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The Physical Origin of the Low Solubility of Nonpolar Solutes in Water

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Synopsis

Elementary but general statistical-mechanical relations are derived that relate the thermodynamic properties of the dissolution process to those of the pure solvent. A number of conclusions are drawn from qualitative arguments that these relations suggest. These include the following: (1) The low solubility of nonpolar solutes in water arises not from the fact that water molecules can form hydrogen bonds, but rather from the fact that they are small in size. (2) The large entropy decrease attending the transfer of an inert solute from a nonaqueous solvent to water is largely due to the decrease in entropy of the nonaqueous solvent as the solvent-solvent interaction is restored on removal of the solute from it. (3) It is improper to use values of thermodynamic quantities obtained from small-molecule transfer studies for those that involve macromolecular folding and interaction.

THEORY AND INTRODUCTION

The standard free-energy change on transferring a nonpolar molecule from the gas phase into a liquid solvent can be expressed as

$$\Delta\mu^* = G_c + G_i \quad (1)$$

where G_c is the work of forming a cavity in the solvent and G_i is the work done by the attractive forces between the solvent and solute molecules. Following Ben-Naim's suggestion,¹ we use standard states based on the molar concentration in both the gas and the liquid phases. Also, thermodynamic quantities are expressed on a molecular basis rather than on a molar basis, as is usual in thermodynamics.

The cavity term can, in turn, be written as

$$G_c = kT\nu \quad (2)$$

where k and T are the Boltzmann constant and absolute temperature, respectively. ν is given by

$$\nu = -\ln P_0 \quad (3)$$

where P_0 is the fraction of configurations in the ensemble of the pure solvent that happen to have the cavity region clear of any solvent molecules. The last equation is a rigorous statistical-mechanical relation between the work of constraining a system and the fraction of configurations in the ensemble of the unconstrained system that happen to have the constrained arrangements of molecules.^{2,3}

If G_i is assumed to be independent of temperature, other thermodynamic quantities of transfer can be written as follows:

$$\Delta h^\bullet = G_i - \sigma_{v,H}^2 \quad (4)$$

$$T\Delta s^\bullet = -G_i - \sigma_{v,H}^2 \quad (5)$$

$$\Delta c_p^\bullet = -\frac{\partial \sigma_{v,H}^2}{\partial T} \quad (6)$$

with

$$\sigma_{v,H}^2 = kT^2 \frac{\partial \nu}{\partial T} = \langle (\nu - \langle \nu \rangle) (H - \langle H \rangle) \rangle \quad (7)$$

Here, Δh^\bullet , Δs^\bullet , and Δc_p^\bullet are the changes in the standard enthalpy, entropy, and heat capacity, respectively, on transfer of a solute molecule from the gas phase into the liquid solvent, and the angled brackets, $\langle \rangle$, denote the ensemble average for the pure solvent. [The right-hand side of Eq. (7) is the ensemble average of the correlation between the fluctuations in ν and the total enthalpy, H , of the pure solvent. Since ν is not a mechanical variable, the fluctuation in ν is defined in the sense of Landau and Lifshitz,⁴ i.e., ν is considered to be an exact function of N , V and E , and the fluctuation in ν is considered to arise from the fluctuations of V and E in an N-P-T ensemble.]

These relations are rigorous and general. (The only assumption made is that the work done by the attractive forces between the solute and solvent molecules is insensitive to temperature.) Yet, their information content is not insignificant. Most important in this regard is Eq. (3), which relates a key thermodynamic quantity of the dissolution process, ν , to a property of the pure solvent, P_0 . The dissolution thermodynamics are thereby linked to the properties of the pure solvent, and ν and its temperature derivatives have a double meaning—first, as a thermodynamic property of dissolution and, second, as a property of the pure solvent. It seems that implications of these general relations have not been explored explicitly in the literature. The purpose of this paper is to bring out these implications in general terms, using as little specific theory as possible.

