Solvent Size vs Cohesive Energy as the Origin of Hydrophobicity

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ABSTRACT

Two main physical explanations of hydrophobicity seem to be currently competing. The classical, intuitive view attributes it to the fact that interactions between water molecules are much stronger than those between water and nonpolar groups. The second, "heretic" view attributes it to the small size of the water molecule which increases the entropic cost of opening up a cavity to accommodate the solute. Here we examine the solvation of methane in water and in model liquids that lack one or more of water's properties and report a detailed decomposition of the solvation free energy, enthalpy, entropy, and heat capacity in these solvents. The results fully support the classical view. It is found that fluids with strong intermolecular interactions favor expulsion of methane to its pure phase or to CCl$_4$, whereas fluids with weak intermolecular interactions do not. However, the specific thermodynamic signature of the hydrophobic effect (entropy driven at room temperature with a large heat capacity change) is a result of the hydrogen-bonding structure of water.

1. Introduction

The term "hydrophobicity" is commonly used to describe the low solubility of nonpolar groups in water which leads to their aggregation in processes such as protein folding and micelle formation.[1] The thermodynamics of solvation of nonpolar groups in water (hydrophobic hydration) is well characterized.[2] The excess chemical potential (solvation free energy) is positive and increases with temperature. At room temperature the solvation entropy is negative and dominates the also negative solvation enthalpy. The heat capacity of solvation is large and positive

so that at high temperature hydrophobic hydration becomes dominated by enthalpy. Sometimes the meaning of "hydrophobicity" is extended to describe this peculiar thermodynamic behavior as well.

The classical qualitative explanation of the hydrophobic effect points to the strong hydrogen-bonding interactions (high cohesive energy density, or excess energy per volume) of water compared to the weak interactions between water and nonpolar substances.[1,3,4] When nonpolar groups are solvated in water, one would expect some strong water–water interactions to be replaced by weak water–nonpolar interactions; solvation should thus be unfavorable. Of course, this "regular solution" analysis is not consistent with the thermodynamic signature of the hydrophobic effect mentioned above; i.e., the solvation enthalpy is negative and it is the solvation entropy that makes the free energy positive at room temperature. This led Frank and Evans to invoke a vague "ordering" of water molecules around the nonpolar solute (the "iceberg" model[5]). Later it was discovered that water molecules adopt a clathrate-like arrangement around small, nonpolar solutes (e.g., ref 6). By adopting certain orientations, water molecules can maintain their four hydrogen bonds and thus avoid losing any energy. But this incurs a loss of entropy because it restricts the orientations that water molecules can have. At higher temperature, entropy is more important, and water molecules "prefer" to sacrifice hydrogen bonds for entropy. The facile switch from entropy dominance to enthalpy dominance is the source of the high heat capacity of hydration of nonpolar groups. These ideas are lucidly presented in a review by Dill[7] and are adopted in most physical chemistry and biochemistry textbooks. Although the specifics of this explanation differ from the strict regular solution view, the ultimate origin of hydrophobicity is, still, the high cohesive energy of water. Obviously, in this view the word "hydrophobic" is a misnomer; it would be more accurate to refer to water being "lipophobic".[8]

While the classical view has been more or less intuitive, the second ("heretic") view is based on the application of

