

The hydrophobic effect

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The thermodynamics of the hydrophobic effect, as measured primarily through the temperature dependence of solubility, is reviewed, and then a class of models that incorporate the basic mechanism of hydrophobicity is described. These models predict a quantitative relation between the free energy of hydrophobic hydration and the strength of the solvent-mediated attraction between pairs of solute molecules. It is remarked that the free energy of attraction being just of the order of the thermal energy kT may be important for the effective operation of the hydrophobic effect in proteins. Deviations from pairwise additivity of hydrophobic forces are also briefly discussed.

I. Introduction

Hydrocarbons are only slightly soluble in water: they are hydrophobic. The accommodation of a hydrocarbon molecule in water is accompanied by an increase in an associated free energy. Hydrocarbons are not the only hydrophobes but they are typical of the class. Characteristically, their solubility decreases with increasing temperature at low temperatures, which provides an important clue to the mechanism of hydrophobicity. At higher temperatures the solubility, after reaching a minimum, often then increases with further increase of temperature.

These effects are illustrated in Fig. 1, which shows the Ostwald absorption coefficient Σ of methane in water (the ratio of the number density of dissolved methane to that in the equilibrium vapor), as a function of temperature.¹ This is at a partial pressure of methane of 1 atm, although there is almost no dependence on the pressure as long as the concentration of methane in both phases is low (Henry's law).

The unfavorable free energy change accompanying the dissolution of the hydrocarbon results from structural changes

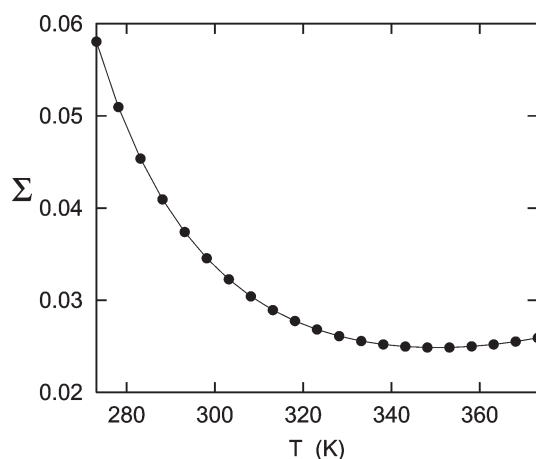


Fig. 1 Ostwald absorption coefficient Σ of methane as a function of temperature T (from compilation of Battino¹).

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in the solvent around each solute molecule. This is the phenomenon of hydrophobic hydration. The total volume of solvent so affected by a pair of solute molecules is less when the two are close together than when they are far apart, as illustrated schematically in Fig. 2. The result is an effective, solvent-mediated attraction between the two. This is the hydrophobic attraction.

These effects have long been recognized to be important in physical chemistry and biochemistry. The subject thus has an enormous literature, ranging from works that are now classic²⁻¹⁷ to those more nearly current,¹⁸⁻⁸⁵ many of these quite sophisticated. A recent authoritative assessment of the status of the field with emphases different from those in the present account is in a review by Pratt.²⁹ A beautiful earlier review by Scheraga⁸⁶ with an account of experimental results and emphasis on the role of hydrophobicity in biochemistry, should also be noted.

The thermodynamics of transfer of a molecule from one phase to another is outlined in Section II, and then the thermodynamics of hydrophobic hydration as inferred from solubility measurements such as those in Fig. 1 is presented in Section III. What is seen there, among other principles, is that the dissolution of a hydrophobe in water is energetically favorable,

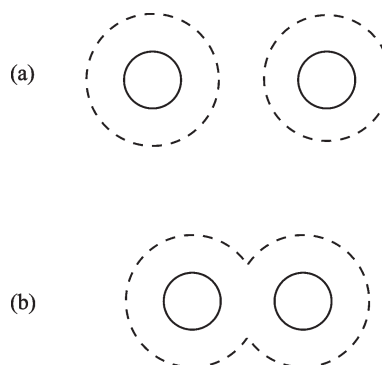


Fig. 2 Two hydrophobic molecules, (a) far apart, and (b) close together. The regions within the dashed curves represent schematically the volumes of solvent that are significantly affected by the presence of the solutes. The total volume so affected by the pair is smaller in (b) than in (a).

perhaps contrary to naïve expectation, but is entropically unfavorable to such an extent that the equilibrium solubility is very low. This was the historic observation that led to our present understanding of hydrophobicity and its implications.² Those two sections are an expanded version of an earlier treatment;⁸⁷ the principles are mostly well known,¹¹ but it is useful to bring them together here for reference.

