Solvent reorganization contribution to the transfer thermodynamics of small nonpolar molecules

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SYNOPSIS

The experimental thermodynamic data for the dissolution of five simple hydrocarbon molecules in water were combined with the solute–solvent interaction energy from a computer simulation study to yield data on the enthalpy change of solvent reorganization. Similar data were generated for dissolving these same solute molecules in their respective neat solvents using the equilibrium vapor pressure and the heat of vaporization data for the pure liquid. The enthalpy and the free energy changes upon cavity formation were also estimated using the temperature dependence of the solute–solvent interaction energy. Both the enthalpy and $T\Delta S$ for cavity formation rapidly increase with temperature in both solvent types, and the free energy of cavity formation can be reproduced accurately by the scaled particle theory over the entire temperature range in all cases. These results indicate that the characteristic structure formation around an inert solute molecule in water produces compensating changes in enthalpy and entropy, and that the hydrophobicity arises mainly from the difference in the excluded volume effect.

INTRODUCTION

In a previous study of hydrophobicity,[1] the process of transferring a small nonpolar molecule from the gas phase into a liquid was broken into two parts: the cavity formation and the attractive interaction. Factors that determine the relative magnitudes of the thermodynamic quantities for the cavity formation process were then considered qualitatively. It was concluded that the cavity enthalpy change should be smaller in water than in nonaqueous solvents because energy-volume fluctuation correlation is smaller in water, and that the cavity free energy change is larger in water because of the dominating influence of the small size of water molecules. Numerical values for these terms, as calculated using the scaled particle theory with methane as the solute, were shown to be consistent with this expectation.

In this article, we present "experimental" estimates for these terms. These are obtained by the difference between the experimental total change, and that due to the attractive interaction between the solute and the solvent. The latter cannot, in general, be obtained by purely experimental means. However, if one considers a pure liquid as a solution of a solute molecule in the solvent that happens to be of the same species as the solute, the attractive interaction energy should bear some simple relationship to the heat of vaporization of the pure liquid. This relationship can be used to estimate this quantity for the nonaqueous neat phase. For the aqueous phase, such a procedure obviously cannot be used since the solute and solvent molecules are of different species. For this case, we take the result from the large sample Monte Carlo simulations by Jorgensen et al.[2] Although computer simulation techniques do not yet yield a reliable estimate of the cavity enthalpy term, they provide a precise, and probably the best available, estimate for the solute-solvent interaction energy.[2] Nevertheless, our "experimental" estimates are not totally experimental and the quotes around the term indicate this fact.

The solute species chosen for this study are the simplest hydrocarbons for which both the experimental and the computer simulation data are available, and which have minimal number of internal degrees of freedom. The latter requirement was im-

posed in order to ensure that the heat of vaporization does not include a significant contribution from the conformational change of the solute molecule upon transfer. For the first two members of this series, methane and ethane, the critical temperature is too low for there to be a neat phase data at room temperature. Important species studied are therefore propane, isobutane, and neopentane.

The "experimental" data obtained were consistent with the qualitative reasoning in that the free energy of cavity formation was indeed much larger in water than in the hydrocarbon liquids and that the enthalpy change upon cavity formation was smaller in water than in the hydrocarbon liquids at room temperature. However, the difference in the enthalpy change was not as large as expected and, in fact, the sign of the difference reversed at higher temperatures. In addition, the scaled particle theory calculations faithfully reproduced the "experimental" cavity enthalpy values for the aqueous solution case but gave values that were much larger than the experimental values for the hydrocarbon case. These observations indicate that the temperature dependence of the solute–solvent interaction energy is not negligible in the hydrocarbon phase. Significant temperature dependence indicates that the solute–solvent interaction causes reorganization of the solvent and that the enthalpy change accompanying this reorganization is significant. The magnitude of this effect can be estimated from the temperature dependence of the heat of vaporization under reasonable approximations. When this term is subtracted from the total solvent reorganization enthalpy change, the cavity enthalpy term that results is indeed much larger than that in water and is in good accord with the scaled particle theory calculations.

We begin in the next section with a description of the standard states followed by a rather detailed description of the procedure and terminologies employed. Terms such as the "structure" of liquids, "structure" of water, and "iceberg" have been used by different authors with different meanings. In order to avoid confusion with these terms, we define the term "solvent reorganization" by means of a set of precise statistical mechanical expressions. Not surprisingly, it is then found that the total change in enthalpy is the sum of the contribution from the solvent reorganization and the direct solute–solvent interaction energy. The solvent reorganization arises both in the cavity formation process and by the solute–solvent interaction. Results are compiled in several tables and figures. They are intended to give a relatively complete picture of both the solute size and the temperature dependences of the various thermodynamic quantities. A discussion section then follows.

THEORY

Choice of the Standard State

In considerations of transfer thermodynamics, Ben-Naim argued[3] that the "local standard" quantities based on the molar concentration have special advantages. This standard is defined by

$$\mu = \mu^{B} + RT \ln m, \qquad (1)$$

where the superscript B denotes Ben-Naim's local standard, μ is the chemical potential of the solute, R is the gas constant, T is the absolute temperature, and m is the molar concentration. This definition applies for all phases, including the gas, the liquid solution at any concentration, and the neat pure liquid phases. For transfer thermodynamics, the choice of Ben-Naim's local standard corresponds to choosing the origin of the coordinate system fixed at a solute molecule. In contrast, the use of the conventional standard states corresponds to choosing the coordinate system fixed to the laboratory, with respect to which the solute molecules move about. In the latter case, the standard free energy includes the translational entropy of the solute molecules, the magnitude of which depends on the total volume available to these molecules. For example, the change in the standard free energy upon transferring any solute species from the infinitely dilute c-hexane solution to the infinitely dilute aqueous solution is always 4.44 kJ/mole greater[4] in the conventional infinite dilution/mole fraction based standard state than in Ben-Naim's local standard. This is because the volume per solute molecule is larger in the c-hexane solution than in the aqueous solution at the same temperature, pressure, and concentration, if the latter is measured in mole fractions.

One characteristic of Ben-Naim's local standard quantities is that they depend on pressure as well as temperature, whereas the conventional standard state quantities are normally defined to be independent of pressure. For a liquid phase this difference is inconsequential as long as the pressure remains moderate. However, for the gas phase, Ben-Naim's standard includes the effect of gas phase imperfection. Since we are not interested in the gas phase except as a convenient reference, the inclusion of the gas phase imperfection in the standard quantities is an unnecessary nuissance. We therefore use a

modified Ben-Naim's standard, which is the same as Ben-Naim's local standard except for the gas phase, for which we take the ideal gas limit of Ben-Naim's standard.

For the pure liquid or the infinitely dilute solution, the mole fraction-based conventional standard state, denoted by the superscript $\bigcirc$, is defined by

$$\mu = \mu^{\circ} + RT \ln x \qquad (2)$$

where x is the mole fraction of the solute. Since the mole fraction in this case is related to the molar concentration by

$$x = m v_1, \qquad (3)$$

where v_1 is the molar volume of the pure liquid or solvent, our modified Ben-Naim standard, denoted by the superscript $\bullet$, is related to the conventional standard by

$$\mu^{\bullet} = \mu^{B} = \mu^{\circ} + RT \ln v_1. \qquad (4)$$

For the gas phase, the pressure-based conventional standard state is defined by

$$\mu = \mu^{\circ} + RT \ln(f/p^{\circ}) \qquad (5)$$

where f is the fugacity of the gas and p° equals one atmosphere, whereas Ben-Naim's local standard is given by

$$\mu = \mu^{B} - RT \ln v \qquad (6)$$

where v is the molar volume of the gas. The relation between these two standards is then

$$\mu^{B} = \mu^{\circ} + RT \ln(fv/p^{\circ}) \qquad (7)$$

which, in the limit of zero pressure, becomes

$$\mu^{\bullet} = \mu^{\circ} + RT \ln(RT/p^{\circ}) \qquad (8)$$

In terms of this modified Ben-Naim standard, the chemical potential is given by

$$\mu = \mu^{\bullet} + RT \ln(f/RT). \qquad (9)$$

For the process wherein a solute species is transferred from the ideal gas phase to its own pure liquid phase or to an infinitely dilute solution, the following relations then relate changes in the modified Ben-Naim's standard and those of the conventional ideal gas-unit mole fraction standard quantities:

$$\Delta G^{\bullet} = \Delta G^{\circ} - RT \ln(RT/p^{\circ}v_1) \qquad (10)$$

and by the Gibbs–Helmholtz equation,

$$\Delta H^{\bullet} = \Delta H^{\circ} + (1 - \alpha_1 T)RT \qquad (11)$$

where α_1 is the thermal expansion coefficient of the liquid or of the pure solvent.