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statistical mechanical theories to this problem. It proposes that the property of water responsible for hydrophobicity is its small size.[9,10] Opening up a cavity to accommodate the solute is entropically unfavorable in any solvent; it is essentially an excluded-volume effect. The very small size of water exacerbates the situation and gives rise to entropies more negative than in other solvents. The strong water−water interactions merely serve to keep water a liquid at ambient conditions. The first basis of these ideas came from the application of scaled particle theory to aqueous solutions.[9,11,12] It was found that the thermodynamics of solvation of nonpolar molecules in water could be reproduced without explicitly accounting for hydrogen bonding. The application of integral equation theory to the problem[13] or the more recent information theory model[14] also was successful in reproducing thermodynamic quantities without explicitly accounting for the orientational structure of water; these theories do account *implicitly* by using the experimental radial distribution function, density, compressibility, and thermal expansivity. Thus, they are not in conflict with the classical view. The heretic view was most clearly articulated and vigorously supported by Lee.[10,15] Madan and Lee[16] showed that the free energy of cavity formation (an essential step in solvation) is very similar in water and nonpolar liquids of the same size. Thus, hydrogen-bonding or strong solvent−solvent interactions do not appreciably affect the solvation free energy. Elsewhere, Lee proposed that the hydrogen-bonding properties of water do play a role in determining the enthalpy and entropy of solvation, but, due to enthalpy−entropy compensation, this effect cancels out and it is the size effect that essentially determines the free energy.[17] Similar ideas have been expressed by other authors using a perturbation theory approach to solvation free energies.[18,19] Durell and Wallqvist[20] studied the solvation of krypton in water and a model solvent of the same size without hydrogen bonds and concluded that the small size of water, rather than hydrogen bonding, is responsible for hydrophobic effects. Rank and Baker[21] studied the potential of mean force of two methane molecules in water and model liquids of varying solvent−solvent interactions and concluded that packing is more critical than hydrogen bonding. Although Pohorille and Pratt[22] showed that the work of cavity formation is ∼20% higher in water than in a hard-sphere (HS) fluid of the same size and packing fraction and found differences in cavity distributions between water and a Lennard-Jones fluid of the same size,[23] the relative importance of size vs cohesive energy has not been resolved.

This paper aims to defend the classical view by proving that the essential property of water that leads to hydrophobic aggregation is the strong water−water interactions and not its molecular size. To do that, we consider hypothetical liquids where one property is eliminated or varied while the others are maintained constant (to the extent that this is possible) and ask whether these liquids exhibit solvophobic association and what would be its thermodynamic characteristics. "Solvophobicity" is defined as a relatively unfavorable solvation free energy

which leads to solute aggregation (see below). If the elimination of a certain property leads to elimination of solvophobicity, this property is a *sine qua non* condition for solvophobicity. To isolate the effect of hydrogen bonding, we consider a Lennard-Jones (LJ) fluid with strong isotropic interactions. To examine the effect of cohesive energy density, we consider a fluid with the same LJ parameters as water but with all partial charges turned off. To examine the effect of size, we consider a scaled-up version of water with the same molar energy. As a model solute we choose methane. [This choice is dictated by the need for computational simplicity and comparison with previous studies. Hydration thermodynamics depends strongly on solute size and shape; see Conclusions.] We calculate the thermodynamic properties of solvation of methane in these model fluids using the "inhomogeneous functional" approach,[6,24−27] which gives a detailed decomposition of the solvation energy and entropy into solute−solvent and solvent−solvent contributions. We use recent results for simple model fluids[26] and water,[27] supplemented by some additional unpublished calculations.

2. Inhomogeneous Functional Approach

The solvation free energy (excess chemical potential) can be written in terms of Ben-Naim's local standard thermodynamic properties,[2] which correspond to insertion of the solute at a fixed point in the solvent at constant temperature and pressure:

$$\mu^{\text{ex}} = \Delta G^* = \Delta E^* - T\Delta S^* + P\Delta V^* \qquad (1)$$

The inhomogeneous functional approach decomposes the solvation energy and entropy into solute−solvent and solvent reorganization terms:[24]

$$\Delta E^* = E_{\text{sw}} + \Delta E_{\text{ww}}^{\text{corr}} \qquad (2)$$

$$\Delta S^* = S_{\text{sw}}^{\text{ord}} + \Delta S_{\text{ww}}^{\text{corr}} \qquad (3)$$

where the subscripts "s" and "w" stand for solute and solvent, respectively. The superscript "corr" denotes the fact that these terms refer to solute insertion at a fixed point (thermal motion of the solute gives rise to additional, "liberation" contributions, which are small in liquids). For pairwise additive potentials, eq 2 is exact but eq 3 involves the neglect of many-body correlations. This approximation was found to give reasonable results in HS and LJ fluids.[26] Explicit expressions for the terms in eqs 2 and 3 as integrals over correlation functions are given in ref 24. For example,

$$S_{\text{sw}}^{\text{ord}} = -k\frac{\rho}{\Omega}\int g_{\text{sw}}(\mathbf{r},\omega) \ln g_{\text{sw}}(\mathbf{r},\omega) \, d\mathbf{r} \, d\omega \qquad (4)$$

where ρ is the solvent density, g_{sw} the solute−solvent correlation function (a function of relative position ($\mathbf{r}$) and water orientation (ω)), Ω the integral over ω, and k Boltzmann's constant. This quantity can be further separated into translational and orientational contributions by

