J. Phys. Chem. 1992, 96, 3847–3855

Entropy of Hydrophobic Hydration: A New Statistical Mechanical Formulation

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(Received: September 26, 1991; In Final Form: December 30, 1991)

A new statistical mechanical formulation is presented for the entropy of solution of simple molecules in water. The formulation is based on the Green–Wallace expansion for the entropy in terms of multiparticle correlation functions, which is derived here for rigid polyatomic fluids and for mixtures. In the latter case, the ideal (combinatorial) entropy of mixing is identified with the one-particle contributions, leading to an expression similar to that of Flory and Huggins. With a factorization assumption for the solute–water correlation function, we have been able to separate the translational and orientational contributions to the entropy of solution. This approach is applied to an infinitely dilute solution of methane in water. The required correlation functions are obtained by Monte Carlo simulation. The orientational contribution, which is due directly to the orientational asymmetry of water–water interactions, is found to be comparable to the translational contribution. We find that the large entropies and heat capacities of hydrophobic hydration are well accounted for by solute–water correlations alone and that large perturbations in water structure are not required to explain hydrophobic behavior.

Introduction

The solution properties of nonpolar compounds in water have been a subject of intense research for almost six decades. Particularly intriguing has been the observation that at room temperature dissolution is slightly favored by enthalpy, but strongly opposed by a large, negative change in entropy.[1,2] These properties, and large positive heat capacities of solution, are the distinguishing features of what is commonly called hydrophobic hydration. An example is given in Table I for the thermodynamic properties of methane dissolved in water and in carbon tetrachloride. This peculiar balance between enthalpy and entropy leads to an extraordinary temperature dependence of the thermodynamic behavior, such as solubility minima and lower critical solution temperatures.[3] Much of the interest in organic aqueous solutions has been stimulated by the suggestion that their properties are important to association phenomena in aqueous environments, such as formation of micelles, protein folding, and molecular recognition.[4,5] The hydrophobic interaction is usually viewed as a partial reversal of the solution process and has been shown to be entropy driven at room temperature,[5,6] although it gradually becomes enthalpy driven as the temperature is increased.[2,7] Therefore, determination of the molecular origin of the observed entropies of solution is imperative for understanding the mechanism of the above processes and identifying the source of enthalpy–entropy compensation phenomena in water.[8]

The first widely accepted explanation for the thermodynamic properties of aqueous solutions of nonpolar molecules was the "iceberg" hypothesis of Frank and Evans,[1] which states that the structure of water around nonpolar solutes is more "ordered" and therefore more stable energetically than bulk water. This change is brought about by strengthening or by an increase in the number of hydrogen bonds between water molecules in the hydration shell. A statistical mechanical implementation of these ideas can be found in the theory of Nemethy and Scheraga,[9] which was based on justifiable, yet unproven, assumptions on the nature of water and the type of structural perturbations induced by the solute. Several experimental techniques[10,11] have been used to substantiate the iceberg hypothesis and to characterize the structural and dynamic properties of hydration water, but such results are amenable to many interpretations (see, for example, ref 12).

Another explanation was based simply on the directional, hydrogen bonding properties of water, which rearranges around the nonpolar solute in order to maintain the maximum possible number of hydrogen bonds.[13] In this view, hydration water need not be different from bulk water; only its orientational freedom is restricted due to the inability of the solute to participate in hydrogen bonds, which makes certain orientations of the adjacent water molecules energetically unfavorable.[14] Of course one could interpret this orientational restriction as "ordering" and consider it a more specific version of the iceberg hypothesis. It is, however, a distinct mechanism, since no enhancement of water–water interactions is invoked. While orientational preferences have been observed in computer simulations,[15] no quantitative assessment of the contribution of this factor to the entropy has been made due to the lack of a direct, theoretical connection between the entropy of solution and angular probability distributions.

An entirely different point of view has emerged since the work of Pierotti, who applied scaled particle theory (SPT) to the calculation of thermodynamic properties of solutes in nonpolar

TABLE I: Solvation Thermodynamics (in Ben-Naim's Standard State) of Methane in Water and Carbon Tetrachloride at 25 °C

	water[a]	CCl_4[d]
ΔS^*/(cal/(mol·K))	−15.94	−1.7
$T\Delta S^*$/(kcal/mol)	−4.75	−0.5
ΔH^*/(kcal/mol)	−2.75	−0.3
ΔG^*/(kcal/mol)	+2.00	+0.2
Δc_p(cal/(mol·K))	+50.0,[b] +56.6[c]	(0 to 10)[e]

[a] Reference 48. [b] Reference 45. [c] Reference 47. [d] From: Wilhelm, E.; Battino, R. *Chem. Rev.* **1973**, *73*, 1, after change of standard states according to ref 48. [e] Although it is established that Δc_p in organic solvents is very small, accurate values are not available. The range given is an estimate taken from: Eley, D. D. *Trans. Faraday Soc.* **1939**, *35*, 1421.

(1) Frank, H. S.; Evans, M. W. *J. Chem. Phys.* **1945**, *13*, 507.
(2) Privalov, P. L.; Gill, S. J. *Adv. Protein Chem.* **1988**, *39*, 191.
(3) Franks, F.; Reid, D. S. In *Water, a comprehensive treatise*; Franks, F., Ed.; Plenum Press: New York, 1973; Vol. 2, Chapter 5.
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(5) Tanford, C. *The hydrophobic effect*, 2nd ed.; Wiley: New York, 1980.
(6) Tucker, E. E.; Lane, E. H.; Christian, S. D. *J. Solution Chem.* **1981**, *10*, 1.
(7) Evans, D. F. *Langmuir* **1988**, *4*, 3.
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(9) Nemethy, G.; Scheraga, H. A. *J. Chem. Phys.* **1962**, *36*, 3401.
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(13) Glew, D. N. *J. Phys. Chem.* **1962**, *66*, 605.
(14) Stillinger, F. S. *Philos. Trans. R. Soc. London B* **1977**, *278*, 97.
(15) (a) Geiger, A.; Rahman, A.; Stillinger, F. H. *J. Chem. Phys.* **1979**, *70*, 263. (b) Rossky, P. J.; Karplus, M. *J. Am. Chem. Soc.* **1979**, *101*, 1913. (c) Pangali, C.; Rao, M.; Berne, B. J. *J. Chem. Phys.* **1979**, *71*, 2982. (d) Postma, J. P. M.; Berendsen, H. J. C.; Haak, J. R. *Faraday Symp. Chem. Soc.* **1982**, *17*, 55. (e) Alagona, G.; Tani, A. *J. Chem. Phys.* **1980**, *72*, 580.

0022-3654/92/2096-3847$03.00/0

liquids[16] and water.[17] Although SPT is strictly a theory of simple, monatomic fluids, the qualitative features of hydrophobic hydration were reproduced surprisingly well, suggesting that the microscopic structure of water is not directly implicated in the solution thermodynamics. Stillinger improved SPT by considering the effect of the hydrogen bonding structure of water on the solute–water radial distribution function.[18] Similarly, in the integral equation theory of Pratt and Chandler,[19] the hydrogen bonding structure of water is taken into account only indirectly through the use of the experimental O–O radial distribution function and the density of water at different temperatures. Here, as in the SPT theories, solute–water orientational correlations are not evaluated as a separate contribution to the entropy. Despite that, their prediction for the entropy of hydration of methane was excellent. As recognized by several authors, the large negative entropies of solution calculated by these methods for water compared to nonpolar solvents are due to the smaller size of water, and not directly to its hydrogen bonding properties.[20,21]

Computer simulations could in principle aid in deciphering the molecular origin of the observed thermodynamic behavior. The main obstacle is that the calculation of entropic quantities cannot be easily accomplished. Free energy simulation methods developed over the past decade have met with considerable success in calculating free energies of solution but have not offered new insights due to our inability to separate effectively the enthalpic and entropic contributions to the free energy. Current methods for doing so, either by finite-difference temperature derivatives[22] or by the simple difference between free energy and enthalpy, are limited by high statistical uncertainties. Direct calculation of the entropy would overcome these limitations and, perhaps more importantly, provide an intuitive understanding of hydrophobic phenomena. Such direct methods have been developed, for example, to obtain the configurational entropy of macromolecules,[23,24] but extension to diffusive, fluid systems has only recently been accomplished.[25,26] The only direct method for calculating hydration entropies[27] relies on the continuum approximation and is intuitively appealing but lacks a rigorous statistical mechanical basis.