Section IV describes a class of models that incorporate the main mechanism of hydrophobicity as revealed by the thermodynamic studies. The models make detailed predictions about hydrophobic attraction including a quantitative connection between the strength of the attraction and the free energy of hydrophobic hydration. These models, too, have been described earlier;⁸⁷ the present account includes some more recent results.

In Section V the geometric idea expressed in Fig. 2 is extended to the simultaneous interaction of three solute molecules, from which it is possible to make some speculative inferences about the three-body contribution to the solvent-mediated interaction energy.

The main results are briefly summarized in the concluding Section VI

II. Thermodynamics of transfer

We ask here for the changes in various thermodynamic quantities accompanying the transfer of a molecule A from a phase α to a phase β . Each phase separately is in complete internal equilibrium both before and after the transfer but the two phases need not be in equilibrium with each other. Later A will be a hydrophobic molecule, α some reference phase containing A, and β water or an aqueous solution, but for now A, α , and β are general.

The cases of most interest are those in which the temperatures T of the two phases are equal and are the same before and after the transfer (isothermal transfer). We will specify that, and then contemplate either of two further circumstances in which the transfer is made: that in which the volume of each phase separately is the same before and after the transfer, or that in which the pressure of each phase separately is the same before and after.

Let μ_A^α and μ_A^β be the chemical potentials of A in the respective phases. In the transfer with the volumes fixed, the difference $\mu_A^\beta - \mu_A^\alpha$ is the net change in the Helmholtz free energy of the two phases together; call it ΔF_V :

$$\Delta F_V = \mu_A^\beta - \mu_A^\alpha. \quad (1)$$

In the transfer with fixed pressures, the same difference $\mu_A^\beta - \mu_A^\alpha$ is the change in the composite system's Gibbs free energy; call it ΔG_p :

$$\Delta G_p = \mu_A^\beta - \mu_A^\alpha. \quad (2)$$

Note that $\Delta F_V = \Delta G_p$, but they are the ΔF and ΔG of different processes.

Significant parts of ΔF_V and ΔG_p result merely from the differing concentrations of A in the two phases, but we wish to know how much of ΔF_V and ΔG_p reflect only the intrinsic energetic and structural changes that occur in the phases as a result of the transfer of the A molecule from one to the other. We thus define

$$\Delta F_V^* = \Delta F_V - kT \ln \frac{c_A^\beta}{c_A^\alpha} \quad (3)$$

$$\Delta G_p^* = \Delta G_p - kT \ln \frac{c_A^\beta}{c_A^\alpha} \quad (4)$$

where k is Boltzmann's constant and c_A^α and c_A^β are the number densities of A in the respective phases; and now $\Delta F_V^* = \Delta G_p^*$. If

either phase is dilute in A the subtracted term accounts for the whole of the dependence of ΔF_V and ΔG_p on the concentration of A in that phase, and the resulting ΔF_V^* and ΔG_p^* are then independent of that concentration. This remains true, and ΔF_V^* and ΔG_p^* remain finite, even when $c_A^\beta \rightarrow 0$; *i.e.*, in the limit in which there is no A in the β phase prior to the transfer; while the original ΔF_V and ΔG_p diverge to $-\infty$ in that limit. When the phases are not dilute in A there is a residual dependence of ΔF_V^* and ΔG_p^* on the concentrations, reflecting the fact that the other A molecules are then a significant part of the environment from or to which the contemplated transfer of the A molecule occurs.