Table 1. Solvation of Methane in Water and Model Fluids at 25 °C^a

	WEAK	STRONG	STRONG′	TIP4P	water (exp)	LJCCL4
			Pure Fluid Properties^b			
e^{ex}	−0.435	−2.396	−2.396	−10.2	−10.5	−4.72
s^{ex}	−5.940	−3.974	−3.974	−13.6	−14.1	−8.07
μ^{ex}	5.424	−1.806	−1.806	−6.1	−6.3	−1.08
pressure (atm)	10537	∼0	∼0	1	1	772
			Methane Solvation			
E_{sw}	−2.40	−5.05	−2.85	−2.945		−3.44
ΔE_{ww}^{corr}	0.79	6.43	12.71	∼0		1.61
ΔE^*	−1.61	1.38	9.86		−2.75^c	−1.83
ΔS_{ww}^{ord}	−13.05	−3.16	2.69	−15.72		−7.42
ΔS_{ww}^{corr}	6.24	7.45	15.9	∼0		3.42
ΔS^*	−6.81	4.29	18.59		−15.94^c	−4.00
ΔC_p^*	6.9	19.5	47.9		50^e	9.1
	(4.1, −1.3, 4.1)^d	(25.7, −6.1, −0.1)	(14.6, 33.7, −0.4)	(1.5, 50, ∼0)		(4.2, 1.6, 3.3)
$P\Delta V^*$	6.78	−0.02	−0.037	∼0		0.81
ΔG^* (sum of above)	7.20	0.08	4.28	2.3^f	2^c	0.17
ΔG^* (test particle)	(8.7)^g	−0.19	2.53	2.3		0.44
			Pure Methane, Same TP			
μ^{ex}	7.76	∼0	∼0	∼0	∼0	

^{a} Energies and free energies in kcal/mol, entropies and heat capacities in cal/(mol K). The values for WEAK, STRONG, and LJCCL4 are obtained from Table 10 of ref 26, converted to Ben-Naim's standard state, except for the heat capacity and test particle results, which are calculated here. ^{b} For the LJ fluids from the LJ equation of state.[28] For water, see ref 2. For TIP4P, see ref 41. ^{c} Reference 2. ^{d} Numbers in parentheses are the contributions from E_{sw}, ΔE_{ww}^{corr}, and $P\Delta V^*$. ^{e} See ref 6. ^{f} Free energy simulation.[41] ^{g} Likely an overestimate. The calculation seems to not have converged.

factoring g_{sw} into the radial distribution function and the orientational correlation function:

$$g_{sw}(\mathbf{r},\omega) = g_{sw}^r(\mathbf{r})\, g_{sw}^{or}(\omega|\mathbf{r}) \qquad (5)$$

$$S_{sw}^{ord} = -k\rho \int g_{sw}^r(\mathbf{r}) \ln g_{sw}^r(\mathbf{r})\, d\mathbf{r} -$$
$$k\frac{\rho}{\Omega}\int g_{sw}^r(\mathbf{r})\, d\mathbf{r} \int g_{sw}^{or}(\omega|\mathbf{r}) \ln g_{sw}^{or}(\omega|\mathbf{r})\, d\omega \quad (6)$$

In all cases methane is modeled as a LJ particle with $\sigma_{ss} = 3.73$ Å and $\epsilon_{ss} = 0.294$ kcal/mol. The results reported here for the LJ fluids use correlation functions obtained from Percus−Yevick theory (correlation functions from Monte Carlo (MC) simulations are similar). The values of the thermodynamic properties of the pure LJ fluids, including the pure methane phase, are obtained using the LJ equation of state.[28]