In this work we present a rigorous statistical mechanical expression for the entropy of solution of a simple solute in water in terms of translational and orientational correlations between the solute and the solvent molecules. The leading terms in this expression are evaluated by Monte Carlo simulations, enabling us to examine quantitatively the influence of orientational restriction and relative solute/solvent size on the entropy of solution. It is emphasized that this is not a theory or a model, since no fundamental assumptions are made about the nature of liquid water and its interaction with the solutes, other than accepting an empirical energy function to be used in the simulations. In addition to providing insights into the hydrophobic effect, this formalism has proven useful in elucidating and unifying concepts, such as the ideal entropy of mixing and communal entropy, within the distribution function approach to the theory of the liquid state.

Entropy of a Pure Polyatomic Fluid

In this section an expansion for the entropy of a pure polyatomic fluid is derived. The derivation is simplest in the canonical ensemble and is similar to that of Wallace[25,28] for a monatomic fluid.

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(22) Brooks, C. L., III. *J. Phys. Chem.* **1986**, *90*, 6680.
(23) Karplus, M.; Kushick, J. N. *Macromolecules* **1981**, *14*, 325.
(24) Edholm, O.; Berendsen, H. J. C. *Mol. Phys.* **1984**, *51*, 1011.
(25) (a) Wallace, D. C. *J. Chem. Phys.* **1987**, *87*, 2282. (b) Wallace, D. C. *Phys. Rev. A* **1988**, *38*, 469. (c) Wallace, D. C. *Phys. Rev. A* **1989**, *39*, 4843. (d) Wallace, D. C. *Proc. R. Soc. London A* **1991**, *433*, 615.
(26) Baranyai, A.; Evans, D. J. *Phys. Rev. A* **1989**, *40*, 3817.
(27) Rashin, A. A.; Bukatin, M. A. *J. Phys. Chem.* **1991**, *95*, 2942.

The nomenclature used is a combination of that of Wallace and that of Gray and Gubbins.[29]

Neglecting intramolecular degrees of freedom, the classical canonical partition function for N molecules of a polyatomic fluid in a volume V at temperature T is

$$Q = \frac{1}{h^{sN} N! \sigma^N} Z \quad (1)$$

$$Z = \int \exp(-\beta H_N)\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N \quad (2)$$

where H_N is the Hamiltonian, σ is the symmetry number (2 for water), h is Planck's constant, $s = 5$ for linear and 6 for nonlinear molecules, $\beta = 1/kT$, k is Boltzmann's constant, $\mathbf{r}^N$ is the Cartesian coordinates of the N molecules, $\mathbf{p}^N$ are the linear momenta, ω^N are the Euler angles ($d\omega = \sin\theta\, d\theta\, d\phi\, d\zeta$), and $\mathbf{J}^N$ are the angular momenta. We define two probability distributions: the dimensionless canonical probability distribution

$$P'_N = \exp(-\beta H_N)/Q \quad (3)$$

which is normalized to

$$\int P'_N\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N = h^{sN} N! \sigma^N \quad (4)$$

and a second, related distribution function

$$P_N = \exp(-\beta H_N)/Z \quad (5)$$

which is normalized to unity. P_N gives the probability of N *specific*, distinguishable molecules having certain positions, orientations, and momenta. The probability of N indistinguishable molecules occupying the same point in phase space is

$$f_N = N! \sigma^N P_N = P'_N / h^{sN} \quad (6)$$

In addition, one can define partial, n-particle distribution functions:

$$P_N^{(n)} = \int P_N\, d\mathbf{r}^{N-n}\, d\mathbf{p}^{N-n}\, d\omega^{N-n}\, d\mathbf{J}^{N-n} \quad (7)$$

$$f_N^{(n)} = \frac{N!}{(N-n)!} \sigma^n P_N^{(n)} = \frac{1}{(N-n)! \sigma^{N-n}} \int f_N\, d\mathbf{r}^{N-n}\, d\mathbf{p}^{N-n}\, d\omega^{N-n}\, d\mathbf{J}^{N-n} \quad (8)$$

which are normalized to

$$\int P_N^{(n)}\, d\mathbf{r}^n\, d\mathbf{p}^n\, d\omega^n\, d\mathbf{J}^n = 1 \quad (9a)$$

$$\int f_N^{(n)}\, d\mathbf{r}^n\, d\mathbf{p}^n\, d\omega^n\, d\mathbf{J}^n = \frac{N!}{(N-n)!} \sigma^n \quad (9b)$$

The function $f_N^{(n)}(\mathbf{r}^n,\mathbf{p}^n,\omega^n,\mathbf{J}^n)$ is the probability that the point $(\mathbf{r}^n,\mathbf{p}^n,\omega^n,\mathbf{J}^n)$ in phase space is occupied. The entropy is

$$S_N = -\frac{k}{h^{sN} N! \sigma^N} \int P'_N \ln P'_N\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N = -\frac{k}{N! \sigma^N} \int f_N \ln (h^{sN} f_N)\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N \quad (10)$$

Our approach will be to factor f_N in such a way that the entropy is expanded in terms involving one-particle, two-particle, etc., correlations. This can be accomplished in the following way:

$$f_N = f_N^{(1)}(1)\, f_N^{(1)}(2) \ldots f_N^{(1)}(N)\, g^{(N)}(\mathbf{r}^N,\omega^N) \quad (11a)$$

where $f_N^{(1)}(\mathbf{r}_i,\mathbf{p}_i,\omega_i,\mathbf{J}_i)$ is denoted by $f_N^{(1)}(i)$ and $g^{(N)}(\mathbf{r}^N,\omega^N)$ is the N-molecule correlation function, which depends only on positions and orientations. The partial distribution functions are factored in a similar way:

$$f_N^{(n)} = f_N^{(1)}(1)\, f_N^{(1)}(2) \ldots f_N^{(1)}(n)\, g^{(n)}(\mathbf{r}^n,\omega^n) \quad (11b)$$

(28) Green, H. S. *The molecular theory of fluids*; North-Holland: Amsterdam, 1952.
(29) Gray, C. G.; Gubbins, K. E. *Theory of molecular fluids*; Clarendon Press: Oxford, U.K., 1984; Vol. 1, Chapter 3.

Since momenta are uncorrelated to positions and orientations,[29] we can also factor the one-particle distribution functions

$$f_N^{(1)}(\mathbf{r}_1,\mathbf{p}_1,\omega_1,\mathbf{J}_1) = p(\mathbf{p}_1)\, p(\mathbf{J}_1)\, p(\mathbf{r}_1,\omega_1) \quad (12)$$

where $p(\mathbf{p}_1)$, $p(\mathbf{J}_1)$, and $p(\mathbf{r}_1,\omega_1)$ are the probability distributions of linear momenta, angular momenta, and position/orientation, respectively. These are normalized to

$$\int p(\mathbf{p}_1)\, d\mathbf{p}_1 = 1$$
$$\int p(\mathbf{J}_1)\, d\mathbf{J}_1 = 1 \quad (13)$$
$$\int p(\mathbf{r}_1,\omega_1)\, d\mathbf{r}_1\, d\omega_1 = N\sigma$$

The N-molecule correlation function is factored as follows[25,28]

$$g^{(N)}(\mathbf{r}^N,\omega^N) = g^{(2)}(1,2)\ \dots\ g^{(2)}(N-1,N)\ \delta g^{(3)}(1,2,3)\ \dots\ \delta g^{(3)}(N-2,N-1,N)\ \dots\ \delta g^{(N)}(1,\dots,N) \quad (14)$$

where $\delta g^{(3)}$ is defined by the relationship

$$g^{(3)}(1,2,3) = g^{(2)}(1,2)\, g^{(2)}(1,3)\, g^{(2)}(2,3)\, \delta g^{(3)}(1,2,3) \quad (15)$$

and similarly $\delta g^{(4)}$ through $\delta g^{(N)}$. In the above factorization for $g^{(N)}$ we have $(1/2)N(N-1)$ pairs, $(1/3!)N(N-1)(N-2)$ triplets, etc.

