than a half of that for CCl_4.

The magnitudes of $\Delta C_{p,c}$ for water are about three times larger than those for CCl_4, and contribute to the greater part of the enormous partial molal heat capacity for aqueous solutions of nonpolar solutes. Then, it may be said that the cause of icebergs formation proposed first by Frank and Evans is attributed to the effect of the large minus $\bar{S}_c$ and the small positive $\bar{H}_c$ for the creation of cavities in water.

The Nature of Hydrophobic Interactions. The hydrophobic interaction is stated as the "tendency of nonpolar groups of proteins to adhere to one another in aqueous environments" according to Kauzmann,[2)] and for the case of two methane molecules in water Ben-Naim made an assertion that the quantity $\delta A_M^{HI} = \Delta\mu_E^\circ - 2\Delta\mu_M^\circ$ serves as a useful measure for the hydrophobic interaction in aqueous media where $\Delta\mu_E^\circ$ and $\Delta\mu_M^\circ$ are the standard free energy of solution of ethane and methane, respectively.[11)] Recently, Dashevsky and Sarkisov have carried out a Monte-Carlo calculation in order to examine the nature of the hydrophobic interactions of nonpolar molecules in water.[12)]

A Measure for Hydrophobic Interactions: Ben-Naim stated that the magnitude of δA_M^{HI} became about −2.15 kcal mol^{-1} at 25 °C when observed values were used for $\Delta\mu_E^\circ$ and $\Delta\mu_M^\circ$. It is certainly stabilized to the amount of about 0.6 kcal mol^{-1} in comparison with that in alcoholic solutions, and then, he asserted that the quantity δA_M^{HI} might serve as a useful index for measuring hydrophobic interactions in water.[11)] Further, the recent remarkable results of Monte-Carlo calculations by Dashevsky and Sarkisov have shown that the free energy of hydrophobic attractions between two methane molecules in 62 water molecules becomes about −2 kcal mol^{-1},[12)] and this supports the idea of Ben-Naim that $\delta A_M^{HI} = \Delta\mu_E^\circ - 2\Delta\mu_M^\circ$ is useful as a relative measure for hydrophobic interactions between two methane molecules in aqueous environments. However, it is not exact to assert directly, as Ben-Naim stated, that "the excess attraction, in water, helps the two particles to approach each other in spite of the thermal energy,"[11)] since in aqueous solutions of methane under ordinary conditions the dimerization of two methane molecules does not occur. The reason for that will be explained in the next section.

As a result of the present calculation, the free energy for hydrophobic interactions between two methane molecules in aqueous environments, ΔG^{HI}, is expressed as a sum of three terms, except the effect of the mixing entropy term which will be introduced later.

$$\Delta G^{HI} = \Delta\bar{G}_c^{HI} + \Delta(\delta H)^{HI} + \bar{U}_{CH_4\text{-}CH_4}, \tag{10}$$

where $\Delta\bar{G}_c^{HI}$ is the contribution from the cavity effect, $\Delta(\delta H)^{HI}$ that from solute-water interactions, and $U_{CH_4\text{-}CH_4}$ the direct solute-solute interactions. $\Delta\bar{G}_c^{HI} = \Delta\bar{H}_c^{HI} - T\Delta\bar{S}_c^{HI}$, where $\Delta\bar{S}_c^{HI}$ and $\Delta\bar{H}_c^{HI}$ are expressed as $\Delta\bar{S}_c^{HI} = \bar{S}_{c,C_2H_6} - 2\bar{S}_{c,CH_4}$ and $\Delta\bar{H}_c^{HI} = \bar{H}_{c,C_2H_6} - 2\bar{H}_{c,CH_4}$, respectively. The valuse of $\Delta\bar{S}_c^{HI}$ and $\Delta\bar{H}_c^{HI}$ are 11.1 cal K^{-1} mol^{-1} and −650 cal mol^{-1}, respectively. Then, $\Delta\bar{G}_c^{HI}$ becomes −3960 cal mol^{-1}. The magnitude of $\Delta(\delta H)^{HI} = \delta H_{C_2H_6} - 2\delta H_{CH_4}$ becomes 2220 cal mol^{-1} using the values given in Table 3. The values of $\bar{U}_{CH_4\text{-}CH_4}$ is about 300 cal mol^{-1} according to the calculation by Dashevsky and Sarkisov.[12)] Thus, the magnitude of ΔG^{HI} at 25 °C becomes about −2 kcal mol^{-1}. This agrees to the estimation by Dashevsky and Sarkisov using the Monte-Carlo method as well as to that by Ben-Naim. It is noticeable that the largest minus contribution to ΔG^{HI} comes from $\Delta\bar{G}_c^{HI}$ and, further, essencially from $\Delta\bar{S}_c^{HI}$.

The Effect of the Change of Mixing Entropy by Hydrophobic Association: According to the result of the Monte-

Carlo calculation by Dashevsky and Sarkisov two methane molecules in 62 water molecules have a trend to associate and the free energy of the methane-methane pair in water becomes about -2 kcal mol^{-1}. Then, the association occurs actually in their simulation. However, in the aqueous solutions of methane being in equilibrium with methane gas at 1 atm no association of solute molecules occurs. The different behavior of methane molecules in these two cases is ascribed to the difference in the concentration of solute particles: in the former case the mole fraction of methane x is about 3×10^{-2} and in the latter x is of the order of 10^{-5}. In order to estimate the effect of concentration thermodynamically we must consider the mixing entropy.