3. Solvation Thermodynamics in Water and Model Fluids

The solvation thermodynamics of methane in water has been analyzed in detail using the inhomogeneous functional approach and MC simulations.[27] The calculation of E_{sw} and S_{sw} is straightforward and precise. The solvent reorganization terms were found to contain two large opposing contributions: one positive, arising from the fact that solvent molecules next to the solute have fewer other solvent molecules to interact with, and one negative due to enhanced local density of solvent next to the solute. The latter term is particularly negative in water due to its characteristic orientation next to small nonpolar groups. Unfortunately, the quantitative results for the solvent reorganization terms have substantial statistical uncertainty. In Table 1, we give approximate values based on the difference between E_{sw} and S_{sw} and the experimental

values for ΔE^* and ΔS^*. By doing this we include any many-body contributions to the entropy in ΔS_{ww}^{corr}.

Characteristic of water is that the solute−solvent terms at room temperature account well for the solvation energy and entropy. About half of the solute−solvent entropy is due to orientational correlations between the water molecules and the solute.[6,27] These orientational correlations are not a result of the solute−water interaction potential but are induced by the water−water interactions: water in the first solvation shell is oriented in such a way that it maintains its full hydrogen-bonding capacity. As a result, the solvent reorganization energy is close to zero. [Solvent reorganization energies for alkanes in water have been recently calculated by Gallichio et al. and found to range from 1.3 kcal/mol for methane to 6.7 kcal/mol for hexane.[29] This quantity depends strongly on the size and shape of the solute; see Conclusions.] For the same reason, the solvent reorganization entropy is close to zero.

The first model liquid (WEAK)[16] has the same LJ parameters as the TIP4P water model ($\sigma_{ww} = 3.15365$ Å, $\epsilon_{ww} = 0.155$ kcal/mol). This solvent has the same molecular size and density as water but lacks both the hydrogen bonding and the high cohesive energy density of water. As a result, it must be maintained at a high pressure. The solvation energy and entropy in this solvent are smaller in magnitude than in TIP4P (Table 1). S_{sw} is almost as large as in TIP4P, despite the lack of orientational correlations. This is due to tighter packing of this solvent around the solute (the first peak in the radial distribution function is 2.77 in WEAK vs 1.92 in TIP4P, see Figure 1). However, there is a positive solvent reorganization contribution that makes the total solvation entropy about half the S_{sw} value. The entropy slightly dominates over the energy, as in water.

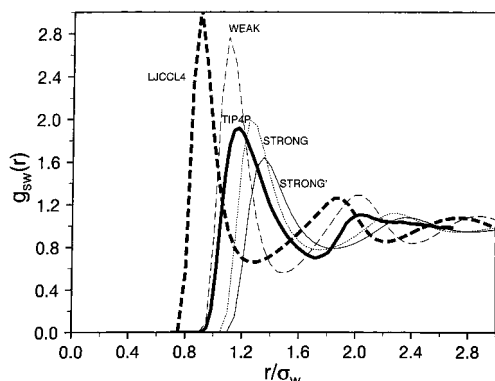The second model solvent[23] (STRONG) has LJ parameters adjusted so as to bring the pressure down to about

FIGURE 1. Methane–solvent radial distribution function. Thick continuous line, TIP4P; thick dashed line, LJCCL4; thin continuous line, STRONG′; thin dashed line, WEAK; thin dotted line, STRONG.