With this factorization we write

$$h^{sN} f_N = h^s f_N^{(1)}(1)\, h^s f_N^{(1)}(2)\ \dots\ h^s f_N^{(1)}(N)\, g^{(N)}(\mathbf{r}^N,\omega^N) \quad (16)$$

so that

$$\ln (h^{sN} f_N) = \sum_{i=1}^{N} \ln (h^s f_N^{(1)}(i)) + \ln g^{(N)} \quad (17)$$

$$= N \ln (h^s f_N^{(1)}) + \frac{1}{2}N(N-1) \ln g^{(2)} + \frac{1}{3!}N(N-1)(N-2) \ln \delta g^{(3)} + \dots$$

where the summation over the one-particle distributions is replaced by a product because all particles are equivalent. Substituting this equation into the entropy expression leads to the desired expansion for the entropy in terms of one-particle, two-particle, three-particle etc., correlations:

$$S_N = -\frac{kN}{N!\sigma^N}\int f_N \ln (h^s f_N^{(1)})\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N - \frac{kN(N-1)}{2N!\sigma^N}\int f_N \ln g^{(2)}\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N - \frac{kN(N-1)(N-2)}{3!N!\sigma^N}\int f_N \ln \delta g^{(3)}\, d\mathbf{r}^N\, d\mathbf{p}^N\, d\omega^N\, d\mathbf{J}^N - \dots$$

$$= -\frac{k}{\sigma}\int f_N^{(1)} \ln (h^s f_N^{(1)})\, d\mathbf{r}_1\, d\mathbf{p}_1\, d\omega_1\, d\mathbf{J}_1 - \frac{k}{2\sigma^2}\int f_N^{(2)} \ln g^{(2)}\, d\mathbf{r}^2\, d\mathbf{p}^2\, d\omega^2\, d\mathbf{J}^2 - \frac{k}{3!\sigma^3}\int f_N^{(3)} \ln \delta g^{(3)}\, d\mathbf{r}^3\, d\mathbf{p}^3\, d\omega^3\, d\mathbf{J}^3 - \dots \quad (18)$$

Using the factorization of $f_N^{(1)}$ (eq 12), we can integrate over the momenta. For a homogeneous fluid, the one-particle density $p(\mathbf{r}_1,\omega_1)$ is constant and, from eq 13, equal to $N\sigma/\Omega V$ where $\Omega = \int d\omega$ [$\Omega = 4\pi$ for linear molecules, and $\Omega = 8\pi^2$ for nonlinear molecules]. With these substitutions we obtain the desired final result

$$S_N = -\frac{kN}{\rho}\frac{\Omega}{\sigma}\int f_N^{(1)} \ln (h^s f_N^{(1)})\, d\mathbf{p}_1\, d\mathbf{J}_1 - \frac{k\rho^2}{2\Omega^2}\int g^{(2)} \ln g^{(2)}\, d\mathbf{r}^2\, d\omega^2 - \frac{k\rho^3}{3!\Omega^3}\int g^{(3)} \ln \delta g^{(3)}\, d\mathbf{r}^3\, d\omega^3 - \dots \quad (19)$$

where ρ is the number density N/V. The above expression is closely analogous to that of Wallace for a monatomic fluid[25] and reduces to it if we omit the constants σ and Ω, and the integrations over orientations and angular momenta.

Equation 19 is an interesting expression for the entropy, since it offers a connection between the entropy of a fluid and familiar quantities, such as the pair correlation function. The one-particle term in this equation is positive and represents, apart from the momentum contribution to the entropy, the freedom of motion of every particle throughout the volume of the system. For a homogeneous fluid, the one-particle distribution is uniform. For an inhomogeneous system or a crystal, where the one-particle distributions will not be uniform but oscillatory, the one-particle contribution to the entropy will be smaller, due to spatial ordering of the particles. Thus the one-particle term contains the so-called "communal entropy", a concept used in older cell theories of the liquid state.[30] The two-particle term in eq 19 is negative and represents the reduction in entropy due to correlations in the positions of the particles. The "sharper" the pair-correlation function is, the lower the entropy. This is reminiscent of Hertz's proposition[10,31] of using the "sharpness" of the correlation function as an indicator of the structural changes of water around a solute. The present formulation allows a quantitative connection between this measure of structure and entropy.

Truncating the series at the three-particle term in eq 19 is tantamount to making the Kirkwood superposition approximation[32] ($\delta g^{(3)}, \dots, \delta g^{(N)} = 1$). That is, the terms beyond the second are essentially corrections to the superposition approximation and can be either positive or negative. While the above expression is exact, its practical utility depends on its convergence, since the calculation of correlations between more than two particles is very difficult in practice. Applications of this approach to argon,[25b] the hard-sphere liquid,[25c] and liquid metals[25d] have been quite encouraging in that the sum of the first two terms in most cases agrees well with the experimental thermodynamic entropy. A different conclusion, however, was reached by Baranyai and Evans. Using an alternate expansion for the entropy,[26] they found that even inclusion of the three-particle term was not sufficient to bring the calculated entropy up to the experimental value.[33] While questions still remain about the nature and the convergence properties of the different entropy expressions, we develop the formalism for the problem of hydrophobic hydration, concentrating on qualitative insights, rather than quantitative results, for the hydration entropies.

Before we proceed, one more issue must be addressed. In the canonical ensemble, because the number of molecules is constant, the limiting value of the correlation functions is not unity but slightly less than that. Therefore, the integrands in eq 19 do not vanish at long distances, and thus the integrals contain contributions from the entire volume of the fluid.[26] In other words, the integrals are not "local". However, this will not be a problem in the present work, since, as will be shown in a following section, the required integral for an infinitely dilute solution is local.

Entropy of a Simple Mixture and the Ideal Entropy of Mixing

In this section an expression for the entropy of mixing two fluids is obtained. For simplicity the derivation is given for two monatomic fluids, but the final results hold for molecular fluids as well. Consider M molecules of type A in volume V_A and $N-M$ of type B in volume V_B mixed at constant temperature and pressure to a total volume V. The canonical partition function and the entropy of the mixture are

$$Q = \frac{1}{h^{3N}(N-M)!M!}\int \exp(-\beta H_N)\, d\mathbf{r}^N\, d\mathbf{p}^N \quad (20)$$

$$S_N = -\frac{k}{h^{3N}(N-M)!M!}\int P'_N \ln P'_N\, d\mathbf{r}^N\, d\mathbf{p}^N \quad (21)$$

(30) Hirschfelder, J. O.; Curtiss, C. F.; Bird, R. B. *Molecular theory of gases and liquids*; Wiley: New York, 1954; pp 273–276.
(31) Hertz, H. G. *Ber. Bunsen-Ges. Phys. Chem.* **1964**, *68*, 907.
(32) Kirkwood, J. G. *J. Chem. Phys.* **1942**, *10*, 394.
(33) Baranyai, A.; Evans, D. J. *Phys. Rev. A* **1990**, *42*, 849.

The distribution function is given by

$$f_N = (N - M)!M!P_N = P'_N/h^{3N} \quad (22)$$

and is normalized to

$$\int f_N \, d\mathbf{r}^N \, d\mathbf{p}^N = (N - M)!M! \quad (23)$$

The partial distribution functions here must be distinguished by two indexes: one for the total number of molecules (n) and one for the number of molecules of type A (m):

$$P_N^{mn} = \int P_N \, d\mathbf{r}^{N-n} \, d\mathbf{p}^{N-n} \quad (24)$$

$$f_N^{mn} = \frac{(N-M)!M!}{(M-m)!(N-M-n+m)!} P_N^{mn} = \frac{1}{(M-m)!(N-M-n+m)!} \int f_N \, d\mathbf{r}^{N-n} \, d\mathbf{p}^{N-n} \quad (25)$$

Here f_N^{mn} is the probability that a certain point in phase space is occupied by m particles of type A and $n - m$ particles of type B.