Let ΔS_V and ΔS_p be the corresponding changes in the composite system's entropy in the two different transfer processes, and define

$$\Delta S_V^* = \Delta S_V + k \ln \frac{c_A^\beta}{c_A^\alpha} \quad (5)$$

$$\Delta S_p^* = \Delta S_p + k \ln \frac{c_A^\beta}{c_A^\alpha}. \quad (6)$$

If either phase is dilute in A there is no dependence of ΔS_V^* and ΔS_p^* on the concentration of A in that phase, but otherwise there is. Again, these remain finite in the limit $c_A^\beta \rightarrow 0$, while ΔS_V and ΔS_p would be infinite.

Now consider first the fixed-volume transfer. Each number density c_A is N_A/V with N_A the number of A molecules in the phase and V its volume. During the transfer, N_A increases or decreases by 1 (in the β or α phase, respectively), while V is fixed. Then from (1), (3), and (5),

$$\Delta S_V = -\frac{\partial \Delta F_V}{\partial T}, \quad \Delta S_V^* = -\frac{\partial \Delta F_V^*}{\partial T} \quad (7)$$

where the temperature differentiations are at fixed numbers of molecules of all the substances in each phase and at fixed volumes of both phases. The change in the composite system's energy, ΔE_V , accompanying the constant-volume transfer, is

$$\Delta E_V = \Delta F_V + T\Delta S_V = \Delta F_V^* + T\Delta S_V^* \quad (8)$$

$$= \frac{\partial \Delta F_V / T}{\partial (1/T)} = \frac{\partial \Delta F_V^* / T}{\partial (1/T)}. \quad (9)$$

The constant-volume heat capacity C_V of the two phases together also changes as a result of the transfer, the net change being

$$(\Delta C_V)_V = \frac{\partial \Delta E_V}{\partial T} = T \frac{\partial \Delta S_V}{\partial T} = T \frac{\partial \Delta S_V^*}{\partial T} \quad (10)$$

$$= -T \frac{\partial^2 \Delta F_V}{\partial T^2} = -T \frac{\partial^2 \Delta F_V^*}{\partial T^2}, \quad (11)$$

where the second subscript V in $(\Delta C_V)_V$ specifies fixed-volume transfer.

In the transfer at fixed pressure the quantities of most interest, besides ΔG_p^* and ΔS_p^* , are the change ΔH_p in the composite system's enthalpy and the change $(\Delta C_p)_p$ in its constant-pressure heat capacity; but now the relations analogous to (7)–(11) are slightly more complicated because the volumes V in $c_A = N_A/V$ are no longer fixed when the temperature changes at fixed pressure and composition. Let ε^α and ε^β be the coefficients of thermal expansion of the two phases. Then from (1), (4), and (6), the analog of (7) is

$$\Delta S_p = -\frac{\partial \Delta G_p}{\partial T}, \quad \Delta S_p^* = -\frac{\partial \Delta G_p^*}{\partial T} + kT(\varepsilon^\beta - \varepsilon^\alpha), \quad (12)$$

where now the temperature differentiations are at fixed numbers of molecules of all the substances in each phase and at fixed pressure of each phase. With the same understanding of what is now held fixed in the temperature differentiations,

the analogs of (8)–(11) are

$$\Delta H_p = \Delta G_p + T\Delta S_p = \Delta G_p^* + T\Delta S_p^* \quad (13)$$

$$= \frac{\partial \Delta G_p / T}{\partial 1/T} = \frac{\partial \Delta G_p^* / T}{\partial 1/T} + kT^2(\varepsilon^\beta - \varepsilon^\alpha) \quad (14)$$

$$\begin{aligned} (\Delta C_p)_p &= -T \frac{\partial^2 \Delta G_p}{\partial T^2} \\ &= -T \frac{\partial^2 \Delta G_p^*}{\partial T^2} + 2kT(\varepsilon^\beta - \varepsilon^\alpha) + kT^2 \frac{\partial(\varepsilon^\beta - \varepsilon^\alpha)}{\partial T}. \end{aligned} \quad (15)$$

A special case of the transfer process is that in which the two phases are in equilibrium with respect to the transfer of A. This is when $\mu_A^\beta = \mu_A^\alpha$, so that $\Delta F_V = \Delta G_p = 0$. Then from (1) and (2),

$$\Delta F_V^* = \Delta G_p^* = -kT \ln \Sigma \quad (\text{equilibrium transfer}), \quad (16)$$

where

$$\Sigma = (c_A^\beta / c_A^\alpha)_{\text{eq}}, \quad (17)$$

the ratio of the number densities of A in the two phases when they are in equilibrium with each other. This is the key to obtaining the thermodynamics of transfer from measurements of equilibrium solubility.