Cavity and Solvent Reorganization Terms

It is convenient to consider the process of inserting a solute molecule at a fixed point in a solvent as that of introducing an external potential ψ. The change in the standard Gibbs free energy is related to ψ by[5,6]

$$\Delta G^{\bullet} = -kT \ln \langle \exp(-\psi/kT) \rangle_p \qquad (12)$$

where k is the Boltzmann's constant and the angle brackets indicate the ensemble average, i.e., for any quantity q that is well defined for a configuration $\mathbf{X}$ of the solvent molecules

$$\langle q \rangle_p = \frac{\displaystyle\int q(\mathbf{X}) \exp[-H(\mathbf{X})/kT] \, d\mathbf{X}}{\displaystyle\int \exp[-H(\mathbf{X})/kT] \, d\mathbf{X}} \qquad (13)$$

where $H(\mathbf{X}) = E(\mathbf{X}) + pV(\mathbf{X})$. Here $E(\mathbf{X})$ is the total interaction energy of the solvent molecules in the configuration $\mathbf{X}$, and p and V are the pressure and volume of the system, respectively. We will consider N-p-T fixed ensembles in this paper so that the pressure and temperature are fixed, whereas the volume varies over different configurations. The subscript p in Eqs. (12) and (13) indicates that the average is over the pure solvent ensemble. Notice also that the expressions for the free energy, enthalpy, and entropy changes given in this subsection are per molecule rather than per mole of the solute species.

The potential ψ can be broken into two parts according to the following expression;

$$\exp(-\psi/kT) = \zeta \exp(-\psi_a/kT) \qquad (14)$$

where $\zeta = \zeta(\mathbf{X})$ of a configuration is equal to zero or one depending on whether or not the hard core of any solvent molecule in this configuration "overlaps" with that of the solute molecule.[7] The ψ_a is the sum of the residual (attractive, additional) potential between the solute molecule and all the other solvent molecules in the given configuration. It can then be

readily shown[6] that the free energy expression (12) can be written as

$$\Delta G^{\bullet} = \Delta G_c + \Delta G_a \qquad (15)$$

where

$$\Delta G_c = -kT \ln \langle \zeta \rangle_p \qquad (16)$$

is the work of forming the cavity and

$$\Delta G_a = -kT \ln \langle \exp(-\psi_a/kT) \rangle_c \qquad (17)$$

is the work done by the attractive potential between the solute and the solvent molecules as ψ_a is "turned on" to the existing cavity. The subscript c in Eq. (17) indicates that the average is over the system with a cavity. This average is given by Eq. (13) except that each configuration $\mathbf{X}$ in the two integrals is weighted by an additional factor $\zeta(\mathbf{X})$. The changes in the standard enthalpy and entropy can be similarly broken into two parts—one due to the cavity formation and the other to the residual attractive potential.

Solvent reorganization contributes importantly to both of these parts. In this paper, the term "solvent reorganization" refers simply to any change in the probability density of solvent configurations. Thus, the solvent reorganization contribution to different thermodynamic quantities is defined by the following set of relations:

$$\Delta H_r = \int H(\mathbf{X}) [\rho'(\mathbf{X}) - \rho(\mathbf{X})] \, d\mathbf{X} \qquad (18)$$

$$\Delta S_r = -k \int [\rho'(\mathbf{X}) \ln(\rho'(\mathbf{X}))$$
$$- \rho(\mathbf{X}) \ln(\rho(\mathbf{X}))] \, d\mathbf{X} \qquad (19)$$

and

$$\Delta G_r = \Delta H_r - T\Delta S_r \qquad (20)$$

where the subscript r indicates the solvent reorganization contribution, $\rho(\mathbf{X})$ and $\rho'(\mathbf{X})$ are the probability densities, respectively, of configuration $\mathbf{X}$ of the solvent molecules before and after the introduction of a perturbation, such as inserting a cavity or turning on ψ_a. It can then be readily shown that changes in the thermodynamic quantities upon introduction of a cavity are entirely due to the solvent reorganization. Generally, the introduction of ψ_a also causes a reorganization of the solvent and one can easily prove that

$$\Delta H_a = \Delta H_{ar} + E_a \qquad (21)$$

$$\Delta S_a = \Delta S_{ar}, \qquad (22)$$

and

$$\Delta G_a = \Delta G_{ar} + E_a \qquad (23)$$

where the subscript r indicates the solvent reorganization contribution and

$$E_a \equiv \langle \psi_a \rangle_s \qquad (24)$$

The subscript s here indicates the ensemble average over the final solution, which is given by Eq. (13) except that each configuration $\mathbf{X}$ in the integrals is now weighted by an additional factor $\exp(-\psi/kT)$.

According to relation (23), ΔG_{ar} is the difference between the work (ΔG_a) and the mean (E_a) of ψ_a. A simple expression for this term can be found by noting that

$$\langle \exp(-\psi_a/kT) \rangle_c$$

$$= \frac{\displaystyle\int \exp(-\psi_a/kT) \zeta \exp(-H/kT) \, d\mathbf{X}}{\displaystyle\int \zeta \exp(-H/kT) \, d\mathbf{X}}$$

$$= \frac{1}{\langle \exp(\psi_a/kT) \rangle_s} \qquad (25)$$

It then follows from the definitions of ΔG_a and E_a that

$$\Delta G_{ar} = kT \ln \langle \exp(x/kT) \rangle_s \qquad (26)$$

where

$$x = \psi_a - \langle \psi_a \rangle_s \qquad (27)$$

By differentiating ΔG_a with respect to temperature, one obtains ΔS_{ar} in terms of ΔG_{ar},

$$T\Delta S_{ar} = T\Delta S_a = -T \frac{\partial G_a}{\partial T}$$

$$= -T \frac{\partial E_a}{\partial T} - T \frac{\partial \Delta G_{ar}}{\partial T} \qquad (28)$$

and by adding ΔG_{ar} to this expression, ΔH_{ar} in terms of the latter,

$$\Delta H_{ar} = -T \frac{\partial E_a}{\partial T} + \left(\Delta G_{ar} - T \frac{\partial \Delta G_{ar}}{\partial T} \right) \qquad (29)$$

By expanding Eq. (26) in Taylor series in x and ignoring terms of higher order than x^2, one obtains the following approximate relation:

$$\Delta G_{ar} = \sigma^2(\psi_a)/2kT \qquad (30)$$

where $\sigma^2(\psi_a)$ is the mean square difference between ψ_a and $\langle \psi_a \rangle_s$. This relation will be valid when the fluctuation of ψ_a around its mean value is small. For the hydrocarbon solutions in water at room temperature, Jorgensen et al.[2] report 0.2–0.3 kJ/mole for σ in their E_{sx} term. Since their E_{sx} term should correspond closely to our ψ_a, the square of this σ value may be taken as a reasonable estimate of $\sigma^2(\psi_n)$. The magnitude of ΔG_{ar} is then estimated to be 0.01–0.02 kJ/mole at 25°C, an entirely negligible range of values compared to the magnitude of E_a. Although the amount of fluctuation in ψ_a may be larger in the neat hydrocarbon phase, the ΔG_{ar} term is probably small in all cases. In this paper, this term and its temperature derivative will be assumed negligible. Notice that this approximation makes the solvent reorganization process upon "turning on" ψ_a an exactly compensating process, i.e., ΔH_{ar} and $T\Delta S_{ar}$ are equal to one another although not necessarily zero individually.