1 atm ($\sigma_{ww} = 2.67$ Å, $\epsilon_{ww} = 0.541$ kcal/mol). This model has the same size, density, and pressure as water but lacks the directional hydrogen-bonding interactions. It can be considered as some form of "isotropic" water. It should be noted, however, that its molar energy (-2.4 kcal/mol) is much smaller than that of water (-10.5 kcal/mol); a LJ fluid of the same molar energy as water would be a solid at room temperature. From Table 1 we see that STRONG is a peculiar solvent in that the solvation energy and entropy are *positive*. This is rarely observed experimentally and arises from the solvent reorganization energy and entropy, which are much more positive than in WEAK and water. The solvent–solvent interactions are isotropic in this solvent and cannot be restored around a solute by adopting specific orientations as in water. [These results are in disagreement with previous results,[20] where it was found that ΔE_{ww} for krypton is similar in water and in a LJ solvent similar to STRONG. We believe our method of calculating the reorganization energy is more reliable. The results of Ikeguchi et al.[30] also agree with ours]. S_{sw} is smaller in magnitude than in WEAK because of less "clustering" of the solvent around the solute (see Figure 1).

For TIP4P, WEAK, and STRONG, the methane–water LJ parameters are obtained as geometric means of those of methane and pure solvent ($\sigma_{sw} = 3.4297$ Å, $\epsilon_{sw} = 0.2135$ kcal/mol for TIP4P and WEAK, $\sigma_{sw} = 3.1558$ Å, $\epsilon_{sw} = 0.3988$ kcal/mol for STRONG). Therefore, the interaction of methane with STRONG is quite strong and does not reflect the weak solute–solvent interaction between nonpolar groups and water. Therefore, we introduce another model, STRONG′, which is identical to STRONG with respect to solvent–solvent interactions but interacts with methane as weakly as WEAK ($\sigma_{sw} = 3.4297$ Å, $\epsilon_{sw} = 0.2135$ kcal/mol). In this solvent, E_{sw} is similar to the value it has in WEAK and TIP4P. S_{sw} is now positive. This is due to a relative "depletion" (or "weak dewetting" [31,32]) of solvent from the vicinity of the solute so that the solute–solvent radial distribution function tends to be on average less than 1 (the first peak of the radial distribution function in STRONG′ is 1.64 vs 1.99 in STRONG, see Figure 1, and the number of solvent molecules within two solvent diameters is 17.07 in STRONG′ vs 18.18 in STRONG). The

same effect leads to solvent reorganization properties that are more positive than in STRONG. The solute–solvent interactions affect the solvent reorganization properties by influencing the distribution of solvent around the solute.

As a typical nonpolar solvent we chose CCl₄ because it is roughly spherical and can be approximately modeled as a LJ fluid (LJCCL4) with $\sigma_{ww} = 5.27$ Å, $\epsilon_{ww} = 0.7378$ kcal/mol. In LJCCL4, the energy of solvation is favorable and the entropy unfavorable. However, the magnitude of these properties is much smaller than in water, in accord with experimental results for CCl₄.[26]

Water exhibits the most negative solvation entropy of all solvents considered here. The origin of this large entropy has been a matter of debate. The heretic view proposes that this entropy is primarily a packing effect (translational entropy) and is particularly large in water due to its small size. That is, configurations with water molecules in the volume occupied by the solute are excluded, which reduces the entropy. This argument is valid for insertion at constant volume but not at constant pressure considered here since the solution expands to accommodate the solute. The entropy we report here for WEAK, a solvent with the same size as water, is much smaller. According to the inhomogeneous functional results,[6,25,27] the large negative entropy in TIP4P is a result of a large S_{sw}^{ord} due to the contribution of solute–solvent orientational correlations (8.3 of the 15.7 e.u.) and a small ΔS_{ww}^{corr}, due to water reorganization around a hydrophobic solute. Therefore, *the large magnitude of the entropy in water is determined primarily by its hydrogen-bonding structure and secondarily by its small size.*

The heat capacity of solvation in water is large. Because the computed solute–solvent energy in TIP4P does not change much with temperature, the heat capacity must be due to a large increase in the solvent reorganization energy with temperature (Figure 12 of ref 27). As the temperature increases, the orientational distribution of water molecules with respect to the solute becomes more uniform, and this leads to loss of water–water hydrogen bonding.