We use numerical results of a specific theory only in order to obtain rough estimates and general trends. For this purpose, we use the simple theory of Pierotti^{5,6}. The data used for this theory are sum-

marized in Table I, and the degree to which this theory reproduces the experimental values is shown by the numbers in Table II. The values given in Tables III and IV are calculated from this theory and used in support of the qualitative arguments presented.

THE FLUCTUATION CORRELATION TERM, $\sigma_{v,H}^2$

$\sigma_{v,H}^2$ is a compensation term: It may affect values of enthalpy and entropy significantly, even changing their signs, but does not affect the solubility in any way. Realization of the existence of such a term seems to have been a take-off point for Lumry and his co-workers on hydrophobicity.^{7,8}

Clearly, the fluctuation in v arises mostly from that of volume. (It is unlikely that P_0 will fluctuate as a result of energy fluctuation when density is fixed.) Now, the correlation between the volume and enthalpy fluctuation is given by the thermal expansion coefficient, α . Therefore, one expects $\sigma_{v,H}^2$ to be directly related to α (except with changed sign). This relation can indeed be derived in an analytical form if one uses the scaled particle theory.³

α is positive for normal solvents. Presumably, an increase in volume of these solvents causes an increase in the average distance between the solvent molecules and raises the potential energy of the system (see Fig. 1). For these solvents, $\sigma_{v,H}^2$ is therefore negative. Its magnitude can be roughly estimated by using the scaled-particle theory. As can be seen from the numbers given in Table III, it is substantial, being fully comparable to that of G_i when the solute is methane.

For water, however, α is zero at 4°C. It becomes positive above this temperature but remains exceptionally small compared with that of other solvents at moderate temperatures (see Table I). Thus, volume fluctuation is largely uncorrelated with energy fluctuation in this solvent at room temperature (see Fig. 1). This behavior is most certainly

TABLE I
Molecular Parameters and Physical Properties at 298.15 K^a

	σ (Å)	v (cm ³ /mol)	ϵ/k (K)	$\alpha_p \times 10^3$ (K ⁻¹)	ξ
Methane	3.70	—	157	—	—
Water	2.75	18.08	85.3	0.255	0.363
c-Hexane	5.63	108.75	573	1.214	0.517
Benzene	5.26	89.41	531	1.240	0.513
CCl ₄	5.37	97.09	536	1.226	0.503
Hydrazine	3.62	31.94	138	0.893	0.468

^a Hard sphere diameter σ , molar volume v , Lennard-Jones energy parameter ϵ/k , thermal expansion coefficient α_p , and the volume packing density ξ calculated from σ and v . Additional data used: polarizability of methane, 2.70 Å³, and dipole moments of water and hydrazine, 1.84 and 1.75 D, respectively. All data for σ , v , and ϵ/k are from Ref. 15 and those for α_p from Ref. 5, except for hydrazine; the α_p and dipole moment of hydrazine are from Ref. 16.

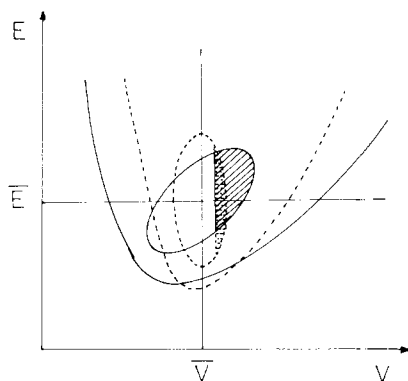


Fig. 1. Schematic drawing of the equipopulation contour of the phase space projected onto the energy-volume plane. This drawing is for illustrative purposes only and does not represent results of any simulation calculations. Solid line is for nonpolar solvent and broken line for water at 4°C. Shaded areas represent the subpopulation with high volume. Note that the average energy of the subpopulation is higher than that for the whole population for the nonpolar solvent but remains unchanged for water.

related to the tendency of the water molecules to form the characteristic tetrahedrally directed hydrogen bonds around themselves. An energy increase causes a breakdown of these hydrogen bonds, which then promotes more efficient packing of molecules and keeps the volume increase in check. Conversely, the small correlation also implies that liquid water can absorb a volume increase without much increase in energy. Presumably, the (fluctuating) hydrogen-bond network in water is highly adaptable and largely maintained when the volume of the system is altered. In other words, any hydrogen bonds that are broken on a volume increase, for example by forming a cavity inside the liquid, must be largely recovered in the form of "iceberg" or clathrate-like hydrogen bonds around the cavity. This type of behavior is, of course, to be expected in view of the strength of hydrogen bonds at room temperature. In any case, the exceptionally small value of α causes the magnitude of $\sigma_{v,H}^2$ to be correspondingly small for water compared to that for normal solvents.