Performing the same factorization as before, we separate the entropy into one-particle, two-particle, etc., terms

$$S_N = -k \int f_A^{(1)} \ln (h^3 f_A^{(1)}) \, d\mathbf{r}_1 \, d\mathbf{p}_1 - k \int f_B^{(1)} \ln (h^3 f_B^{(1)}) \, d\mathbf{r}_1 \, d\mathbf{p}_1 - \frac{k}{2} \int \rho_A{}^2 g_{AA}^{(2)} \ln g_{AA}^{(2)} \, d\mathbf{r}^2 - k \int \rho_A \rho_B \, g_{AB}^{(2)} \ln g_{AB}^{(2)} \, d\mathbf{r}^2 - \frac{k}{2} \int \rho_B{}^2 g_{BB}^{(2)} \ln g_{BB}^{(2)} \, d\mathbf{r}^2 - ... \quad (26)$$

where $f_A^{(1)} = f_N^{11}$ and $f_B^{(1)} = f_N^{01}$. By factoring the momenta out of the one-particle distribution functions, we obtain for the one-particle terms

$$S_{1p} = -kN \int p(\mathbf{p}) \ln p(\mathbf{p}) \, d\mathbf{p} - k \int p_A(\mathbf{r}) \ln p_A(\mathbf{r}) \, d\mathbf{r} - k \int p_B(\mathbf{r}) \ln p_B(\mathbf{r}) \, d\mathbf{r} \quad (27)$$

where, for a homogeneous system, $p_A(\mathbf{r}) = M/V = \rho_A$ and $p_B(\mathbf{r}) = (N - M)/V = \rho_B$. The one-particle terms for the pure systems A and B are

$$S_{1p,A} = -kM \int p(\mathbf{p}) \ln p(\mathbf{p}) \, d\mathbf{p} - k \int p_A(\mathbf{r}) \ln p_A(\mathbf{r}) \, d\mathbf{r} \quad (28)$$

$$S_{1p,B} = -k(N - M) \int p(\mathbf{p}) \ln p(\mathbf{p}) \, d\mathbf{p} - k \int p_B(\mathbf{r}) \ln p_B(\mathbf{r}) \, d\mathbf{r} \quad (29)$$

where here $p_A(\mathbf{r}) = M/V_A$ and $p_B(\mathbf{r}) = (N - M)/V_B$.

The momentum terms in eqs 27–29 cancel, and thus the one-particle contribution to the mixing entropy is

$$\Delta S_{1p} = -kM \ln \left(\frac{M}{V}\right) - k(N - M) \ln \left(\frac{N-M}{V}\right) + kM \ln \left(\frac{M}{V_A}\right) + k(N - M) \ln \left(\frac{N-M}{V_B}\right) = -kM \ln \left(\frac{V_A}{V}\right) - k(N - M) \ln \left(\frac{V_B}{V}\right) \quad (30)$$

or

$$\frac{\Delta S_{1p}}{N} = -kX_A \ln \left(\frac{V_A}{V}\right) - kX_B \ln \left(\frac{V_B}{V}\right) \quad (31)$$

where X_A and X_B are mole fractions. If the particles are the same size and the interactions between them are identical, then $V = V_A + V_B$ and $V_A/V = X_A$, $V_B/V = X_B$. In this case,

$$\Delta S_{1p}/kN = -X_A \ln X_A - X_B \ln X_B \quad (32)$$

which is the well-known expression for the entropy of forming an ideal mixture. One can also show that the second and higher order terms in the entropy expression are identically zero in this case. However, these terms are expected to contribute when the particles are not the same size and/or the interactions between them are different. The question is then which expression, eq 31 or eq 32, should one accept as the "ideal" (or "combinatorial" or "cratic") contribution to the entropy of mixing. Of course, what one calls the ideal part of a nonideal entropy of mixing is a matter of definition. However, our choice should be the one that separates most clearly that part of the entropy due to specific interactions of the solute with the solvent. Since ΔS_{1p} contains no information on the specific interactions of molecules A and B (except implicitly, in that they determine the total volume of the system at constant T and P), it is *this* quantity that should be identified with the ideal contribution to the mixing entropy and not eq 32. We will call eq 31 the Hildebrand expression, since it was first derived by Hildebrand based on intuitive arguments.[34]

Flory and Huggins, on the other hand, have shown that in polymer solutions, the large deviations from Raoult's law are due to the disparate size between the solute and the solvent, rather than disparate energetics.[35] On the basis of lattice models, they obtained the following expression for the combinatorial contribution to the entropy of mixtures containing long, flexible molecules

$$\frac{\Delta S_{mix}^{c}}{kN} = -X_A \ln \Phi_A - X_B \ln \Phi_B \quad (33)$$

where Φ_A and Φ_B are volume fractions of A and B in the mixture. This expression can also be obtained from the Hildebrand formula by assuming no volume change on mixing. Although the validity of the Flory–Huggins equation has been established for polymer solutions, its application to mixtures containing small or bulky molecules has long been debated.[36] In such cases, the entropy of mixing was shown to conform better to eq 32 rather than eq 33. For example, the entropy of mixing two hard-sphere liquids of different molecular size is overestimated by the Flory–Huggins formula, while it is slightly underestimated by the ideal mixture formula.[37] Since this mixing process occurs with a negative volume change, one possible reason for the discrepancy could be the inability of the Flory–Huggins expression to account for changes in volume upon mixing. The Hildebrand formula, however, does account for such volume changes and would give an entropy of mixing between these two limits. In addition, there is a nonzero "packing" entropy contribution, represented by the second and higher order terms in the entropy expansion. This could well account for the remaining discrepancy between the ideal and the actual entropy of mixing.

An alternative way of deriving eq 31 is through the expression for the chemical potential. The chemical potential of a pure component and that for the same component in a mixture is given by

$$\mu_{A,pure} = \mu_{A,pure}^{res} + kT \ln (\rho_{A,pure} \Lambda_A{}^3)$$

$$\mu_{A,mix} = \mu_{A,mix}^{res} + kT \ln (\rho_{A,mix} \Lambda_A{}^3) \quad (34)$$

where Λ_A is the de Broglie wavelength. The first term in these two expressions is the residual chemical potential, which can be interpreted as the reversible work of inserting the solute A into a fixed position in the solvent.[38] The second term is the ideal gas chemical potential (or "liberation free energy" according to Ben-Naim[38]), which, for a real fluid, contains the contribution of momenta and the freedom of the molecules to "wander" throughout the volume of the system. If we mix n_A moles of pure A and n_B moles of pure B, the total Gibbs free energy of mixing will be

(34) Hildebrand, J. H.; Scott, R. L. *The solubility of nonelectrolytes*, 3rd ed.; Reinhold: New York, 1950; p 108.
(35) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953; Chapter 12.
(36) Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. *Regular and related solutions*; Van Nostrand Reinhold: New York, 1970.
(37) Meroni, A.; Pimpinelli, A.; Reatto, L. *J. Chem. Phys.* **1987**, *87*, 3644.
(38) Ben-Naim, A. *J. Phys. Chem.* **1978**, *82*, 792.

$$\Delta G_{\text{mix}} = n_A\mu_{A,\text{mix}} + n_B\mu_{B,\text{mix}} - n_A\mu_{A,\text{pure}} - n_B\mu_{B,\text{pure}}$$

$$= n_A(\mu^{\text{res}}_{A,\text{mix}} - \mu^{\text{res}}_{A,\text{pure}}) + n_B(\mu^{\text{res}}_{B,\text{mix}} - \mu^{\text{res}}_{B,\text{pure}}) +$$

$$n_A kT\left(\ln\left(\frac{n_A\Lambda_A^3}{V}\right) - \ln\left(\frac{n_A\Lambda_A^3}{V_A}\right)\right) + n_B kT\left(\ln\left(\frac{n_B\Lambda_B^3}{V}\right) - \ln\left(\frac{n_B\Lambda_B^3}{V_B}\right)\right)$$

which is separated into residual and ideal parts. The ideal part is entirely entropic and can be set equal to $-T\Delta S^{\text{ideal}}_{\text{mix}}$. Thus

$$\Delta S^{\text{ideal}}_{\text{mix}} = -kn_A \ln\left(\frac{V_A}{V}\right) - kn_B \ln\left(\frac{V_B}{V}\right)$$

which is eq 31.