The entropy of mixing for an ideal solution is expressed as

$$\Delta S_{\mathrm{mix}}(x) = -R\{x\ln x+(1-x)\ln(1-x)\}. \tag{11}$$

When all solute molecules are present as dimers, $\Delta S_{\mathrm{mix}}(x)$ varies to $\Delta S_{\mathrm{mix}}(x/2)$, and then the difference $\delta(\Delta S_{\mathrm{mix}})$ becomes

$$\begin{aligned}\delta(\Delta S_{\mathrm{mix}}) &= \Delta S_{\mathrm{mix}}(x/2) - \Delta S_{\mathrm{mix}}(x)\\ &= R\{(x/2)\ln(2x)+(1-x)\ln(1-x)\\ &\quad -(1-x/2)\ln(1-x/2)\}. \end{aligned} \tag{12}$$

In the case of $x\ll1$, $\delta(\Delta S_{\mathrm{mix}})$ becomes, to the order of x^2,

$$\delta(\Delta S_{\mathrm{mix}}) = R\left\{\frac{x}{2}(\ln(2x)-1)+\frac{3}{8}x^2\right\}. \tag{14}$$

For nonpolar molecules such as those tabulated in Table 3 the magnitudes of x are very small and of the order of 10^{-5}, and the change of the mixing entropy per mole of solute molecules by dimerization is safely expressed as $\delta(\Delta S_{\mathrm{mix}})/x=1.15\log x-0.15$ according to Eq. 14. For methane x is 2.48×10^{-5} and the value becomes -10.9 cal K^{-1} mol^{-1}. That is, if a dimerization $2(\mathrm{CH_4})\rightarrow(\mathrm{CH_4})_2$ would occur in aqueous solutions of methane at equilibrium with methane gas (1 atm), the change of the mixing entropy per mole of solute species amounts to -10.9 cal K^{-1} mol^{-1}. This contributes to the free energy for the formation of methane-methane pairs in water to about $+3$ kcal mol^{-1} at 25 °C and its total amount becomes positive, and thus, the dimerization can not occur. In the case of Dashevsky and Sarkisov's simulation, x is about 3×10^{-2} and the magnitude becomes -3.8 cal K^{-1} mol^{-1}, and the contribution to free energy is about 1.1 kcal mol^{-1}. Thus, the total amount of free energy remains negative and the dimerization occurs.

As a result of the consideration described above, we can say conclusively as follows:

a) methane molecules (or methyl groups) certainly have a tendency to adhere to one another in aqueous environments, its magnitude being expressed by ΔG^{HI} (authors) or δA^{HI} (Ben-Naim),

b) the largest minus contribution to ΔG^{HI} comes from the cavity effect $\Delta\bar{S}_{\mathrm{c}}^{\mathrm{HI}}$,

c) in the aqueous solutions of methane at ordinary conditions the association of solute molecules does not occur, because the decrease of the mixing entropy fully cancels out the entropy ascribed to the cavity effect,

d) in more concentrated solutions ($x\gtrsim0.01$), for example, in the aqueous solutions of proteins where the local concentration of hydrophobic groups becomes larger to the order of $x\simeq0.01$ or more, the decrease of the mixing entropy becomes smaller in magnitude than the entropy from the cavity effect, and then the tendency to adhere to one another appears actually. This may be also the case for the formation of micelles.

References

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

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

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

4) K. Shinoda, *Kagaku To Kogyo*, **21**, 1400 (1968); *J. Phys. Chem.*, **81**, 1300 (1977).

5) K. Arakawa, *Kagaku Sosetsu*, **11**, 13 (1976).

6) O. Ya. Samoilov, "Water and Aqueous Solution," ed by R. A. Horne, Wiley, New York (1972), Chap. 14; G. A. Krestov, *Zh. Strukt. Khim.*, **3**, 137 (1962).

7) H. S. Frank and W-Y. Wen, *Discuss. Faraday Soc.*, **44**, 133 (1957).

8) H. Reiss, *Adv. Chem. Phys.*, **9**, 1 (1965).

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

10) F. Hirata and K. Arakawa, *Bull. Chem. Soc. Jpn.*, **48**, 2139 (1975).

11) A. Ben-Naim, *J. Chem. Phys.*, **54**, 1387 (1971); "Water and Aqueous Solutions," Plenum Press, New York (1974).

12) G. Dashevsky and N. Sarkisov, *Mol. Phys.*, **27**, 1271 (1974).

13) R. A. Pierotti, *J. Phys. Chem.*, **67**, 1840 (1963); **69**, 281 (1965).

14) The "radius of cavity" r in the conditional distribution function $G(r)$ defined in the beginning of this section corresponds to this a_{12}.

15) K. Arakawa, K. Tokiwano, and K. Kojima, *Bull. Chem. Soc. Jpn.*, **50**, 65 (1977).

16) J. F. Hinton and E. S. Amis, *Chem. Rev.*, **71**, 627 (1971).

17) E. R. Nightingale, Jr., "Chemical Physics of Ionic Solutions," ed by B. E. Conway and R. G. Baradas, Wiley, New York (1966), p. 87.

18) P. R. Bienkowski and K. C. Chao, *J. Chem. Phys.*, **62**, 615 (1975); A. P. Kudchadker, G. H. Alani, and B. J. Zwolinski, *Chem. Rev.*, **68**, 659 (1968); J. F. Mathews, *ibid.*, **72**, 71 (1972).