The final relations obtained after neglecting both ΔG_{ar} and $T\partial \Delta G_{ar}/\partial T$ terms are similar to those presented earlier.[1] (Note that the $\sigma^2_{r,H}$ term in the earlier work is the same as $-\Delta H_c$ term here.) The difference is that the $T\partial \Delta E_a/\partial T$ term was also neglected in the earlier work. As can be seen in the calculated data presented later, this term is not negligible in the hydrocarbon neat phase.

METHODS

The relations derived in the previous section were used to obtain (modified Ben-Naim) standard thermodynamic quantities for the process of transferring a nonpolar solute from the gas phase to the neat or aqueous solution phases. These quantities were computed for the total process and for its two subprocesses; the cavity insertion and the process of turning on ψ_a. The thermodynamic quantities for the latter subprocess was again broken into two parts: one that represents direct interaction energy E_a between the solute and solvent, and the other due to the attendant solvent reorganization. The methods used to calculate these quantities are detailed in the following two subsections—first for the transfer to the neat phase and the second for the transfer to the aqueous phase. The last subsection

describes some details of the scaled particle theory calculations.

Transfer to the Neat Solvent (g → n Process)

We assume that the gas phase obeys the virial equation of state,

$$pv = RT + Bp \qquad (31)$$

where v is the molar volume of the gas and B is the second virial coefficient, which is a function of temperature only. The fugacity can be computed in terms of p and B for such a gas. It can then be easily shown, using standard thermodynamic techniques, that the change in the molar standard Gibbs free energy upon transfer of a solute molecule from the gas phase to its own neat solvent phase is given by

$$\Delta G^\bullet = RT \ln(p_{equil}v_1/RT) + Bp_{equil}, \qquad (32)$$

where p_{equil} is the equilibrium vapor pressure. Similarly, the change in the molar standard enthalpy is given by

$$\Delta H^\bullet = -\Delta H_{vap} + (1 - \alpha_1 T)RT \\ + p_{equil}(B - B'T) \qquad (33)$$

where ΔH_{vap} is the heat of vaporization of the pure liquid (per mole) and B' denotes the temperature derivative of B. Pure liquid properties of the hydrocarbons were obtained from tabulated data[8] on volume, heat of vaporization, and equilibrium vapor pressure by four-point interpolation.

The solute–solvent attractive interaction energy E_a for the neat phase can be obtained from the heat of vaporization as follows. If the internal and external degrees of freedom are assumed separable, the molar enthalpy of a pure system will be given by

$$H = NE_i + (N - 1)E_a/2 + pv \qquad (34)$$

whether the system is a liquid or a gas, where N is Avogadro's number, E_i is the internal energy of a molecule, and E_a is the interaction energy of a molecule with all other molecules in the system. In terms of the difference between the liquid and the gas phases in equilibrium, one then has

$$-\Delta H_{vap} = N\Delta E_i + (N/2)\Delta E_a + p_{equil}\Delta v \qquad (35)$$

where -1 was dropped because it is small compared

to N. Now, it can easily be shown from expression (34) that, for a virial gas obeying Eq. (31), $(N/2)E_a = -pB'T$. Therefore, if it is assumed that the internal energy of a molecule does not change upon vaporization, E_a in the liquid phase is given by

$$E_a = (2/N)[-\Delta H_{vap} + RT$$
$$- p_{equil}(v_1 - B + B'T)] \quad (36)$$

E_a can be computed from this equation since all quantities on the right-hand side of this equation are available from experimental data.[8]

The total solvent reorganization contribution to the enthalpy change ΔH_r, was obtained by the difference between $\Delta H^\bullet$ and E_a. The temperature derivative of E_a was obtained from the slope of the quadratically interpolated curve for E_a and then used to calculate ΔS_{ar} and ΔH_{ar} according to Eqs. (28) and (29). [This procedure produces the temperature derivative of E_a along the gas–liquid equilibrium line instead of the strictly required constant pressure temperature derivative, which Eq. (36) does not supply. For this procedure to be valid, E_a must be assumed independent of pressure.] The free energy, enthalpy, and entropy changes for the cavity formation were then obtained by the difference between the total solvent reorganization contribution and that upon turning on the attractive potential alone.

Transfer to water (g → w Process)

For the transfer into water, the enthalpy and entropy changes at room temperature were obtained from the experimental data[9] after conversion into the modified Ben-Naim's standard according to relations (10) and (11). The temperature dependence

of these quantities were obtained using the heat capacity formula of Gill et al.[10]

The values of E_a were assumed to be the same as the E_{sx} values of Jorgensen et al.[2] These are the ensemble averages of the solute–solvent interaction energy obtained from large-scale Monte Carlo simulations of dilute aqueous solutions of simple solute molecules.

It is unfortunate that the values of E_a are available at one temperature only. However, its temperature derivative is probably small in the aqueous solution: it can be shown that, in general,

$$\frac{\partial E_a}{\partial T} = \frac{\partial \langle \psi_a \rangle_s}{\partial T} = \frac{\sigma^2(\psi_a) + \sigma^2(\psi_a, H)}{kT} \quad (37)$$

where

$$\sigma^2(\psi_a, H) = \langle (\psi_a - \langle \psi_a \rangle_s)(H - \langle H \rangle_s) \rangle_s \quad (38)$$

is the correlation between fluctuations in ψ_a and H. In the aqueous solution, it has already been pointed out that the $\sigma^2(\psi_a)/kT$ term is small. The correlation between fluctuations in ψ_a and H is likely to be small in aqueous solution since, unlike the neat phase, the nature of the forces that characterize these interactions, van der Waals for ψ_a and hydrogen bonding for H, is very different. Notice that this is also a compensation term and has no effect on the free energy change in any case.

For these reasons and for lack of experimental data, E_a for the aqueous solution was assumed independent of temperature. According to Eqs. (28) and (29), and again ignoring the ΔG_{ar} and $T\partial \Delta G_{ar}/\partial T$ terms, this amounts to assuming that $\Delta S_{ar} = \Delta H_{ar} = 0$. Other quantities were obtained from these quantities as for the case of the neat phase.

Table I   The Hydrocarbon Species Used and Some of Their Properties[a]

	NBP (°C)	T_c (°C)	p_{equil} at 25°C (atm)	σ (Å)	Accessible Surface Area (Å²)
Methane	−161.49	−82.60	—	3.73	132
Ethane	−88.63	32.18	41.33	4.39	160
Propane	−42.07	96.87	9.47	5.01	189
Isobutane	−11.72	134.99	3.47	5.40	209
Neopentane	9.5	160.62	1.69	5.80	230

[a] The first three properties listed are the normal boiling point (NBP), the critical temperature, and the equilibrium vapor pressure at 25°C of the pure liquid. These are from Ref. 8. The fourth property listed is the effective diameter of the molecule, chosen to make the volume of the molecule the same as that of the interlocking set of atomic spheres, each with the diameter equal to the Lennard-Jones σ parameter used by Jorgensen.[14] The last property is the accessible surface area of this interlocking set of atomic spheres. These were calculated using Lee and Richard's algorithm.[15] The size of the probe used to define the accessibility was 2.75 Å in diameter.