Finally, we should discuss the choice of standard state for the thermodynamic quantities of solution. Following Ben-Naim,[38] the "local" standard Gibbs free energy of solution, denoted here by an asterisk, is identified with the residual part of the chemical potential:

$$\Delta G^* = \mu^{\text{res}}_A \tag{35}$$

As mentioned above, the ideal gas chemical potential contains the contribution of momenta and the freedom of the molecules to wander throughout the volume of the system. In the present formulation, these contributions are included in the one-particle term; thus the local standard (residual) entropy of solution corresponds to

$$\Delta S^* = \Delta S_{2p} + \Delta S_{3p} + \ldots \tag{36}$$

Entropy of Solution at Infinite Dilution

In this section we obtain an expression for the entropy of solution of a monatomic solute (S) from an ideal gas (IG) phase into water (W) at infinite dilution. The process we consider is

$$\underset{[\text{S}]}{(1 \text{ molecule of solute, IG})} + \underset{[\text{W}]}{(N-1 \text{ molecules of water})} \rightarrow \underset{[\text{M}]}{(1\text{S} + (N-1)\text{W mixture})}$$

The entropy of solution is given as

$$\Delta S_{\text{sol}} = S_M - S_S - S_W$$

For comparison, the solute partial molar entropy at infinite dilution in the mixture is

$$\overline{S_S} = S_M - S_W$$

in the limit $N \rightarrow \infty$. As above, one can derive an expression for the entropy of the mixture M

$$S_M = -\frac{k}{\sigma}\int f^{(1)}_W \ln(h^s f^{(1)}_W)\, d\mathbf{r}_1\, d\mathbf{p}_1\, d\omega_1\, d\mathbf{J}_1 - k\int f^{(1)}_S \ln(h^3 f^{(1)}_S)\, d\mathbf{r}_S\, d\mathbf{p}_S - \frac{k}{2\sigma^2}\int f^{(2)}_{WW} \ln g^{(2)}_{WW}\, d\mathbf{r}^2\, d\mathbf{p}^2\, d\omega^2\, d\mathbf{J}^2 - \frac{k}{\sigma}\int f^{(2)}_{SW} \ln g^{(2)}_{SW}\, d\mathbf{r}_1\, d\mathbf{r}_S\, d\mathbf{p}_1\, d\mathbf{p}_S\, d\omega_1\, d\mathbf{J}_1 - \frac{k}{3!\sigma^3}\int f^{(3)}_{WWW} \ln \delta g^{(3)}_{WWW}\, d\mathbf{r}^3\, d\mathbf{p}^3\, d\omega^3\, d\mathbf{J}^3 - \frac{k}{2\sigma^2}\int f^{(3)}_{SWW} \ln \delta g^{(3)}_{SWW}\, d\mathbf{r}^2\, d\mathbf{r}_S\, d\mathbf{p}^2\, d\mathbf{p}_S\, d\omega^2\, d\mathbf{J}^2 - \ldots \tag{37}$$

where the subscripts S and W stand for the solute and water, respectively. In the nomenclature of the previous section the distribution functions in eq 37 are $f^{(2)}_{WW} = f^{02}_N$, $f^{(2)}_{SW} = f^{12}_N$, etc. The entropy of pure water (W) is

$$S_W = -\frac{k}{\sigma}\int f^{(1)}_W \ln(h^s f^{(1)}_W)\, d\mathbf{r}_1\, d\mathbf{p}_1\, d\omega_1\, d\mathbf{J}_1 - \frac{k}{2\sigma^2}\int f^{(2)}_{WW} \ln g^{(2)}_{WW}\, d\mathbf{r}^2\, d\mathbf{p}^2\, d\omega^2\, d\mathbf{J}^2 - \frac{k}{3!\sigma^3}\int f^{(3)}_{WWW} \ln \delta g^{(3)}_{WWW}\, d\mathbf{r}^3\, d\mathbf{p}^3\, d\omega^3\, d\mathbf{J}^3 - \ldots \tag{38}$$

The integrations in eqs 37 and 38 are performed over the volume of the system in each case.

For the ideal gas in the canonical ensemble, the contribution of the multiparticle correlations to the entropy is not zero, but k per molecule.[26] The contribution of the two-particle term amounts to $^1/_2k$, that of the three-particle term to $^1/_6k$, etc. Thus, the entropy of system S is

$$S_S = -k\int f^{(1)} \ln(h^3 f^{(1)})\, d\mathbf{r}_1\, d\mathbf{p}_1 + k(\tfrac{1}{2} + \tfrac{1}{6} + \ldots)$$

$$= k\{\tfrac{3}{2} - \ln(\rho\Lambda^3)\} + k = k\{\tfrac{5}{2} - \ln(\rho\Lambda^3)\} \tag{39}$$

The residual entropy of solution is

$$\Delta S^* = \Delta S_{2p} + \Delta S_{3p} + \ldots \tag{36}$$

The pure water terms ($g^{(2)}_{WW}$, $\delta g^{(3)}_{WWW}$, etc.) cancel in the limit $N \rightarrow \infty$, and thus

$$\Delta S^* = -\frac{k}{\sigma}\int f^{(2)}_{SW} \ln g^{(2)}_{SW}\, d\mathbf{r}_1\, d\mathbf{r}_S\, d\mathbf{p}_1\, d\mathbf{p}_S\, d\omega_1\, d\mathbf{J}_1 - \tfrac{1}{2}k - \frac{k}{2\sigma^2}\int f^{(3)}_{SWW} \ln \delta g^{(3)}_{SWW}\, d\mathbf{r}^2\, d\mathbf{r}_S\, d\mathbf{p}^2\, d\mathbf{p}_S\, d\omega^2\, d\mathbf{J}^2 - \tfrac{1}{6}k + \ldots \tag{40}$$

with the major contribution coming from the two-particle term, which can be further developed as follows:

$$\Delta S_{2p} = -\frac{k}{\sigma}\int f^{(1)}_W f^{(1)}_S g^{(2)}_{SW} \ln g^{(2)}_{SW}\, d\mathbf{r}_1\, d\mathbf{r}_S\, d\mathbf{p}_1\, d\mathbf{p}_S\, d\omega_1\, d\mathbf{J}_1 - \tfrac{1}{2}k$$

$$= -\frac{k}{\sigma}\int p(\mathbf{r}_1,\omega_1)\, p(\mathbf{r}_S) g^{(2)}_{SW} \ln g^{(2)}_{SW}\, d\mathbf{r}_1\, d\mathbf{r}_S\, d\omega_1 - \tfrac{1}{2}k \tag{41}$$

For a homogeneous system, $p(\mathbf{r}_1,\omega_1) = (N-1)\sigma/V\Omega$ and $p(\mathbf{r}_S) = 1/V$. Substituting these and performing the integration over $\mathbf{r}_S$, we obtain

$$\Delta S_{2p} = -\frac{k(N-1)}{V\Omega}\int g^{(2)}_{SW} \ln g^{(2)}_{SW}\, d\mathbf{r}_1\, d\omega_1 - \tfrac{1}{2}k \tag{42}$$

The radial distribution function $g^{(2)}_{SW}$ depends on the distance r between solute and solvent (the oxygen nucleus is taken as the center of the water molecule) and the orientation of the solvent. The orientation of a nonlinear molecule, such as water, is fully described by three angles. The definition of these angles is given in Figure 1. One of them (θ) is defined as the angle between the dipole vector (OZ) and the solute–oxygen axis (Z). The second angle (χ) is defined as the angle between the hydrogen–hydrogen vector (H_1H_2) and the normal to the plane defined by Z and OZ.

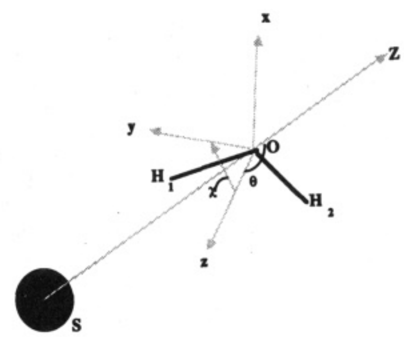

Figure 1. Definition of the angles used to describe the orientation of water molecules with respect to the solute S. xyz is the body-fixed coordinate system.

If we further define a coordinate system xyz fixed on the water molecule as in Figure 1, then θ and χ are recognized to be the Euler angles [ref 29, p 459] of this coordinate system with respect to a coordinate system XYZ whose Z axis coincides with the solute–water axis. The third Euler angle, ϕ, characterizes rotation around the Z axis. For a spherical solute the probability distribution will be uniform with respect to ϕ. Therefore the exact position of the axes X and Y is immaterial and we only need two angles to specify the relative orientation of a water molecule with respect to a spherical solute. The range of the angles will be 0–π for θ, 0–2π for ϕ, and 0–2π for χ. For χ, only the range 0–π produces distinguishable configurations due to the symmetry of water. However, since the symmetry number has been included explicitly in the derivation, the integration in eq 42 should be performed over the full range of χ, 0–2π.