From the point of view of dissolution thermodynamics, the $-\sigma_{v,H}^2$ term represents the increase in enthalpy associated with the destruction of solvent-solvent attractive interaction that accompanies the insertion of the cavity. In normal solvents, this term is large and substantially cancels the decrease in enthalpy, the G_i term, that results when the solute-solvent interaction is turned on (see Fig. 2). In contrast, the abnormally small value of $-\sigma_{v,H}^2$ for water at room temperature makes the net enthalpy change essentially the same as G_i , which is large and negative.

Turning now to entropy, we note that there are again two features that are important in determining the entropy change that accompanies the dissolution process. On the one hand, the process of insertion increases the volume of the system. The reduction in the solvent-

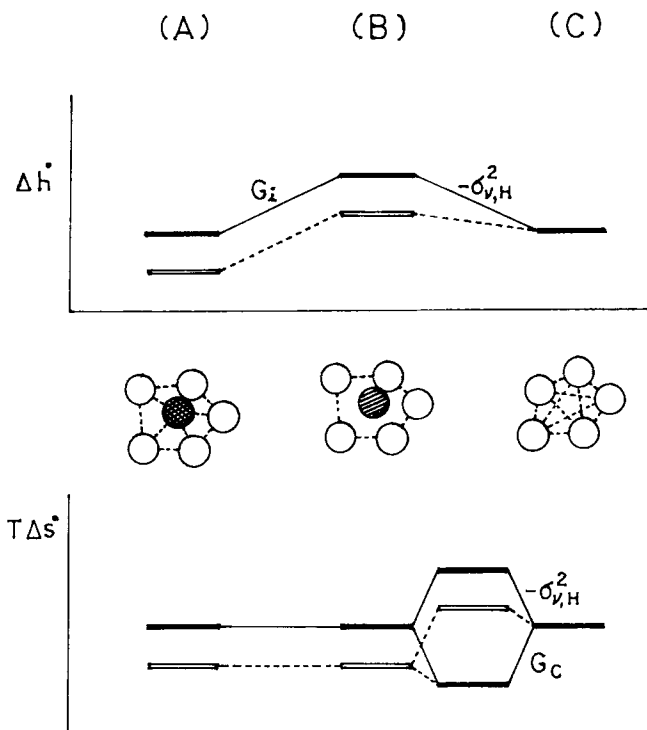


Fig. 2. Illustration of the origin of the terms that contribute to Δh^\bullet and $T\Delta s^\bullet$ of the transfer process. Solid line is for nonpolar solvent and the broken line for water, both with inert solute. For simplicity, we assume that the magnitudes of G_c , G_b and $-\sigma_{v,H}^2$ are all the same when the solvent is nonpolar. This is approximately the case when methane is the solute. (A) represents the (infinitely dilute) solution, (C) the pure solvent, and (B) the hypothetical intermediate state wherein the shaded circle represents a cavity of the size of the solute. The splitting in the level of $T\Delta s^\bullet$ between states (B) and (C) represents the two different causes that contribute to the entropy change. The entropy levels between states (A) and (B) may be different if temperature dependence of G_i is significant.

solvent interaction accompanying this volume increase causes a rise in entropy, the magnitude of which is given by the $-\sigma_{v,H}^2$ term. On the other hand, the process also restricts the number of arrangements possible for the solvent molecules. This causes a reduction in entropy, the magnitude of which is given by the G_c term. As in the case with enthalpy, the large decrease in entropy for the water solvent comes about as a result of abnormal lack of cancellation of the two contributions, which usually occurs with normal solvents. Presumably, the small value of $-\sigma_{v,H}^2$ for water indicates that, at room temperature, water molecules are fairly well tied down by the hydrogen bonds, even after the volume expansion. The restriction in the configuration of solvent molecules is still operative, resulting in a large net decrease in entropy.