Table II   Changes in the Modified Ben-Naim's Standard Thermodynamic Quantities, the Solute–Solvent (Attractive) Interaction Energy, and the Solvent Reorganization Enthalpy, All in Units of kJ/mole

	$\Delta H^\bullet$	$T\Delta S^\bullet$	$\Delta G^\bullet$	E_a	ΔH_r
Transfer from gas phase to its own neat phase as indicated tempertaure and pressure					
Methane (−161.49°C, 1 atm)	−7.7	−2.6	−5.1	−14.7	7.0
Ethane (−88.63°C, 1 atm)	−14.0	−5.4	−8.7	−26.8	12.7
Propane (−42.07°C, 1 atm)	−18.1	−7.4	−10.7	−34.4	16.3
Propane (25°C, 9.50 atm)	−15.6	−6.9	−8.7	−26.7	11.1
Isobutane (25°C, 3.33 atm)	−19.2	−8.5	−10.6	−35.1	15.9
Neopentane (25°C, 1.69 atm)	−21.2	−9.2	−12.0	−39.6	18.4
Transfer from gas phase to water at infinite dilution at 25°C and 1 atm					
Methane	−10.9	−19.3	8.3	−12.1	1.2
Ethane	−17.2	−24.9	7.6	−20.1	2.9
Propane	−21.0	−29.2	8.2	−27.6	6.6
Isobutane	−21.9	−31.6	9.7	−32.7	10.8
Neopentane	−22.8	−33.3	10.5	−36.0	13.2

Scaled Particle Theory Calculation

The cavity terms calculated from the experimental and Monte Carlo simulation data as described above were compared with the results from the scaled particle theory.[4,11,12,13] For this calculation, the effective diameters of the hydrocarbon molecules were chosen such that the volume of the sphere was the same as that of the molecule when it is assumed to be a collection of interlocking atomic spheres whose diameters are given by the Lennard–Jones σ parameters used by Jorgensen et al.[2,14] The effective diameter used for water was 2.75 Å. These were assumed independent of temperature so that the temperature dependence arises solely from that of the density and the thermal expansion coefficient, which were obtained from the experimental data at each temperature.

RESULTS

Size Dependence

The solute species used for this study are listed in Table I along with some of their physical properties. These are five of the smallest alkane molecules with little internal degrees of freedom. Note that none of these are liquid at room temperature under atmospheric pressure. For the purpose of examining the size dependence, the methane and ethane data were calculated at their normal boiling points while the isobutane and neopentane data were calculated at

room temperature under their equilibrium vapor pressures. For propane, the calculations were done at both of these conditions. These data are listed in Tables II and III, and plotted in Figure 1 and 2 against their accessible surface area.[15]

Table III   The Enthalpy and Free Energy of Solvent Reorganization upon Formation of a Cavity of the Size of the Solute Molecules Indicated[a]

	Exp ΔH_c	SPT ΔH_c	Exp ΔG_c	SPT ΔG_c
Neat phase at indicated temperature and pressure				
Methane (−161.49°C, 1 atm)	14.0	6.3	9.6	7.1
Ethane (−88.63°C, 1 atm)	27.5	17.5	18.1	15.6
Propane (−42.07°C, 1 atm)	40.1	33.5	23.7	24.6
Propane (25°C, 9.50 atm)	48.5	46.5	18.0	20.4
Isobutane (25°C, 3.33 atm)	49.8	40.8	24.4	23.6
Neopentane (25°C, 1.69 atm)	51.7	44.1	27.6	27.5
Aqueous phase at 25°C and 1 atm				
Methane	1.2	3.3	20.4	21.3
Ethane	2.9	4.5	27.7	27.9
Propane	6.6	5.6	35.8	34.9
Isobutane	10.8	6.5	42.4	39.8
Neopentane	13.2	7.4	46.5	45.1

[a] The columns labeled "Exp" give the "experimental" estimates and those labeled "SPT" give the scaled particle theory estimates. All quantities are in kJ/mole units.
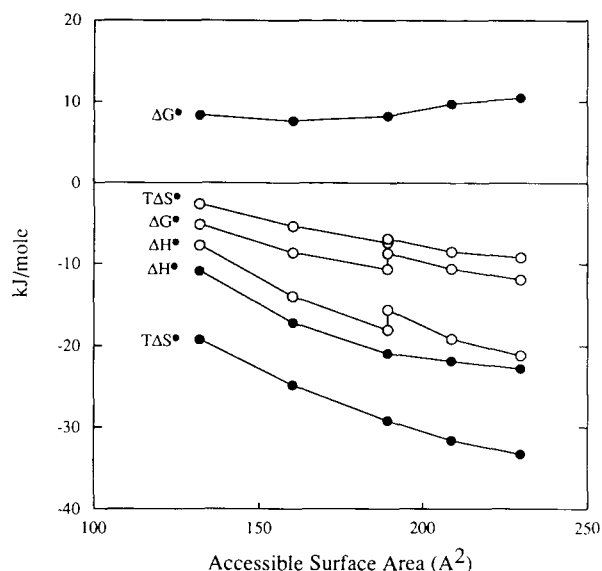
Figure 1. The surface area dependence of the changes in the modified Ben-Naim standard free energy, enthalpy, and entropy upon transfer of small hydrocarbon molecules from the gas phase into their own neat phase (open circle) and into water (solid circle). The solute species are, in increasing order of their accessible surface area, methane, ethane, propane, isobutane, and neopentane. The temperature and pressure of the transfer are as given in Tables II and III. Note that two points are plotted for the neat phase transfer of propane; the lower point is for the transfer at its normal boiling point while the upper point is for the transfer at 25°C under its own vapor pressure.

The break in trend seen for the g → n processes at propane is undoubtedly due to the fact that temperatures and pressures for the data for the first three entries are different from those for the last three entries. The magnitude of the break in ΔH_r is essentially half that of E_a. Since moderate pressure changes generally have little effect on the properties of a liquid, the primary cause for this break is presumably the difference in temperature. The significant temperature dependence of E_a in the hydrocarbon liquid is initially surprising in view of the fact that the solute–solvent attractive interaction potential parameters are not strong functions of temperature. However, E_a should depend on the density of the solvent, which is sensitive to temperature change for the hydrocarbon liquid. The large temperature dependence of ΔH_r in the neat phase is clearly seen in Figure 7 and will be discussed more fully later.

The standard thermodynamic quantities for the transfer to water also shows a smaller but clearly discernible break in trend at propane. In particular, the standard free energy change decreases with area

for small solutes but increases for the larger ones. This reversal in trend is unlikely to be due to experimental error: the solubility in water of many large gaseous species decreases with their size[16] whereas that of the noble gases increases with size.[17] Franks and Reid[18] noted this reversal in trend before and considered it as an evidence of clathrate-type structure formation around an inert solute molecule. Since molecules of interest in biological systems are considerably larger than methane, this phenomenon makes methane less than an ideal model for the study of the hydrophobic effect in such systems.

The entropy change for the transfer to water is large and negative (Figure 1). This decrease in entropy is commonly ascribed to the structure formation in water. Note, however, that the entropy change for the transfer to the hydrocarbon phase is also negative and significant, although smaller than that for the transfer into water. Another interesting feature is that the enthalpy of solvent reorganization in water is positive at room temperature (Figure 2). This appears to be opposite to what one would expect if "iceberg" or other such structures were formed around the inert solute. The solute–solvent interaction energy E_a is remarkably similar for the two kinds of solvents at room temperature.
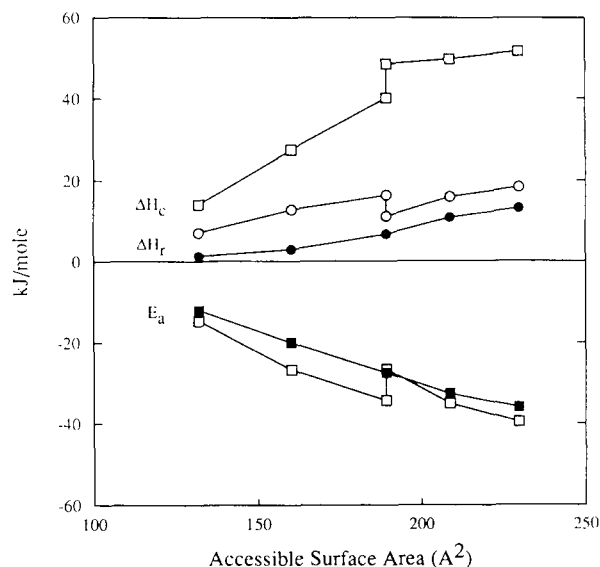