When β is a liquid or solid solution dilute in A and α is a dilute gas, Σ is the Ostwald absorption coefficient, a common measure of gas solubility, as illustrated for methane in Fig. 1. Since β is then a hardly compressible condensed phase its properties as a solvent are insensitive to the pressure to moderate pressures; and the equilibrium ratio $(c_A^\beta / c_A^\alpha)_{\text{eq}}$ of the concentrations of A in these dilute phases is independent of their separate values (Henry's law); so Σ is practically a function of the temperature alone (as remarked in Section I). This circumstance, in which both phases are dilute in A, is also, we saw, that in which ΔF_V^* , ΔG_p^* , ΔS_V^* , and ΔS_p^* , and so also ΔE_V , ΔH_p , $(\Delta C_V)_V$, and $(\Delta C_p)_p$, are independent of the concentrations. Thus, their values are independent of whether or not the transfer of the A molecule from α to β occurs with the ratio c_A^β / c_A^α equal to that for which the two phases are in equilibrium. In this case, then, the significance of (16) and (17) is that ΔF_V^* , ΔG_p^* , and the quantities derivable from them are *the same as* when the transfer occurs with the two phases in equilibrium, even when it does not; and these quantities are then obtainable from the *equilibrium* solubility Σ , which is virtually a function of the temperature alone.

When α and β are both condensed phases, but both again dilute in A, the same considerations apply. The equilibrium ratio Σ in (17) is then the partition coefficient of A between the phases at equilibrium, and is virtually independent of the pressure and of the separate values of c_A^β and c_A^α ; it is practically a function of the temperature alone; and ΔF_V^* and ΔG_p^* , as given by (16) and (17), and the quantities obtainable from them, are the same as when the transfer occurs with the two phases in equilibrium even when it does not.

Another case of practical interest is that in which the α phase is pure or nearly pure liquid or solid A while β is again a condensed phase dilute in A. We continue to define ΔF_V^* and ΔG_p^* by (3) and (4) and ΔS_V^* and ΔS_p^* by (5) and (6), so the remaining relations (7)–(17), which follow from (3)–(6), still all hold. Now c_A^α in the denominator of the argument of the logarithms in (3)–(6) is practically a constant, and, since we are supposing β to be dilute in A, both ΔF_V^* and ΔG_p^* are independent of the remaining variable c_A^β . Thus, (16) with (17) hold in the case, too.

Summarizing, there are three common situations in which all the relations (7)–(16) hold, with Σ , defined by (17), practically a function of the temperature alone; *i.e.*, practically independent of pressure to moderate pressures and independent of the concentration of A in the dilute phase(s). These situations

are those in which β is a condensed phase dilute in A (or from which A is absent), while (i) α is a dilute gas containing A; or (ii) α is a condensed phase dilute in A; or (iii) α is a condensed phase that is pure or nearly pure A.

In these situations the temperature derivatives of Σ may be written as total derivatives, d/dT , and the thermodynamic quantities of interest are obtainable from Σ , *i.e.*, from the equilibrium partition coefficient, by the formulas

$$\frac{\Delta F_V^*}{kT} = \frac{\Delta G_p^*}{kT} = -\ln \Sigma \quad (18)$$

$$\frac{\Delta S_V^*}{k} = \frac{d}{dT}(T \ln \Sigma), \quad \frac{\Delta S_p^*}{k} = \frac{d}{dT}(T \ln \Sigma) + T(\varepsilon^\beta - \varepsilon^\alpha) \quad (19)$$

$$\frac{\Delta E_V}{kT} = T \frac{d}{dT} \ln \Sigma, \quad \frac{\Delta H_p}{kT} = T \frac{d}{dT} \ln \Sigma + T(\varepsilon^\beta - \varepsilon^\alpha) \quad (20)$$

$$\frac{(\Delta C_V)_V}{k} = T \frac{d^2(T \ln \Sigma)}{dT^2} \quad (21)$$

$$\frac{(\Delta C_p)_p}{k} = T \frac{d^2(T \ln \Sigma)}{dT^2} + 2T(\varepsilon^\beta - \varepsilon^\alpha) + T^2 \frac{\partial(\varepsilon^\beta - \varepsilon^\alpha)}{\partial T} \quad (22)$$

as now follow from the more general formulas stated earlier.