As with Lumry,^{7,8} we believe the compensation term reflects the

uniquely characteristic hydrogen-bonding feature of water molecules. In our dissection scheme, however, this term reflects the degree of correlation in the fluctuation of energy and the volume of the pure solvent. It is the abnormal *smallness* of this term that produces the abnormal enthalpic and entropic behavior of the water solvent. In any case, we conclude, with Lumry, that the characteristic hydrogen-bonding property of water molecules does not directly affect the free energy (except indirectly by reducing the density, see below), since its effects on enthalpy and entropy precisely cancel each other. Thus, we must look elsewhere for the cause of the low solubility of nonpolar solutes in water.

Before considering the free-energy change of dissolution, we note one interesting result of the above interpretation. It is well known that when a nonpolar solute molecule is transferred from a nonpolar solvent to water, there is a large reduction in entropy. To say that this is caused by the formation of hydrogen bonds around the solute molecule in water tends to be misleading, since it leaves the false impression that additional structure is formed over and above that already present in pure water. However, the small value of the compensation entropy term, $-\sigma_{v,H}^2$, implies that the net amount of structure formed (or destroyed) in water is small. Rather, the above dissection scheme enables us to note that, notwithstanding the small difference in the G_c terms for the two solvents (see below), the decrease in entropy is caused primarily by the large difference in the $-\sigma_{v,H}$ term. Roughly speaking, this means that the decrease reflects the reduction in entropy of the *nonpolar solvent* as the solvent-solvent attractive interaction is restored on removal of the solute molecule from this solvent.

THE EFFECTIVE SOLVATION NUMBER, ν

Solubility is determined solely by the two terms G_c and G_i . We will not discuss G_i because consideration of this term requires detailed and specific theories. However, it may be noted that Pierotti's theory, which reproduces experimental values very well (see Table II), indicates that the G_i term is similar for all solvents (Table III) and is therefore unlikely to contain the essence of hydrophobicity.

It is well known³ that G_c can be calculated by counting the number of solvent molecules encountered by the solute cavity as it grows in size from nothing to that of the solute. Both the scaled-particle theory (Fig. 3) and the more realistic theory by Pratt and Chandler (as calculated from the numbers given in Table II of Ref. 9) show that this number, ν , is essentially proportional to the surface area of the solute. Clearly, this number is dominated by the number of solvent molecules bombarding the cavity at the last stages of its growth. It is effectively a solvation number.

TABLE II
Change in Chemical Potential, Enthalpy, and Entropy on Dissolution of a Mole of Methane in Several Solvents at 298.15 K^a

	$\Delta\mu^\bullet$	Δh^\bullet	$T\Delta s^\bullet$
Water	2.00	-2.61	-4.60
	1.61	-2.64	-4.24
c-Hexane	0.18	-0.21	-0.39
	0.09	0.03	-0.06
Benzene	0.34	0.07	-0.27
	0.26	0.28	0.03
CCl ₄	0.19	-0.34	-0.53
	0.08	-0.06	-0.14

^a All values refer to Ben-Naim's "local" standard state and given in kcal/mol. The experimental values, given in the first line for each solvent, are from Refs. 17 and 18 after appropriate change of standard states. The theoretical values calculated using Pierotti's procedure (Refs. 5 and 6) are given in the second line.