Figure 2. The surface area dependence of the solute–solvent (attractive) interaction energy (E_a, squares), the enthalpy of solvent reorganization upon dissolution of the solute (ΔH_r, circles), and the enthalpy of cavity formation (ΔH_c, squares). The open symbols are for the transfer to the neat solvents and the solid ones for the transfer to water. The solute species and transfer conditions are as for Figure 1.
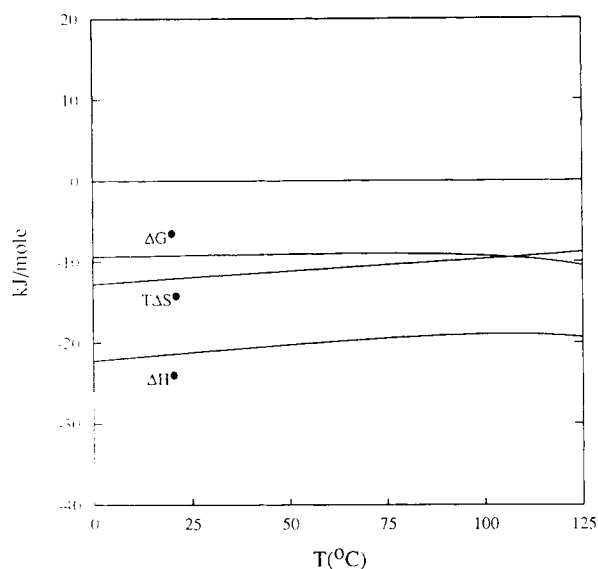
Figure 3. Temperature dependence of the changes in the modified Ben-Naim standard free energy, enthalpy, and entropy upon transfer of neopentane from the gas phase into its own neat phase.

Temperature Dependence of the Neat Phase to Water (n → w) Transfer Process

The calculated data at several temperatures are summarized in Tables IV and V. The two smallest species, methane and ethane, are not included in these tables because their critical temperatures are too low (Table I) and because these are too small to be proper models for biologically important mol-

Table IVb   Transfer Thermodynamics for Isobutane[a]

Temperature (°C)	$\Delta H^\bullet$	$T\Delta S^\bullet$	$\Delta G^\bullet$	E_a	ΔH_r
From gas to the neat phase at equilibrium vapor pressure					
0	−20.2	−8.7	−11.4	−37.9	17.7
25	−19.2	−8.5	−10.6	−35.1	15.9
50	−18.4	−8.5	−9.9	−32.2	13.8
75	−18.0	−8.8	−9.2	−29.0	11.0
From gas to the aqueous phase at 1 atm					
0	−31.8	−38.4	6.6	−32.7	0.9
25	−21.9	−31.9	9.7	−32.7	10.8
50	−13.1	−25.0	12.0	−32.7	19.6
75	−5.3	−18.9	13.6	−32.7	27.4

[a] All quantities are in kJ/mole units.

ecules (see above). All the figures, other than Figures 1 and 2, are for the largest species, neopentane, which serves as a representative example.

Figure 5 shows the difference in the standard thermodynamic quantities between g → n and g → w processes, corresponding to the transfer of neopentane from its neat phase to water (n → w process). This figure is similar to those reported for similar transfer quantities by Privalov and Gill.[19] The characteristic feature of this figure is the strong temperature dependence of enthalpy and entropy;

Table IVa   Transfer Thermodynamics for Propane[a]

Temperature (°C)	$\Delta H^\bullet$	$T\Delta S^\bullet$	$\Delta G^\bullet$	E_a	ΔH_r
From gas to the neat phase at the equilibrium vapor pressure					
0	−16.4	−7.0	−9.4	−29.7	13.3
25	−15.6	−6.9	−8.7	−26.7	11.1
50	−15.3	−7.2	−8.0	−23.3	8.1
75	−16.6	−9.4	−7.2	−18.7	2.1
From gas to the aqueous phase at 1 atm					
0	−29.8	−35.2	5.4	−27.6	−2.2
25	−21.0	−29.2	8.2	−27.6	6.6
50	−13.1	−23.4	10.3	−27.6	14.5
75	−6.1	−18.0	11.9	−27.6	21.5

[a] All quantities are in kJ/mole units.

Table IVc   Transfer Thermodynamics for Neopentane[a]

Temperature (°C)	$\Delta H^\bullet$	$T\Delta S^\bullet$	$\Delta G^\bullet$	E_a	ΔH_r
From gas to the neat phase at equilibrium vapor pressure					
0	−22.2	−9.4	−12.8	−42.3	20.1
25	−21.2	−9.2	−12.0	−39.6	18.4
50	−20.3	−9.1	−11.2	−36.7	16.5
75	−19.5	−9.0	−10.4	−33.7	14.2
From gas to the aqueous phase at 1 atm					
0	−33.4	−40.6	7.2	−36.0	2.6
25	−22.8	−33.3	10.5	−36.0	13.2
50	−13.3	−26.2	12.9	−36.0	22.7
75	−5.0	−19.6	14.6	−36.0	31.0

[a] All quantities are in kJ/mole units.

Table Va Cavity Enthalpy and Free Energy for Propane[a]

Temperature (°C)	Exp ΔH_c	SPT ΔH_c	Exp ΔG_c	SPT ΔG_c
Neat phase at equilibrium vapor pressure				
0	45.3	41.0	20.3	22.4
25	48.5	46.5	18.0	20.4
50	56.3	54.5	15.3	17.9
75	89.6	72.7	11.5	14.5
Aqueous phase at 1 atm				
0	−2.2	−1.2	33.0	32.2
25	6.6	5.6	35.8	34.9
50	14.5	11.5	37.9	37.2
75	21.5	17.1	39.5	38.9

[a] The columns labeled "Exp" give the "experimental" estimates and those labeled "SPT" give the scaled particle theory estimates. All quantities are in kJ/mole units.

Table Vc Cavity Enthalpy and Free Energy for Neopentane[a]

Temperature (°C)	Exp ΔH_c	SPT ΔH_c	Exp ΔG_c	SPT ΔG_c
Neat phase at equilibrium vapor pressure				
0	49.3	39.8	29.5	28.7
25	51.7	44.1	27.6	27.5
50	54.4	48.7	25.5	25.9
75	58.1	54.2	23.3	24.0
Aqueous phase at 1 atm				
0	2.6	−1.6	43.2	41.5
25	13.2	7.4	46.5	45.1
50	22.7	15.0	48.9	47.9
75	31.0	22.3	50.6	50.2

[a] The columns labeled "Exp" give the "experimental" estimates and those labeled "SPT" give the scaled particle theory estimates. All quantities are in kJ/mole units.

the free energy change is relatively independent of temperature. Figures 3 and 4 show that this strong temperature dependence is due to that of the g → w process. The reasons for the difference in the temperature dependence between g → n and g → w processes will be discussed later. Baldwin[20] and Murphy et al.[21] found that the temperature at which the entropy change is zero (T_s) and to a lesser extent, the temperature at which the enthalpy change is zero (T_h) are nearly the same for the n → w transfer process for many different solute species

Table Vb Cavity Enthalpy and Free Energy for Isobutane[a]

Temperature (°C)	Exp ΔH_c	SPT ΔH_c	Exp ΔG_c	SPT ΔG_c
Neat phase at equilibrium vapor pressure				
0	48.2	36.8	26.5	24.9
25	49.8	40.8	24.4	23.6
50	52.3	46.2	22.3	22.0
75	59.3	54.8	19.8	19.8
Aqueous phase at 1 atm				
0	0.9	−1.4	39.3	36.7
25	10.8	6.5	42.4	39.8
50	19.6	13.1	44.7	42.3
75	27.4	19.6	46.3	44.3