Applications of these formulas to the transfer of gaseous hydrocarbons into water are described in the next section, where they illustrate the principles of hydrophobic hydration.

III. Hydrophobic hydration

In Table 1 we give the results for the transfer of a molecule of methane, ethane, propane, or n-butane from the gas phase into water, at 300 K, as derived from (18)–(22), with Σ taken from the compilations of Battino.^{1,88–90} The β phase is pure or practically pure water. For ε^β and its temperature derivative, required for the correction terms in (19), (20) and (22), we took the data from the compilation by Rowlinson and Swinton.⁹¹ Those data are for water as it coexists with its vapor, so not at 1 atm, whereas the data for Σ are at 1 atm, but the distinction is of no importance since neither the coefficient of thermal expansion of water nor the Ostwald absorption coefficient Σ varies significantly with the pressure over this range. What makes the pressure variation of ε^β even smaller is that it is proportional to the temperature variation of the isothermal compressibility,⁹² and 300 K is not too far from 320 K, where the compressibility of water has a temperature minimum.⁹¹ The α phase, meanwhile, is a dilute, practically ideal gas, for which $\varepsilon^\alpha = 1/T$ and $d\varepsilon^\alpha/dT = -1/T^2$. The correction terms in (19), (20), and (22) are small; the difference between $\Delta S_V^*/k$ and $\Delta S_p^*/k$ and between $\Delta E_V/kT$ and $\Delta H_p/kT$ at 300 K is only 0.9. By coincidence, the two correction terms on the right-hand side of (22), which are opposite in sign, nearly cancel each other, with the result that $(\Delta C_V)_V$ and $(\Delta C_p)_p$ are nearly equal at 300 K.

Table 1 has many important lessons. The first and most obvious is that the free energy of transfer is positive and is several multiples of the thermal energy kT , which, *via* (18), just reflects the low solubility of the hydrocarbons in water. It is the next entries in the table that tell the hydrophobicity story: that the low solubility is a consequence of an unfavorable

Table 1 Thermodynamics of transfer of a hydrocarbon molecule from the gas phase into water at 300 K

	$\frac{\Delta F_V^*}{kT} = \frac{\Delta G_p^*}{kT}$	$\frac{\Delta S_V^*}{k}$	$\frac{\Delta S_p^*}{k}$	$\frac{\Delta E_V}{kT}$	$\frac{\Delta H_p}{kT}$	$\frac{(\Delta C_V)_V}{k}$	$\frac{(\Delta C_p)_p}{k}$
CH ₄	3.4	-7.5	-8.4	-4.1	-5.0	29	29
C ₂ H ₆	3.1	-9.7	-10.6	-6.6	-7.5	36	36
C ₃ H ₈	3.4	-11.0	-11.9	-7.6	-8.5	41	41
n-C ₄ H ₁₀	3.6	-12.5	-13.4	-8.9	-9.8	40	40

(negative) entropy change that overweighs a favorable (negative) energy change. The difference between $-\Delta S_V^*/k$ and $-\Delta E_V/kT$ (or, equivalently, between $-\Delta S_p^*/k$ and $-\Delta H_p/kT$), which is $\Delta F_V^*/kT (= \Delta G_p^*/kT)$, is nevertheless smaller than either one separately; *i.e.*, $-\Delta E_V/kT$, while less than $-\Delta S_V^*/k$, is nevertheless more than half of it ($-\Delta H_p/kT$ is more than half of $-\Delta S_p^*/k$), so there is considerable cancellation between them. That the entropy of transfer is negative at 300 K means, from (7), that at this temperature the free energy of transfer becomes more positive (more unfavorable) with increasing temperature; and that the energy of transfer is negative at 300 K means, from (20), that at this temperature the solubility decreases with increasing temperature. Thus, at 300 K, these hydrocarbons—and hydrophobes generally—become more hydrophobic with increasing temperature.