The solvation heat capacity for the LJ fluids is calculated as the temperature derivative of the solvation enthalpy:

$$\Delta C_p{}^* = \left(\frac{\partial \Delta H^*}{\partial T}\right)_P = \left(\frac{\partial E_{sw}}{\partial T}\right)_P + \left(\frac{\partial \Delta E_{ww}^{corr}}{\partial T}\right)_P + P\left(\frac{\partial \Delta V^*}{\partial T}\right)_P \quad (7)$$

The derivatives are approximated by finite differences from calculations at the same pressure and at 288.15 and 308.15 K. The heat capacity of solvation in WEAK is much lower than that in water. A positive contribution is made by the E_{sw} and PV terms and a negative contribution by the ΔE_{ww} term. The heat capacity of solvation in STRONG is intermediate between that in WEAK and that in water. In addition, it arises mostly from the solute–solvent energy term. Interestingly, the heat capacity in STRONG′ is almost as large as that in water, and a large fraction of it comes from the solvent reorganization term, as in water.

However, the mechanism for this is different: in water the high heat capacity is due to increased orientational freedom as temperature increases, but here it is due to increased depletion of the solvent around the solute with temperature (the number of solvent molecules within two solvent diameters is 17.87 at 288 K and 16.04 at 308 K).

4. Solute Expulsion at Constant *T* and *P*

A crucial element in our discussion is the criterion for deciding whether a given fluid will induce solvophobic aggregation of the solute. It is important to note that a positive solvation free energy is not such a criterion. Positive solvation free energies can arise even in ideal solutions. For example, solvation of a hard sphere in a liquid of hard spheres of the same size is accompanied by a positive free energy change. However, no "solvophobic" effect is operative here; this is an ideal solution. On the other hand, the hydration free energy of a solute is sometimes negative (e.g., benzene), and still the solute exhibits solvophobic aggregation because its solvation free energy in its own phase is even more negative. Therefore, "hydrophobicity" implies a relatively unfavorable hydration free energy which can lead to association of the particles or at least the expulsion of the particles into some other solvent.

One possible approach to measure aggregation is to consider the potential of mean force of two solutes, and particularly the depth of the contact minimum (e.g., ref 21). However, a contact minimum in the potential of mean force is not an infallible measure of solvophobic interactions. To invoke the ideal hard-sphere solution again, two hard-sphere solutes in a hard-sphere solvent of the same size will also have a contact minimum in the potential of mean force due to a trivial packing effect (all liquid-phase pair correlation functions exhibit oscillations due to packing). Separating this trivial packing effect from true solvophobic effects is not straightforward. Furthermore, significant differences exist between this "pairwise" interaction and the "bulk" hydrophobic interaction (transfer from water to a bulk nonpolar phase).[33] In this Account we shall adopt the latter as a measure of solvophobicity, i.e., the free energy of transfer of methane from the solvent under examination to the pure methane phase or to CCl_4 at the *same temperature and pressure*. We obtain the free energies by summing the entropic and enthalpic contributions calculated above. As an additional check, we perform test particle calculations.

First we consider expulsion of methane from each solvent to its own pure phase (be it a gas or a liquid) at the same temperature and pressure. The solvation free energy in WEAK is larger than that in water, in agreement with Madan and Lee;[16] most of it is due to the large *PV* term. At the pressure of WEAK, methane is a dense supercritical fluid with $\Delta G^* = 7.76$ kcal/mol, higher than the ΔG^* of methane in WEAK. Thus, the transfer of methane from WEAK to the pure phase is *unfavorable*.

STRONG, STRONG′, and water are at low pressure where pure methane is in the vapor phase with μ^{ex}, $\bar{e}^{ex}$,

$\bar{s}^{ex} \sim 0$ (nearly ideal gas). The solvation free energy of methane in water is about +2 kcal/mol; therefore, transfer is strongly favored. In STRONG the solvation free energy is close to zero; therefore, the transfer free energy is also close to zero. The solvation free energy in STRONG′ is 4.28 kcal/mol, higher even than that in water. This value is likely an overestimate; the test particle calculation gives only 2.53 kcal/mol. [The reason for the apparent overestimation of ΔG^* by the inhomogeneous functional method may lie in the underestimation of ΔS_{ww}^{ord} and ΔS_{ww}^{corr} due to the fact that the relative depletion of the solvent next to the solute is long-ranged; i.e., the radial distribution function is still slightly less than unity even 10 solvent diameters away from the solute.] This difference between STRONG and STRONG′ is entirely due to weakening the solute−solvent interactions. Transfer of methane from STRONG′ to its pure phase is clearly favorable. However, the thermodynamic signature of this behavior for STRONG′ is very different from that in water. Methane expulsion at room temperature would be *entropy driven* in water but *enthalpy driven* in STRONG′.