[a] The columns labeled "Exp" give the "experimental" estimates and those labeled "SPT" give the scaled particle theory estimates. All quantities are in kJ/mole units.

and possible reasons for this have been presented.[22] Our values (Table VI) for neopentane are indeed similar to those found by Baldwin. (The free energy maximum does not coincide exactly with T_s because the entropy and the free energy data come from independent experiments. The free energy maximum is rather broad so that the difference in the free energy at T_{gmax} and T_s is small in any case.) For smaller solutes they are considerably lower but this may be
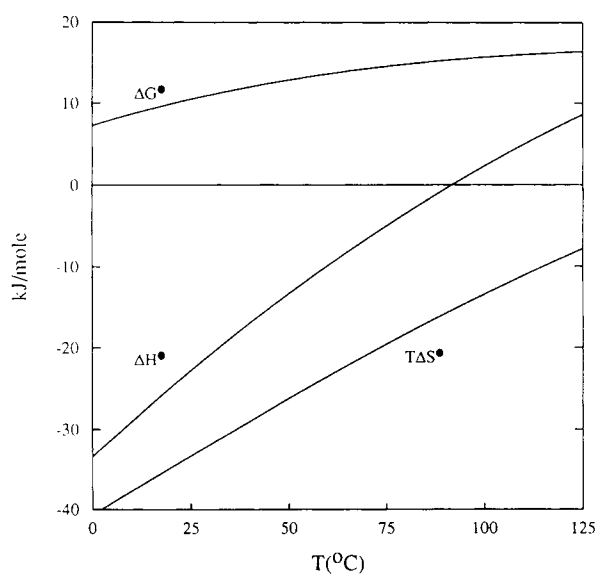

Figure 4. Temperature dependence of the changes in the modified Ben-Naim standard free energy, enthalpy, and entropy upon transfer of neopentane from the gas phase into water.
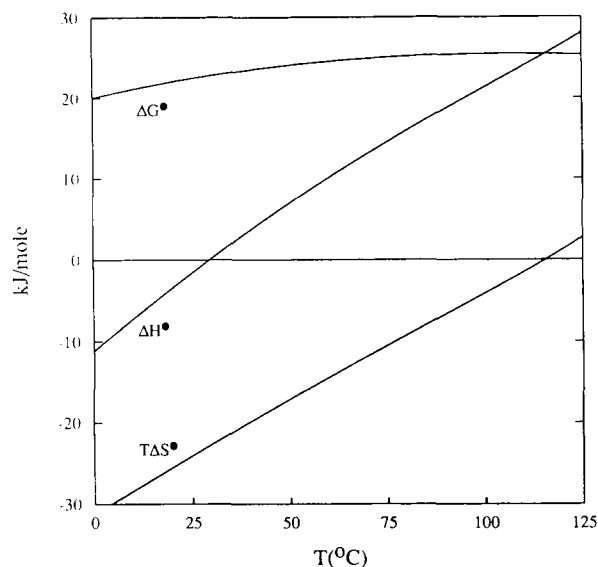
Figure 5. Temperature dependence of the changes in the modified Ben-Naim standard free energy, enthalpy, and entropy upon transfer of neopentane from its own neat phase into water.
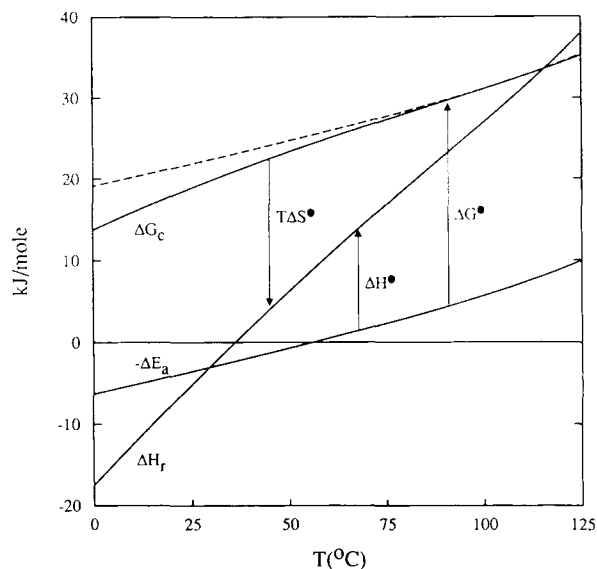

Figure 6. Temperature dependence of the changes in the cavity free energy, solute–solvent interaction energy, and the solvent reorganization enthalpy upon transfer of neopentane from its own neat phase into water. The standard thermodynamic quantities can be obtained as various differences between the plotted quantities as indicated in the figure. The dotted line is a line drawn parallel to the $-E_a$ line but that touches the ΔG_c line at the temperature where ΔG^* is maximum. The difference between this line and the ΔG_c line gives the variation of ΔG^* with temperature.

related to the fact that the critical temperatures are low for these species.

The changes in the cavity free energy and the solute–solvent interaction energy upon the n → w process are shown in Figure 6. When ΔG_{ar} is assumed negligible, the total free energy change is given by the difference between the ΔG_c and $-\Delta E_a$. The change in the solvent reorganization enthalpy upon this transfer process increases rapidly with temperature and cuts the $-\Delta E_a$ line at T_h and the ΔG_c line at T_s. Notice that the ΔH_r line serves to divide the nearly temperature independent total free energy change into its enthalpic and entropic components, each of which changes rapidly with temperature. The free energy change is not exactly constant over temperature; given the temperature dependence of $-\Delta E_a$, the free energy change would be constant if the ΔG_c line were parallel to the $-\Delta E_a$ line. The dashed line in the figure shows such a line, passing through the ΔG_c line at T_{gmax}. The difference between this line and the actual ΔG_c line shows the extent of the temperature dependence of ΔG^*. Privalov and Gill[19] pointed out that this difference could provide a mechanism for the cold denaturation of globular protein molecules.

Temperature Dependence of the Enthalpy of Solvent Reorganization

The ΔH_r for the n → w process is the difference between those for the g → n and g → w processes. These are shown as the bottom two curves in Figure

7. They behave qualitatively differently in that the g → n ΔH_r decreases whereas the g → w ΔH_r increases with temperature. The origin of this difference becomes readily apparent when the g → n ΔH_r term is broken into its two components, ΔH_c and ΔH_{ar}. These are shown as the upper two curves in Figure 7. They are both very large in magnitude; the total ΔH_r is relatively small only because these two terms have opposite signs. (The strong curvature at the high end of the temperature range is probably related to the fact that critical temperature is ap-

Table VI Characteristic Temperatures of the Hydrocarbon Species Studied[a]

	T_h (°C)	T_s (°C)	T_{gmax} (°C)	ΔG^*_{max} (kJ/mole)
Ethane	24	29	26	13.0
Propane	43	88	82	19.1
Isobutane	33	> 96	> 96	> 23.1
Neopentane	29	116	106	25.4