We will now make a factorization "ansatz" for $g_{SW}^{(2)}$. We will assume that the orientational distribution is independent of distance within the first hydration shell and neglect orientational correlations beyond the first hydration shell:

$$g_{SW}^{(2)}(r,\theta,\phi,\chi) = g_{SW}^r(r)\, g(\theta,\chi,\phi) \qquad \text{for } r \le r_{sh} \tag{43}$$
$$g_{SW}^{(2)}(r,\theta,\phi,\chi) = g_{SW}^r(r) \qquad \text{for } r \ge r_{sh}$$

where g_{SW}^r is the orientationally averaged solute–oxygen radial distribution function and r_{sh} is the radius of the first hydration shell, defined by the first minimum of g_{SW}^r. The above approximation would certainly be poor for molecules of highly nonspherical shape, where the ability of these molecules to rotate varies rapidly with intermolecular distance. Water, however, is nearly spherical around the oxygen. Indeed, most water potentials have a single van der Waals interaction site located at the oxygen nucleus. Therefore, the rotation of water molecules is not inhibited by van der Waals repulsions, but only by electrostatic interactions, which vary smoothly with distance ($\sim 1/r$). The neglect of orientational correlations beyond the first hydration shell also appears justified based on neutron and X-ray diffraction data,[39] which show that orientational correlations in pure water die out much faster than positional correlations and are virtually nonexistent between second and higher nearest neighbors. It is reasonable to expect similar behavior for hydrophobic solute–water interactions which are much weaker. In any case, the above assumptions could be easily relaxed by calculating orientational distributions as a function of distance within and beyond the first hydration shell.

Since the orientational correlation function $g(\theta,\chi,\phi)$ will be uniform with respect to ϕ, we can set it equal to

$$g(\theta,\chi,\phi) = p(\theta,\chi)c$$

where c is a constant determined from the normalization condition of $g_{SW}^{(2)}$:

$$\int g_{SW}^{(2)}\, d\mathbf{r}_1\, d\omega_1 = V\Omega \tag{44}$$

Now, since

$$\int g_{SW}^{(2)}\, d\mathbf{r}_1\, d\omega_1 = \int_0^{r_{sh}} g_{SW}^r\, d\mathbf{r}_1 \int p(\theta,\chi)c\, d\omega_1 + \Omega \int_{r_{sh}}^{\infty} g_{SW}^r\, d\mathbf{r}_1 \tag{45}$$

we demand

$$\int p(\theta,\chi)c\, d\omega_1 = \Omega \tag{46}$$

so that

$$\int_0^{\infty} g_{SW}^r\, d\mathbf{r}_1 = V \tag{47}$$

Thus

$$c = \frac{\Omega}{2\pi \int p(\theta,\chi) \sin\theta\, d\theta\, d\chi} \tag{48}$$

(39) Narten, A. H. *J. Chem. Phys.* **1972**, *56*, 5681.

With this factorization ansatz we have separated the two-particle term into translational and orientational contributions:

$$\Delta S_{2p} = -\frac{k(N-1)}{V}\int g_{SW}^r \ln g_{SW}^r\, d\mathbf{r}_1 - \tfrac{1}{2}k - \qquad \text{(translational)}$$
$$\frac{k(N-1)V_i}{V\Omega}\int p(\theta,\chi)c \ln\{p(\theta,\chi)c\}\, d\omega_1 \qquad \text{(orientational)} \tag{49}$$

where $V_i = \int_0^{r_{sh}} g_{SW}^r\, d\mathbf{r}_1$. The quantity $(N-1)V_i/V = \rho_W V_i$, where ρ_W is the number density of water, is the coordination number of the solute.

The form of eq 49 allows a qualitative discussion of the factors that determine the entropy of solution. First, the residual entropy of solution is due to the introduction of translational and orientational correlations between the solute and the solvent molecules. For a solvent that does not orient preferentially with respect to the solute, $p(\theta,\chi)$ will be uniform ($p(\theta,\chi)c = 1$) and the orientational contribution will be zero. Water, however, is known to orient itself in such a way as to optimize its interaction energy with its water neighbors. This is expected to lower the entropy of solution according to the equation above.

It has been observed experimentally that a correlation exists between the solution thermodynamic properties and either the exposed surface area[40] or the number of water molecules in the first hydration shell.[2] The linear dependence of the orientational entropy on the coordination number is explicitly shown in eq 49. In addition, the translational entropy should depend on the size of the solute too. As the solute size increases, the peaks of the radial distribution function will move to greater separations and thus make a greater contribution to the integral. An alternative rationalization of this effect could be that the packing of solvent around the solute becomes "tighter" as the relative size of the solute grows,[41] thus restricting the "free volume" of the solute. This is exactly the effect accounted for by scaled particle theory, which nevertheless neglects entirely the orientational term.

Finally, since the normalization condition for g_{SW}^r is given by eq 47, the limiting value of g_{SW}^r at long separations should be unity and thus the integral of g_{SW}^r is local. Therefore, no corrections are needed for long-range contributions when this integral is calculated from computer simulations.

Application and Results

Equation 49 suggests a direct method of calculating the entropy of solution, at least within the superposition approximation: the distribution functions $g_{SW}^r(r)$ and $p(\theta,\chi)$ can be obtained by computer simulations. This method is illustrated here by application to a simple model system, methane in water. Monte Carlo (MC) simulations of one methane molecule in 215 water molecules have been performed using Jorgensen's BOSS program,[42] modified to calculate the required orientational distribution function. Methane was represented by a simple Lennard-Jones particle (σ = 3.73 Å, ϵ = 0.294 kcal/mol), while the TIP4P model[43] was used for water.

A sensitive test of the method should be the variation of entropy with temperature. Thus, we performed a number of simulations between 5 and 65 °C at a constant pressure of 1 atm. [Strictly speaking, the present formulation requires simulations at constant volume rather than pressure. We have verified, however, that this leads to no systematic differences in the calculated entropies.] This allows the calculation of the heat capacity increment from

$$\Delta c_p = \left(\frac{\partial \Delta H^*}{\partial T}\right)_P = T\left(\frac{\partial \Delta S^*}{\partial T}\right)_P \tag{50}$$

(40) (a) Hermann, R. B. *J. Phys. Chem.* **1972**, *76*, 2754. (b) Reynolds, J. A.; Gilbert, D. B.; Tanford, C. *Proc. Natl. Acad. Sci. USA* **1974**, *71*, 2925.
(41) Lee, B. *J. Phys. Chem.* **1983**, *87*, 112.
(42) Jorgensen, W. L. BOSS, version 2.8; Yale University: New Haven, CT, 1989.
(43) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.

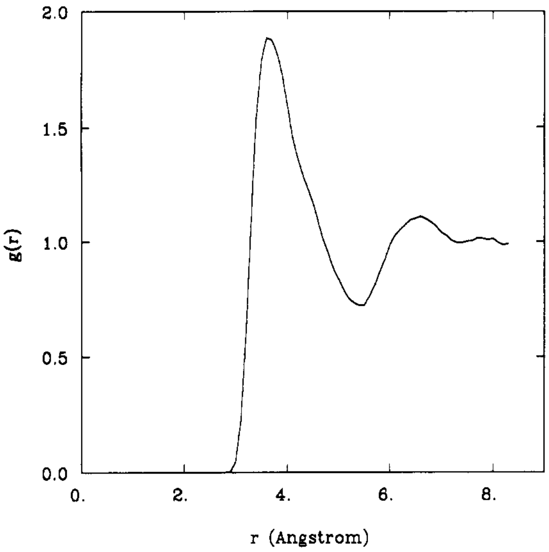

Figure 2. Methane–water oxygen radial distribution function at 25 °C.

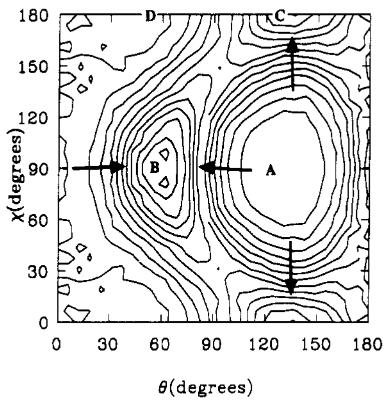

Figure 3. Contour plot of the calculated orientational probability distribution $p(\theta,\chi)$ of water molecules in the first hydration shell of methane at 25 °C. Arrows indicate the direction of increasing probability. Letters denote characteristic orientations: (A) hydrogen radially inward (θ = 125°, χ = 90°); (B) hydrogen radially outward (θ = 55°, χ = 90°); (C) lone pair radially outward (θ = ~125°, χ = 0°); (D) lone pair radially inward (θ = ~55°, χ = 0°).