Regardless of the nature of the solvent-solvent interactions, and as long as the solvent is a liquid wherein molecules are free to move about, the solvation number about an inert solute must depend primarily on two geometrical properties of the solvent—its molecular size and the average packing density. The smaller the size and the higher the density, the higher the solvation number will be. Water is strikingly different in these geometrical properties from other common solvents. Water molecules are the smallest of all common solvent molecules. On the other hand, a water solvent has the lowest packing density, undoubtedly because of the unique hydrogen-bonding tendencies of water molecules. These two features should exert opposite effects on the value of ν . This is an important conclusion because it implies that hydrogen bonds, by decreasing the packing density of the solvent, actually *aids* the dissolution process and that the ultimate cause of hydrophobicity, i.e., the low solubility of inert solutes in water, must therefore be the small size of water molecules. Lucas¹⁰ reached the same conclusion earlier through the use of the scaled-particle theory. The importance of the small size of water molecules was also recognized in connection with the study of the partial molar volume.¹¹

TABLE III
Attractive, Cavity, and Fluctuation Correlation Terms Contributing to Thermodynamics of Dissolution of a Mole of Methane in Several Solvents^a

	G_i	G_c	$-\sigma_{v,H}^2$
Water	-3.42	5.02	0.78
c-Hexane	-3.74	3.83	3.77
Benzene	-3.88	4.14	4.17
CCl ₄	-3.72	3.80	3.66
N ₂ H ₄	-3.21	5.77	3.92

^a All entries are calculated values in kcal/mol at 298.15 K using Pierotti's procedure.

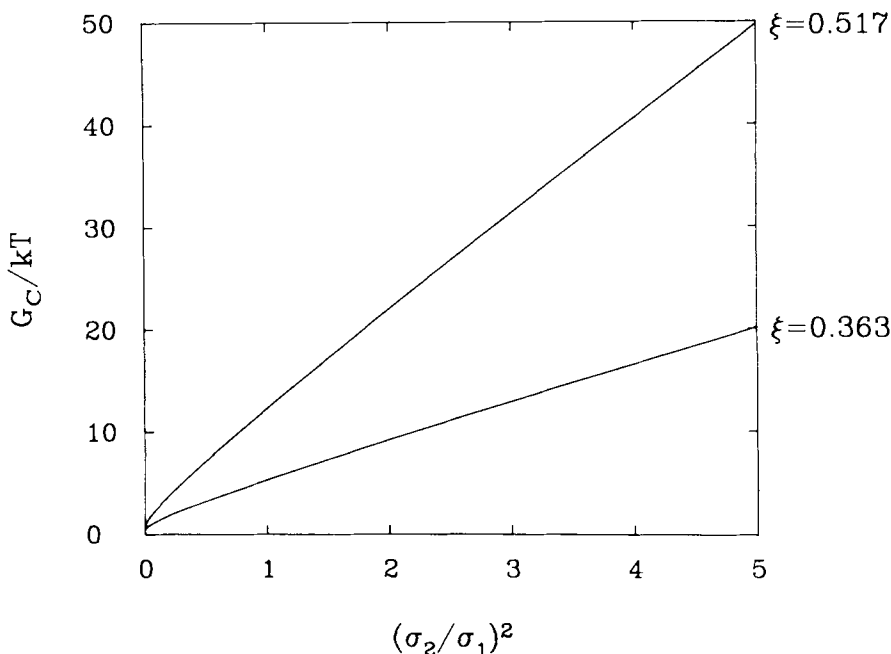


Fig. 3. Effective solvation number $\nu = G_c/kT$ as a function of the square of the solute-solvent size ratio at two different packing densities. The calculation is made using the scaled-particle theory at 298.15 K and 1 atm. The solvent packing densities chosen are for water (lower curve) and c-hexane (upper curve).

It is not possible to estimate the relative magnitudes of the size and density effects from qualitative considerations alone. Calculation by the scaled-particle theory shows that each of these effects is huge, and hydrophobicity depends on the precariously small residual difference between these two large effects (see Fig. 4 and Table IV). It is interesting to note that hydrazine is somewhat larger in molecular size than water but has a high packing density, nearly approaching that of common nonpolar solvents (Table I). The scaled-particle theory calculation predicts that the solubility of inert solutes in this solvent should be even smaller than that in water (Table III), which is in accord with the experimental result.⁷ It may also be predicted that inert solutes should exhibit solvophobic behavior toward other small molecule solvents, e.g., liquid methane (under high pressure in order both to keep it in liquid form at room temperature and to keep the packing density high).