[a] T_h, T_s, and T_{gmax} are temperatures at which $\Delta H^* = 0$, $\Delta S^* = 0$, and ΔG^* is maximum, respectively, when the hydrocarbon species are transferred from their pure liquid phase to water. ΔG^*_{max} is the value of ΔG^* at T_{gmax}.
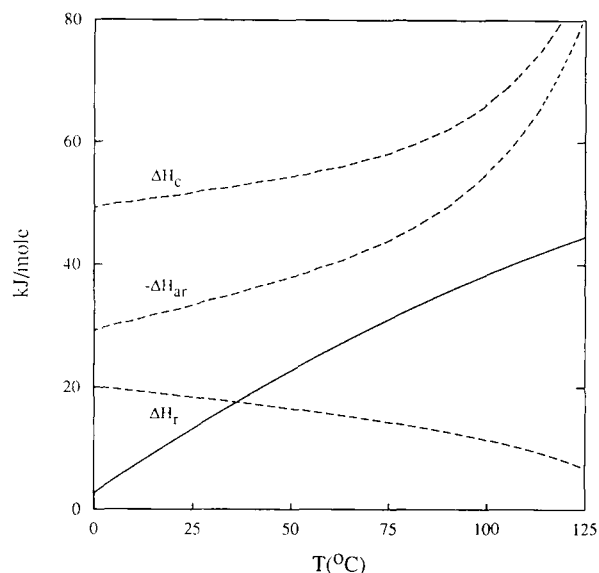
Figure 7. Solvent reorganization enthalpies for neopentane. Dotted lines are for the neat phase and the solid line is for the aqueous phase. Note that, under the approximations used in this paper, $\Delta H_{ar} = 0$ and $\Delta H_c = \Delta H_r$ for the aqueous phase.

proached at this temperature range.) Note that the ΔH_r term for the aqueous solution is all ΔH_c since the ΔH_{ar} term is assumed zero in this case (see the Methods section). Thus the qualitative behavior of the ΔH_c term is similar in the two solvents and the reason for the opposite behavior in the temperature dependence of ΔH_r is the difference in magnitude of ΔH_{ar} in the two solvents. That the ΔH_c term in the nonaqueous phase should be larger than that in the aqueous phase is as expected from earlier qualitative considerations.[1]

The various contributions to the total heat capacity change upon n → w process at 25°C are sum-

Table VII   The Changes in the Heat Capacity, in J/mole/°C Units, upon Transfer of Indicated Solutes from the Neat Phase to the Aqueous Phase at 25°C[a]

	ΔC_p (total)	ΔC_p (E_a)	ΔC_{par}	ΔC_{pc}	ΔC_p (SPT)
Propane	309	−126	275	160	−10
Isobutane	339	−114	152	301	97
Neopentane	363	−112	168	307	144

[a] The first column gives the total heat capacity change. The second, third, and fourth columns give the contributions from the difference in the temperature dependence of E_a, ΔH_{ar}, and the cavity enthalpy, respectively. The calculation assumes that E_a in water is independent of temperature. The last column gives the heat capacity change calculated from the scaled particle theory.

marized in Table VII. These were calculated from the slope of the least squares line that fit the ΔH_c, ΔH_{ar}, and ΔE_a data over the temperature range of 15–35°C. The calculation is not highly accurate because it depends on high-order temperature derivatives of E_a and because E_a in aqueous phase was assumed independent of temperature. The numerical values given in this table are, therefore, meant to give only a qualitative picture. Disregarding the data on propane, which are even more suspect because of the low critical temperature, the qualitative picture one obtains is that the total heat capacity change is still dominated by the cavity term; the heat capacity change upon "turning on" the attractive interaction is small because the temperature dependence of the enthalpy of the solvent reorganization is canceled by the opposite temperature dependence of the attractive interaction energy.

The Cavity Formation

The three thermodynamic quantities for the formation of the neopentane cavity in the neat phase is shown in Figure 8. That the enthalpy change is large and positive is not surprising since some solvent–solvent interaction must be broken in order to create the cavity. The entropy change is also substantial and positive at all temperatures, but always significantly less than the enthalpy change. The free energy change *decreases* with temperature, as it must since the sign of the entropy change is positive.
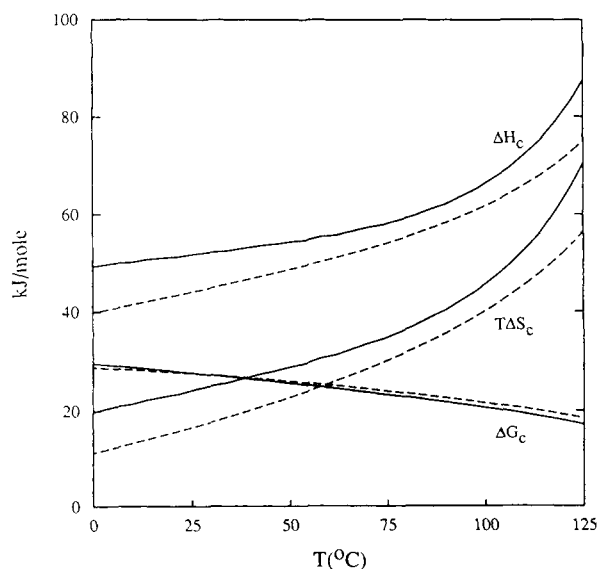

Figure 8. Cavity thermodynamics for neopentane in the neat phase. Solid lines are the "experimental" values. The dotted lines are calculated from the scaled particle theory.
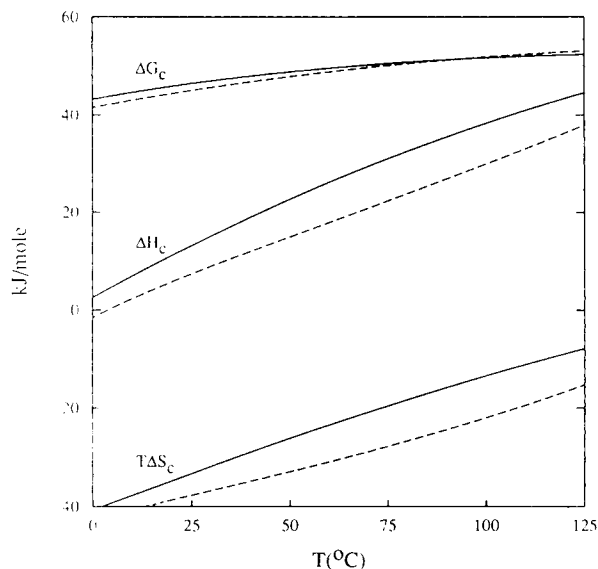
Figure 9. Cavity thermodynamics for neopentane in water. Solid lines are the "experimental" values. The dotted lines are calculated from the scaled particle theory.

The cavity thermodynamics in the aqueous solution, shown in Figure 9, provides a strong contrast in many respects; the enthalpy change is much smaller, the entropy change is large and negative, and the free energy change *increases* with temperature. However, some similarities may also be noted: On the one hand, the entropy line is always below the enthalpy line so that the free energy change is positive in both solvents. On the other hand, the enthalpy and entropy changes both increase with temperature in both solvents. It is a common behavior of all hydrocarbon liquids studied, as well as water, that a weakening in the solvent–solvent interaction with temperature, as measured by the rise in ΔH, is accompanied by an increase in entropy, of a magnitude comparable or greater (in terms of $T\Delta S$) than that in enthalpy.

The dashed lines in Figures 8 and 9 are the calculated values from the scaled particle theory. As is evident from the figures and the tabulated data (Tables III and V), the agreement between the scaled particle theory and the "experimental" data is particularly impressive in the case of the free energy change, but it is good also for the enthalpy and entropy changes over the entire temperature range. (We note in passing that the agreement in the nonaqueous phase is attained only after subtracting the large ΔH_{ar} term from ΔH_r. Pierotti's original application of the scaled particle theory to the solubilities[12] ignored the ΔH_{ar} term.) On the other hand, the scaled particle theory does a rather poor job in

reproducing the heat capacity change upon the n → w cavity transfer (Table VII). This poor agreement results from an *over*estimation of the temperature dependence of the cavity enthalpy in the nonaqueous solvent, on the one hand (see Figure 8), and an *under*estimation of the same dependence in the aqueous solution, on the other (see Figure 9).

DISCUSSION

There appears to be many meanings attached to the term "hydrophobicity."[23] Here, we take the most straightforward meaning of the word, that the solubility of nonpolar molecules is lower in water than in nonpolar solvents. Since the solubility difference is simply related to the standard Gibbs free energy of transfer, we shall normally measure the hydrophobicity by the magnitude of the latter. The two quantities are not the same, especially in their temperature dependencies, but the essence of hydrophobicity can be captured just as well by using the Gibbs free energy as by using the solubility. Therefore, we focus on the reason that the free energy of the hydrocarbon molecules is higher in water than in their neat solvents.