Next we consider transfer of methane from water to LJCCL4. The solvation free energy of methane in LJCCL4 is calculated to be 0.17 kcal/mol. However, LJCCL4 has a pressure of 772 atm at the experimental density of CCl_4. If we perform a constant *T,P* MC simulation of this fluid at 1 atm and then a test particle calculation, we obtain −0.36 kcal/mol. Therefore, transfer of methane from water and STRONG′ to it is favorable. Transfer from STRONG is only slightly favorable. At the pressure of WEAK, LJCCL4 is predicted to be well within the solid region of the LJ fluid phase diagram.[28] Indeed, simulation of LJCCL4 at that pressure leads to formation of a hexagonal close-packed crystal. A test particle calculation for methane insertion into this crystal gives $\Delta G^* = +17.5$ kcal/mol. Thus, transfer from WEAK to LJCCL4 at the same pressure is *unfavorable*.

A similar result is obtained using HS equations of state. Consider the transfer of a HS of $\sigma = 3.73$ Å from a HS fluid of $\sigma = 3.15365$ and $\rho = 0.033$ Å^{-3} to another one with $\sigma = 5.27$ at the same pressure. Using a HS equation of state (eq 22 of ref 26), we obtain $\Delta G^*/kT = 34.24$ in the small spheres and 35.46 in the large spheres; i.e., transfer from the small spheres to the large spheres is slightly *un*favorable. The condition of constant pressure is crucial in obtaining this result. Transfer at the same packing fraction ($\eta = \pi\rho\sigma^3/6$) favors the large spheres, but transfer at constant pressure does not (see also the discussion of this issue by Sharp et al.[34]).

Finally, we consider what would happen if water were larger in size with the same molar energy and at the same pressure. To do that we would scale the LJ σ parameter by a factor *f*, leaving ϵ the same, and increase the partial charges by a factor of $\sqrt{f}$ ($\sqrt{f}q_i\sqrt{f}q_j/fr = q_iq_j/r$). This scaling of the partial charges would maintain the relative importance of hydrogen bonding and the structural properties. Therefore, scaling up the size of the solvent is equivalent to scaling down the size of the solute. It is well known that this decreases the solvation free energy. But the

solvation free energy should remain positive, and expulsion of the solute to its pure phase would still be favorable. To confirm this prediction, we create a large-size version of the TIP4P model by setting $\sigma = 5.27$, scaling the bond lengths accordingly. We started from a box of TIP4P water and gradually changed the parameters while performing constant T,P MC simulation. In agreement with the above scaling scheme, by increasing the partial charges from $+0.52$ and -1.04 to $+0.67$ and -1.34, the molar energy remained the same (~ -10 kcal/mol), and the system equilibrated to a number density of 0.0073464 Å^{-3}. A test particle calculation done on 20 million configurations gave $\Delta G^* = 1.23$ kcal/mol, less than what was found in TIP4P (2.3 kcal/mol), but higher than what was found in LJCCL4, a nonpolar solvent of the same size. Thus, as predicted above, an increase in solvent size decreases but does not abolish hydrophobicity. This size effect is easy to rationalize within the classical view: as the solvent size increases, fewer solvent molecules are in contact with the solute. If water were not as small as it is, hydrophobic phenomena would not be as strong, but they would still be present.

5. Conclusions

These results show that the essential condition for solvophobicity in the systems studied here is that solvent−solvent interactions be much stronger than solute−solvent interactions. A small solvent size does play a role in enhancing the magnitude of the effect but is not a *sine qua non* condition. Experimental data seem to support this idea. For example, the fact that xenon is more soluble in alkanes than in alcohols of the same size[35] is consistent with the primacy of the cohesive forces.