Each MC run consisted of 5 million (or more) configurations for equilibration and 20 million for sampling, which was found adequate for convergence of the distributions. All simulations were performed on a SGI 4D-220 workstation. On this machine, 5 million configurations of our system took about 28 single processor CPU h. The preferential sampling[44] facility of BOSS was employed.

The calculated methane–water radial distribution function is shown in Figure 2. The size of the first hydration shell and the coordination number were found to be approximately the same at all temperatures (r_{sh} = 5.4 Å, N_{coord} = 20.25 ± 0.4). For the calculation of $p(\theta,\chi)$ a two-dimensional histogram was prepared with data taken from the first hydration shell. Because the probability distribution is symmetric around χ = 90 °C, the range of the histogram was 0–π for θ and 0–$\pi/2$ for χ. The probability distribution is obtained from this histogram after dividing by sin θ, to account for the dependence of the volume element on θ. To assess the systematic error arising from discretization and the artifical "roughness" in the calculated distribution, a number of interval sizes were used for the histogram: 3°, 6°, 10°, 15°, and 18°. According to the suggestion of Edholm et al.,[24] the best value of the entropy, S_0, can be obtained from the formula

$$S(n) = S_0 - nA + \frac{B}{n^2} \tag{51}$$

through a best fit of the constants S_0, A, and B to results $S(n)$ obtained with different numbers of intervals n. After we used this formula for a number of results, we found that the 6-deg interval was always closest to the best value, and we subsequently used the results for this interval. For the radial distribution function the interval 0.1 Å was used.

(44) Owicki, J. C.; Scheraga, H. A. *Chem. Phys. Lett.* **1977**, *47*, 600.

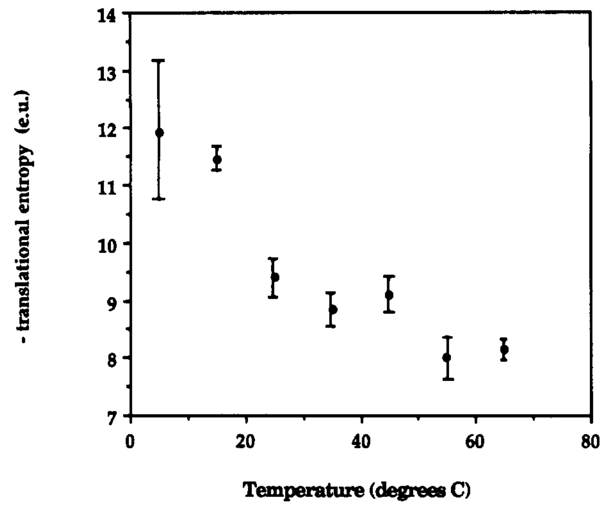

Figure 4. Translational contribution to the entropy of solution (in entropy units) as a function of temperature.

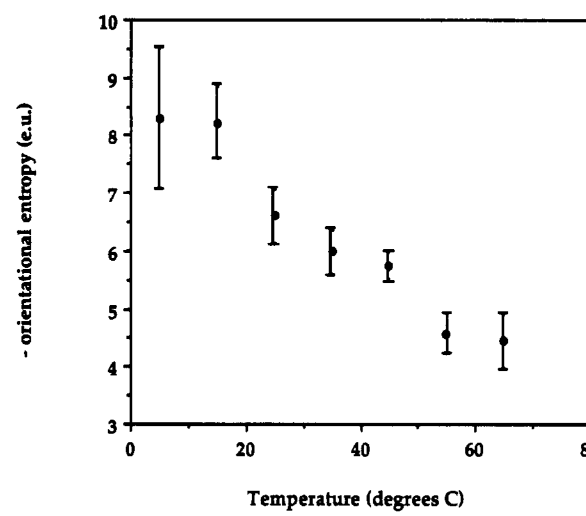

Figure 5. Orientational contribution to the entropy of solution (in entropy units) as a function of temperature.

The calculated orientational distribution function $p(\theta,\chi)$ at 25 °C is shown in Figure 3. The letters A–D denote characteristic orientations of the water molecules around the solute. From this figure it is concluded that the orientations where one of the vertices of the tetrahedral coordination of water is pointing outwards (B or C) are most probable, while those orientations where one of the vertices points toward the solute (A or D) are least probable. This is an expected result and has been observed in many previous simulations.[15] At 25 °C, the relative probability of the orientations is approximately 1:20:20:4 for A:B:C:D, respectively. The calculated orientational distribution was similar at all temperatures, while the peaks of the maxima become less pronounced at higher temperatures.

For the translational entropy in eq 49, we calculated the radial distribution function (RDF) up to a distance of 8 Å, assuming that beyond this distance the function takes its limiting value of unity. For internal consistency, we required that the integral of the RDF up to that point is equal to the volume of a sphere of radius 8 Å and enforced this by scaling the RDF by a constant. The results for the translational entropy are shown in Figure 4. All quantities are per mol of solute. The error bars were estimated here as the maximum deviation between the result from the full 20 million data points and those from different subsets of 15 million data points. The calculated orientational entropy is shown

TABLE II: Standard Entropy of Solution of Methane in Water at Several Temperatures Calculated by Monte Carlo Simulations [All Values in eu (1 eu = 1 cal/(mol·K)); Experimental Values Given in Parentheses]

T/°C	translational	orientational	total
5	−11.9 ± 1.2	−8.3 ± 1.2	−20.2 ± 1.7
15	−11.5 ± 0.2	−8.2 ± 0.6	−19.7 ± 0.6
25	−9.4 ± 0.3	−6.6 ± 0.5	−16.0 ± 0.6 (−15.94,[a] −15.43[b])
35	−8.8 ± 0.3	−6.0 ± 0.4	−14.8 ± 0.5
45	−9.1 ± 0.3	−5.7 ● 0.2	−14.8 ± 0.4
55	−8.0 ± 0.4	−4.6 ± 0.3	−12.6 ± 0.5
65	−8.1 ± 0.2	−4.4 ± 0.5	−12.5 ± 0.5
Δc_p at 25 °C	28.3	23.9	52.2 (56.6,[b] 50.0[c])
$\mathrm{d}\Delta c_p/\mathrm{d}T$ at 25 °C	−0.92	−0.31	−1.23 (−0.25,[b] −0.17[c])

[a] Reference 48. [b] van't Hoff analysis of gas solubility.[47] [c] Direct calorimetry.[45]

in Figure 5. The error bars were obtained as above. As expected, both contributions diminish with increasing temperature.

To obtain the heat capacity increment, the results were analyzed in exactly the same way as experimental data.[45,46] Using eq 50, the entropy is expanded in Taylor series around a reference temperature θ

$$\Delta S^* = \Delta S^*(\theta) + \frac{\Delta c_p(\theta)}{\theta}(T-\theta) + \frac{1}{2}\left[\frac{1}{\theta}\left(\frac{\mathrm{d}\Delta c_p}{\mathrm{d}T}\right)_\theta - \frac{\Delta c_p(\theta)}{\theta^2}\right](T-\theta)^2 + \ldots \quad (52)$$

Truncating the series at the third term and performing a least-squares fit, we obtain Δc_p(25 °C) = 52.2 cal/(mol·K) (28.3 translational and 23.9 orientational) and $(\mathrm{d}\Delta c_p/\mathrm{d}T)$(25 °C) = −1.23 cal/(mol·K^2) (−0.92 translational and −0.31 orientational). The experimental values are Δc_p(25 °C) = 50.0 ± 0.7 cal/(mol·K), $(\mathrm{d}\Delta c_p/\mathrm{d}T)$(25 °C) = −0.25 ± 0.05 cal/(mol·K^2) from direct calorimetry[45] and Δc_p(25 °C) = 56.6 ± 0.7 cal/(mol·K), $(\mathrm{d}\Delta c_p/\mathrm{d}T)$(25 °C) = −0.17 ± 0.14 cal/(mol·K^2) from van't Hoff analysis of gas solubility data.[47]

These results are summarized in Table II and plotted, along with experimental values, in Figure 6. The total entropy of solution at 25 °C is found to be −16 ± 0.6 eu, which is virtually identical to the experimental value (−15.94 eu[48]). This excellent agreement must be, at least in part, a result of cancellation of errors. The agreement is less satisfactory at other temperatures. This leads to an overestimation of the temperature dependence of the heat capacity increment.