TEMPERATURE DEPENDENCE OF $\sigma_{\nu,H}^2$

Continuing to neglect the temperature dependence of the G_i term, the change in heat capacity is given by the rate of change of $-\sigma_{\nu,H}^2$ with temperature. Since $-\sigma_{\nu,H}^2$ and α are related as discussed earlier,

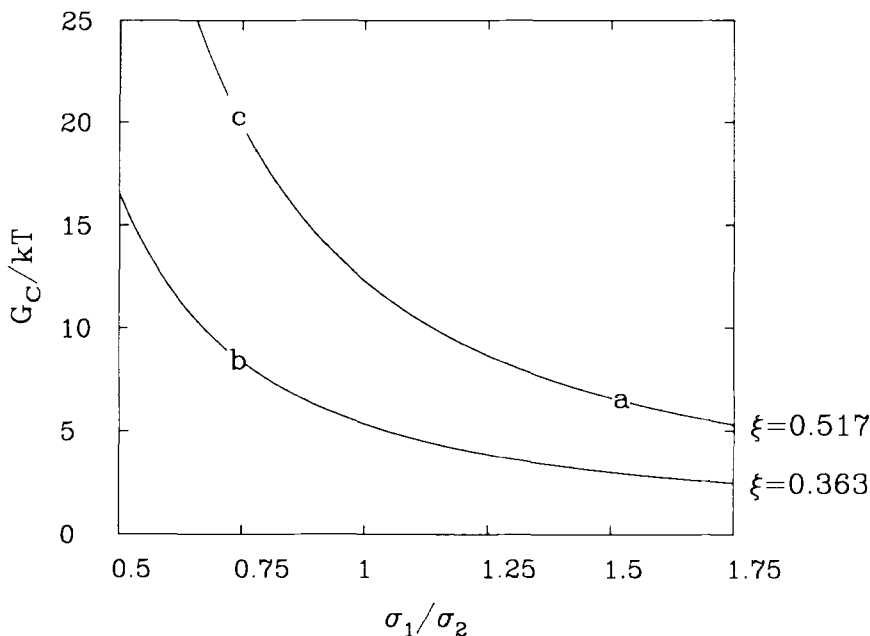


Fig. 4. Effective solvation number $\nu = G_c/kT$ as a function of the size and packing density of the solvent. The calculation is made using the scaled-particle theory at 298.15 K and 1 atm. The solvent packing densities chosen are as with Fig. 3. Point "a" is for dissolution of methane in c-hexane, "b" for the same in water, and "c" for the same in a hypothetical solvent, which has the same molecular size as water but the packing density of c-hexane. This hypothetical solvent has properties that water would presumably have if it were incapable of making the characteristic hydrogen bonds.

their temperature dependences are also likely to be similarly related. The abnormal temperature dependence of α on water is well known: α starts from negative values below 4°C, passes through zero at 4°C, and rises to values comparable to those of the normal solvents at high temperatures. This strong positive temperature dependence on the correlation between volume and energy fluctuations is clearly one

TABLE IV
Change in $\nu = G_c/kT$ on Transfer of a Methane Molecule from Various Solvents to Water Calculated by the Scaled-Particle Theory

From	$\Delta\nu_t^a$	$\Delta\nu_s^b$	$\Delta\nu_t^c$
c-Hexane	-11.77	13.78	2.01
Benzene	-11.28	12.78	1.49
CCl_4	-10.14	12.20	2.06
Hydrazine	-6.82	5.55	-1.26

^a Effect of the change in solvent packing density.

^b Effect of the change in solvent size.

^c Sum of the preceding two columns.

reason why the heat-capacity change is abnormally large with a water solvent.