The recent results for water,[27] partly summarized here, are fully consistent with the classical view of hydrophobicity.[7] The entropy of hydrophobic hydration at room temperature is larger than that in nonpolar solvents, mainly because of the strong orientational preferences of water molecules in the first solvation shell with respect to the solute. These preferences also diminish the solvent reorganization entropy from the large positive value expected from the excluded volume effect of the solute, to nearly zero at room temperature. Similarly, the solvent reorganization energy is close to zero at room temperature, and the main contribution to solvation energy comes from the solute−solvent interaction. The high heat capacity arises from the increased loss of water−water interactions as the temperature is raised. Thus, it is reasonable to say that at room temperature water structure is not "enhanced", but simply "maintained",[36] and is progressively "broken" as the temperature rises.

However, some refinement of the textbook descriptions is needed. The hydrophobic effect is not necessarily an entropic phenomenon; it can be enthalpic or entropic depending on the temperature and the geometric characteristics of the solute.[7,25,37,38] Methane is a rather atypical nonpolar solute because it can fit well into the water structure without much loss of water−water hydrogen bonding. Larger solutes are more prone to breaking the

water structure, giving rise to larger solvent reorganization energies[29] and smaller solvent reorganization entropies (enthalpy−entropy compensation). In a concave hydrophobic cavity, water molecules cannot maintain their full hydrogen-bonding capacity, no matter how they orient. Therefore, displacement of those water molecules will be accompanied by a favorable enthalpy. The origin of hydrophobicity is the same in all these cases, but its thermodynamic manifestation is different depending on the ability of the water hydrogen-bonding network to rearrange around the solute.

STRONG′ is also a solvent that could give rise to solvophobic phenomena, although with thermodynamic characteristics totally different from those in water. The *sine qua non* condition for solvophobicity is not hydrogen bonds but strong solvent−solvent interactions (note that micelle formation has been observed in fused salts and hydrazine[39]). Our results show that a fluid with strong, isotropic interactions could be more "lipophobic" than water because the strong solvent−solvent interactions would not be maintained around the solute. In this sense, the presence of directional interactions "helps" the dissolution process.[40] Hydrogen bonds enhance solubility compared to a fluid of isotropic interactions of similar magnitude but diminish solubility relative to a fluid with weak intermolecular interactions.

The argument showing that WEAK does not give rise to solvophobicity appears a bit artificial, since it involves the calculation of transfer free energies at extremely nonambient conditions. Indeed, solute transfer processes at this high pressure have little relevance to hydrophobic phenomena because their thermodynamic origin is different. For example, transfer of small solutes from WEAK to a solvent whose molecules could not pack closely would be favorable because it would lead to a reduction in total volume. However, this process is dominated by the volume change, unlike what is observed in hydrophobic association processes in biology, in which the volume change can be positive or negative.

The analysis of solvation thermodynamics from the point of view of cavity formation, as in the information theory model,[14] is perfectly valid and useful. It is true that the work of cavity formation does not differ much between water and hard spheres of similar size. However, the physical origin and the thermodynamic decomposition of this work can be very different. In hard spheres it consists of packing entropy and PV work. In water, it also includes contributions from loss of water−water interactions and orientational entropy.

It is often said that the hydrophobic effect is poorly understood. In contrast, we find that the classical, intuitive picture of hydrophobic hydration is basically correct. However, the modeling of hydrophobic interactions is not a trivial problem. Many important quantitative details need to be worked out, especially with regard to the hydrophobic interaction; for example, how the association between two, three, or more hydrophobic groups differs from transfer to a bulk nonpolar phase. Such differences may have important implications for the kinetic mecha-

nism of self-assembly phenomena, such as nucleation of protein folding. In developing quantitative models, approximate but detailed decompositions of the solvation energy and entropy like the one performed here may also be useful in developing a better physical understanding of these processes and in guiding the construction of models.

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