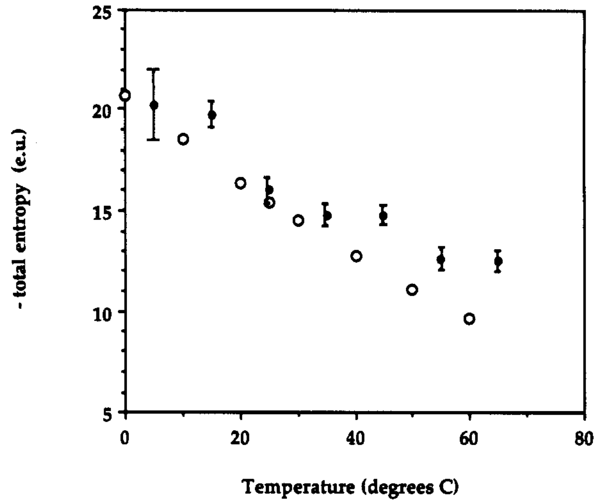

Figure 6. Total entropy of solution calculated by the present method (filled circles). Experimental values are indicated by the open circles (data from ref 47, after change of standard states).

Conclusions

Our statistical mechanical formulation as applied to methane in water allows two important conclusions to be drawn about the molecular origin of the large hydrophobic entropies of hydration.

(a) A significant portion of the entropy of solution (35–42%, see Table II) is due to reduced orientational options for water molecules interacting with the solute. It is important to note, however, that statements such as "hydration water has lower entropy than bulk water" are not strictly correct. The orientational entropy defined here refers to *correlations* between solute and water molecules and cannot be "assigned" to water alone (see also ref 48, p 2025). The existence of orientational preferences by no means implies that hydration water is less "mobile" or more "ordered" than bulk water, as suggested elsewhere.[13] Water molecules in the hydration shell of *another* water molecule will also exhibit strong orientational preferences, presumably the opposite of those observed next to nonpolar solutes.

(b) The contribution of translational correlations seems to be higher than in nonpolar solvents. For example, the standard entropy of solution of methane in CCl_4 is −1.7 eu (Table I) and that of xenon in a great number of organic solvents is on average −4.1 ± 0.5 eu.[49] The two-particle entropy of the Lennard-Jones fluid at high densities has been calculated to be −5.5 to −7 eu at reduced temperature 1.15.[26] Apparently, the small size of water is involved in increasing the translational contribution. Scaled particle theory would be expected to predict this effect with sufficient accuracy, since the translational term in the present formulation corresponds to the *entropy of solution in a fluid that has the density, packing fraction, and radial distribution function of water but no orientational degrees of freedom*. However, the fact that this theory has given entropies of solution as high as the experimental ones, while totally neglecting the orientational contribution, suggests that the translational contribution must be overestimated by SPT. The source of the error may lie with the use of the actual thermal expansion coefficient of water in the SPT formulas. Our calculations with SPT show that if the theoretical, hard-sphere expansion coefficient is used, the translational contribution does increase with size disparity between solute and solvent, but only moderately and not dramatically as in the original SPT calculations.[17,20] This issue will be addressed in a later publication. Within the present formalism, further work is needed to characterize the dependence of the translational contribution on relative solute–solvent size. To this end, simulations of a variety of solutes in water are currently underway in our laboratory.

The observed temperature dependence of solute–water orientational correlations suggests a mechanism for the change in the nature of hydrophobic hydration from entropic to enthalpic as the temperature is raised. If water molecules oriented randomly with respect to the solute, the orientational contribution to the entropy of solution would vanish and the enthalpy of solution would be positive due to the loss of hydrogen bonding interactions. This hypothetical solvent can be identified with what Frank called "inhibited water".[50] In actuality, water will seek an orientational distribution which corresponds to a state of minimum free energy. At low temperatures, enthalpic contributions to the free energy are more important and water molecules sacrifice orientational freedom in order to minimize interaction energy. This is consistent with Shinoda's statement that, at lower temperatures, water reorganization ("iceberg formation") enhances solubility.[51] As temperature is increased, however, entropic contributions to the free energy prevail and the orientational distribution becomes more

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and more uniform at the expense of enthalpy. Thus, the hydrophobic effect may appear entropic in some instances and enthalpic in others.

The numerical results from the present study at the superposition approximation level are judged to be quite satisfactory. We need to note, though, that the empirical potential used for water has been parametrized with data at 25 °C only,[43] and the degree to which it reproduces the structure of water at other temperatures is not known. This may be one reason for the discrepancies in the calculated entropies at higher temperatures (Figure 6). In any case, more work is needed to ensure that the agreement is not entirely fortuitous. First, the basic assumption, namely, the factorization of the radial distribution function, should be examined independently. Geiger et al.[15a] have reported that two different subshells of the first hydration shell are characterized by different orientational distributions. If this is the case, averaging over the whole hydration shell might result in an underestimation of the magnitude of the entropy. In contrast, no subshells in the radial distribution function could be discerned in this work (Figure 2), or in calculations by others.[52b] Zichi and Rossky[52b] also found no differences in orientational preferences within the first hydration shell and only a slight broadening of the peaks in the orientational distribution function. Furthermore, the distributions calculated by Geiger et al. appear quite noisy, and therefore the differences they observed may be due to inadequate sampling. The possibility of longer range orientational correlations, e.g. in the second hydration shell, should also be examined.

Second, the accuracy of the calculation of the translational entropy should be improved. This contribution is very sensitive to the values of the radial distribution function at relatively long separations, just before it reaches unity. Therefore, one needs very accurate estimates of the RDF at that range of separations. Finally, the contributions from the terms omitted in the entropy expansion in eq 40 should be examined. Particularly interesting would be the three-particle solute–water–water term, which should contain any "water-structure enhancement" effects. Structure enhancement or increased hydrogen bonding would be manifested in enhanced correlations between water molecules in the first hydration shell.[52] There has been conflicting evidence about this in the simulation literature. Alagona and Tani[15c] have calculated water–water radial distribution functions in the bulk and in the hydration shell of argon and found no appreciable difference. Differences, however, were observed in the calculations of Geiger et al.[15a] Several studies have found a slight enhancement in water–water interaction energy near nonpolar groups.[15a–c,52b] From the results of the present work, water-structure enhancement is not required to explain the large entropies of solution, in accord with Stillinger's view.[14] The major contributions to the entropy come from solute–water correlations.

As to the question of utility of the entropy expansion for practical, quantitative calculations, we believe that the conclusion of Baranyai and Evans[33] needs to be reexamined. In addition to improving the numerical accuracy of the calculations, another possible direction for future work would be to develop and test alternative factorization/reduction schemes for the N-particle correlation function.

Acknowledgment. We are grateful to Prof. R. H. Wood for numerous helpful discussions. We also thank Prof. W. L. Jorgensen for making the program BOSS available to us and Dr. Wallace for communicating to us unpublished results. This work was supported by the National Science Foundation (Grant CPE8351228). Partial support was also provided by Union Carbide, Merck, and Exxon.

Registry No. Methane, 74-82-8; water, 7732-18-5.

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Influence of Quantum Effects on the High-Pressure Phase Behavior of Binary Mixtures Containing Hydrogen

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The critical properties of binary mixtures containing hydrogen + argon, nitrogen, carbon monoxide, carbon dioxide, methane, and ethane are calculated and compared with experimental data. The properties of these mixtures are likely to be influenced by the quantization of translational motion at high densities. It is shown that the addition of a theoretically based quantum correction term to the equation of state can dramatically improve the quality of the agreement between theory and experiment. Even the simple van der Waals equation can then be used to calculate the critical properties of these mixtures with a reasonable degree of accuracy. The only additional experimental input data are the molecular weights of the constituent components. The experimental ξ_{12} parameters obtained from the analysis indicate weak interaction between the different component molecules of the mixture.

Introduction

The phase behavior of fluid mixtures is a direct manifestation of the influence of intermolecular interactions. The diversity of critical phenomena[1] is perhaps the most interesting aspect of the high-pressure equilibria of binary fluid mixtures. The nature of the critical line can be related, at least qualitatively, to the nature of the components. For example, binary mixtures constituted of components which differ substantially in size often exhibit liquid–liquid criticality,[2] and in some cases a discontinuity (i.e., type III or type IV behavior) is observed in the gas–liquid critical properties. This discontinuity of gas–liquid critical properties is frequently observed in mixtures containing at least one polar component such as water[3] or ammonia,[4] whereas a continuity of

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