In a more theoretical vein, it can easily be shown that

$$\frac{\partial \alpha}{\partial T} = [\sigma_{V,H^2}^2 - 2\alpha T - (\alpha T)^2]/T^2 \quad (8)$$

where

$$\sigma_{V,H^2}^2 = \langle \delta V \cdot (\delta H^2 - \langle \delta H^2 \rangle) \rangle \quad (9)$$

with $\delta V = (V - \langle V \rangle)/\langle V \rangle$ and $\delta H = (H - \langle H \rangle)/kT$. The right-hand side of Eq. (9) is an expression for the correlation between the volume fluctuation and the fluctuation in the breath of enthalpy fluctuation. The large value of $\partial \alpha / \partial T$ implies that this term is large (relative to αT and in comparison with the values for normal solvents). Thus, another way of stating the reason for the large heat-capacity change is that a volume increase in pure water causes an abnormally large increase in the extent of energy fluctuation, even while the average energy remains relatively unchanged.

Implications of the Hydrophobic Interaction Involving Macromolecules

Thermodynamic data obtained from the transfer processes are often used in applications involving hydrophobic interactions. As pointed out by Pratt and Chandler⁹ and others, however, hydrophobic hydration and hydrophobic interaction are two distinct concepts. The crucial feature of this distinction is that the transfer thermodynamics are determined as much by the properties of the nonpolar solvent as by those of water. The above discussions, especially those on entropy change, make this point abundantly clear. Hydrophobic interaction, of course, occurs in only one solvent, namely, water. The thermodynamic properties of these two processes will directly correlate only if one of the molecules in the solute molecular complex, formed in the aqueous solution by the hydrophobic interaction, can be regarded as a nonpolar solvent by itself. This is, of course, grossly improper if the solute is a small molecule.

The situation is better if the solute is a macromolecule whose size is large enough to provide an environment approximating a bulk phase. Even in this case, however, properties of the interior of the macromolecule may not be sufficiently similar to those of a bulk phase for the approximation to be useful. In the case of globular proteins, obvious major differences are the high density^{12,13} and the solidlike rigidity, as reflected by the low compressibility,¹⁴ of the protein interior. These differences make it difficult to justify general use of the

small-molecule transfer data in quantitative studies of multimeric protein association and protein folding. Such difficulty was pointed out earlier in connection with the study of partial molar volume.¹¹

References

1. Ben-Naim, A. (1978) *J. Phys. Chem.* **82**, 792–803.
2. Tolman, R. C. (1938) *The Principles of Statistical Mechanics*, Oxford University Press, London, Chap. 14.
3. Reiss, H. (1966) *Adv. Chem. Phys.* **9**, 1–84.
4. Landau, L. D. & Lifshitz, E. M. (1958) *Statistical Physics*, Addison-Wesley, Reading, Mass., Chap. 12.
5. Pierotti, R. A. (1963) *J. Phys. Chem.* **67**, 1840–1845.
6. Pierotti, R. A. (1965) *J. Phys. Chem.* **69**, 281–288.
7. Lumry, R., Battistel, E. & Jolicœur, C. (1982) *Faraday Symp. Chem. Soc.* **17**, 93–108.
8. Ramadan, M. S., Evans, D. F. & Lumry, R. (1983) *J. Phys. Chem.* **87**, 4538–4543.
9. Pratt, L. R. & Chandler, D. (1977) *J. Chem. Phys.* **67**, 3683–3704.
10. Lucas, M. (1976) *J. Phys. Chem.* **80**, 359–362.
11. Lee, B. (1983) *J. Phys. Chem.* **87**, 112–118.
12. Klapper, M. H. (1971) *Biochim. Biophys. Acta* **229**, 557–566.
13. Richards, F. M. (1974) *J. Mol. Biol.* **82**, 1–14. •
14. Gavish, B., Gratton, E. & Hardy, C. J. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 750–754.
15. Wilhelm, E. & Battino, R. (1971) *J. Chem. Phys.* **55**, 4012–4017.
16. Marsh, W. R. & Knox, P. B. (1970) USAF Propellant Handbooks Report AFRPL-TR-69-149, *Hydrazine Fuels*, Vol. 1, p. 2-3-1, Bell Aerospace Co., Buffalo, N. Y.
17. Rettich, T. R., Handa, Y. P., Battino, R. & Wilhelm, E. (1981) *J. Phys. Chem.* **85**, 3230–3237.
18. Wilhelm, E. & Battino, R. (1973) *Chem. Rev.* **73**, 1–9.

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