Figure 2 shows that the solute–solvent interaction energy is nearly the same in the two types of solvents. The hydrophobicity, therefore, arises mainly from the difference in the solvent reorganization terms. It was shown in the Theory section that the free energy contribution by the solvent reorganization upon turning on the solute–solvent interaction ΔG_{ar} is negligible in water. Although the magnitude of this term in the neat phase is not known, it is unlikely that it is large enough to account for the hydrophobicity. Therefore, it is the difference in the free energy of cavity formation in the two solvents that seems largely responsible for the hydrophobicity.

The free energy of cavity formation in water is large (Tables III and V). At room temperature, the enthalpy change is small and this free energy change is dominated by the negative entropy change. These features are commonly rationalized by supposing that "iceberg" or clathrate-like structure forms around a cavity in water. However, Figure 9 clearly demonstrates difficulties associated with this explanation. If the negative entropy change is due to the structure formation, its rapid rise with temperature indicates that the structure dissolves rapidly as the temperature is raised. If, in addition, the formation of such structure is the reason for hydrophobicity, then one must expect the free energy change to de-

crease as rapidly with temperature. This is not the case; the entropy rise is accompanied by a comparable rise in enthalpy and the net free energy change *increases* with temperature. Shinoda and Fujihira[24] noted this feature before, as well as Hvidt,[25] who therefore concluded that such a structure formation is not the cause of the low solubility but rather *aids* dissolution in water. Lumry and his coworkers[26] also argued that the "characteristic fluctuation behavior" related to the "flickering cluster" formation in water is not the cause of hydrophobicity because it only produces compensating changes in enthalpy and entropy. The suggestion that the positive free energy change arises from something other than a structure formation is supported by theoretical arguments, presented independently by Ben-Naim[27] and Grunwald,[28] that the structure formation can only affect the enthalpy and entropy in an exactly compensating manner.

The cavity thermodynamics in the hydrocarbon phase (Figure 8) presents a clear case wherein factors other than the structure formation need be considered. Although the entropy change is positive in this case, it is still significantly smaller than the enthalpy change. Since the resulting positive free energy change cannot be explained by an "iceberg"-like structure formation is this solvent type, there is clearly another mechanism that raises the free energy in this solvent.

A plausible nature of this mechanism has been suggested from the scaled particle theory[4,29] and from a general qualitative consideration.[1] It is geometrical in nature, operates in all solvents, and arises from the restriction in the translational degree of freedom of the solvent molecules, or the excluded volume effect of the cavity: Whenever a nonsolvent molecule is placed in a solvent, a large number of solvent configurations that were available in the pure state becomes unavailable because these produce solute–solvent hard-core overlap. A reduction in the number of available configurations causes the entropy of the system to decrease with corresponding increase in the free energy. An important property of this effect is that it depends markedly on the size of the solvent molecules.[1,4,29] Clearly, a cavity of a given size is effective bigger in the solvent made of small molecules, and therefore more difficult to produce, than in that of larger molecules. This causes hydrophobic effect since water molecules happen to be substantially smaller in size than any of the common nonaqueous liquids.

This effect is inherently entropic in origin and will operate even in the hard-sphere liquid. However, in any real liquid, the solvent reorganization that must accompany the volume exclusion necessarily involves a change in energy and an additional, presumably compensating, entropy change. It seems impossible, experimentally or even theoretically, to separate the contribution due to the volume exclusion effect alone from the total change.

The simplest theory that comes close to computing the excluded volume effect alone is the scaled particle theory.[11] The dotted lines in Figures 8 and 9 are the results calculated from this theory. The agreement in the free energy values is impressive over the entire range of temperature for both solvents. In fact, the values given in Tables III and V show that the agreement is excellent at all temperatures for all solvents. That the theory works well for the nonaqueous solvent is perhaps not too surprising but that it works about equally well for the aqueous phase is informative. Scaled particle theory handles the excluded volume effect, but also the general enthalpic and entropic effects that affect the volume change of the solvent. However, it deals with spherical molecules and contains nothing that accounts for the possible entropic and enthalpic effects arising from the directional nature of the hydrogen bonds in water. Thus the impressive success of the theory would seem possible only if these effects are compensatory and result in little changes in the free energy.

The success of this theory in the case of the aqueous phase has been found by many authors.[13,30-32] It may be noted that the highly successful theory of Pratt and Chandler[33] also does not explicitly include the hydrogen-bonding properties of water. Recently, Pohorille and Pratt[34] reported that the scaled particle theory significantly underestimates the cavity work for large cavities (by 20% at 300 K for a cavity of 2.0 Å radius). Our data also indicate (Table V) that the scaled particle theory underestimates ΔG_c, but the magnitude of the discrepancy is much less than they report. The difference may arise from the fact that they obtain the free energy of cavity formation directly from the computer simulation whereas the present data uses only the average solute–solvent interaction energy from the computer simulation. In any case, this difference is small compared to the total hydrophobic effect. Their main conclusion that the natural cavities in water are present in smaller packets than in other nonaqueous solvents is a more precise (but somewhat more cumbersome) way of stating what we describe here as the excluded volume effect.

The agreement between the scaled particle theory

and "experimental" values are not as good for the enthalpy and entropy. This may simply be a reflection of the poor quality of the theory. However, other possibilities exist. In the case of the aqueous solution, the temperature dependence of E_a was neglected. However, since $\partial \Delta E_a / \partial T$ is likely to be positive beyond 4°C, inclusion of this term will exaggerate the discrepancy. It is possible that the discrepancy represents the effect of the directional nature of the hydrogen bonds. If so, the data indicates that this effect *increases* entropy and enthalpy when a cavity is inserted. This is contrary to the expectations from the "iceberg" formation but consistent with the notion that a disruptive perturbation such as insertion of a cavity will generally weaken the interaction between solvent molecules, resulting in an increase in both enthalpy and entropy. The discrepancy in the hydrocarbon solvent may also reflect the effect of neglecting the orientational entropy. However, since the molecules are nearly spherically symmetric in this case, this effect may be small. It is easier in this case to suppose that it reflects errors in the "experimental" data. These could be caused by an inaccurate estimation of the temperature derivative of E_a, or more probably, by the neglect of the temperature derivative of ΔG_{ar} (see the Theory section).

One of the most striking features of the hydrophobic effect is the large heat capacity change associated with it. The heat capacity change has generally been considered to be due to an unusually large fluctuation in the structure of water that forms around the solute molecule, and as such, is often used both as the signature of the presence of the hydrophobic effect and as an evidence for the importance of the structure formation around the solute molecule. (The temperature dependence of the thermodynamic quantities for the aqueous solution was obtained by using a formula for the heat capacity change derived from such a model.[10] However, it was used simply as a way of describing the experimental data; its use need not constitute an endorsement of the model from which it was derived.)

The temperature dependencies of the standard enthalpy change in the two solvent types, shown in Figures 3 and 4, indeed contrast strongly. When the effect of the temperature dependence of E_a is subtracted (Figure 7), the contrast is even stronger. However, a significant part of this difference is due to the fact that the effect from the solute–solvent interaction is larger in the hydrocarbon solvent than in water. The estimated values for the contributions from the cavity part, as given in Table VII, are not

highly accurate (see the Results section) and meant to be used only for qualitative considerations. Nonetheless, it is interesting that the scaled particle theory predictions are poor in this case and that the reason is that the theory overestimates the heat capacity in the nonaqueous phase while it underestimates it in the aqueous phase (Figures 8 and 9). This indicates that the directional hydrogen-bonding properties of water is indeed important in determining the heat capacity change. However, any such effect applies to both the enthalpy and the entropy changes so that its influence on the free energy change appears to be rather small.

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