The heat capacity changes on transfer, $(\Delta C_V)_V$ and $(\Delta C_p)_p$, are positive and huge: many multiples of the Boltzmann constant k . This was one of the earliest observations of a “hydrophobic effect”.^{13,93} This and the negative energetic and entropic changes are ascribable to structural changes in the solvent, generally thought to be the strengthening of (or formation of additional) hydrogen bonds among the water molecules neighboring the solute.²

A further observation from the table is the manifestation of “enthalpy–entropy compensation”,^{15,94,95} according to which free-energy changes (free energies of transfer in this instance) are nearly constant through a homologous series, although the changes in the separate energetic and entropic components of the free energy vary substantially through the series.

Often when a solute can itself form hydrogen bonds with water the result is a closed-loop solubility curve,⁹⁶ illustrated here in Fig. 3. The figure shows the temperature dependence of the mutual solubility of two hypothetical substances A and B at a fixed pressure (or while simultaneously in equilibrium with vapor). The tilt of the solubility curve is exaggerated in the figure to make clear that in general the temperature T_1 of minimum solubility of A in B is not the same as the temperature T_4 of minimum solubility of B in A (although in theoretical models with an artificial symmetry it may be⁹⁷). One may think of the A-rich side of the loop as the phase earlier called α and the B-rich side as the aqueous phase β . Since on the lower part of the loop the solubility of A in B (as well as that of B in A) is decreasing with increasing temperature, it is manifesting the hydrophobic effect.²³ That

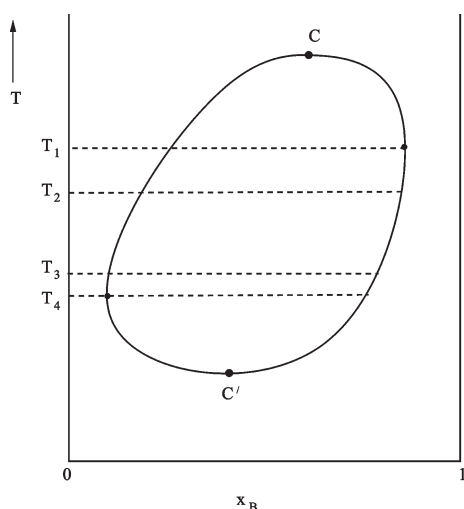


Fig. 3 Closed-loop solubility curve with components A and B. Concentration variable x_B is the mole or mass fraction of B. Points C and C' mark the lower and upper critical solution points. Temperatures T_1 and T_4 are those of the minimum solubility of A in B and of B in A, respectively, while the intermediate temperature T_2 is that at which ΔH_A and ΔS_A vanish, and T_3 that at which ΔH_B and ΔS_B vanish.

the solubility passes through a minimum with increasing temperature and thereafter increases is a characteristic also of the solubility of most hydrocarbons in water^{1,88–90} (as seen for methane in Fig. 1).

For the transfer of a molecule between coexisting phases at temperature T , the enthalpy and entropy changes ΔH and ΔS ($\neq \Delta S^*$) are related by $\Delta H = T\Delta S$ ($\neq T\Delta S^*$). Referring still to Fig. 3, we will for now use the notation ΔH_A ($= T\Delta S_A$) for the enthalpy of transfer of an A molecule from the phase α relatively rich in A to the phase β poorer in A, and ΔH_B ($= T\Delta S_B$) for the enthalpy of transfer of a molecule B from β to α . One may then show that ΔH_A and ΔS_A are negative for temperatures below some temperature T_2 between T_1 and T_4 , they vanish at T_2 , and are positive above T_2 ; while ΔH_B and ΔS_B are negative below some temperature T_3 between T_1 and T_4 , they vanish at T_3 , and are positive above T_3 ; with $T_3 < T_2$ if the coexistence curve is oriented as in the figure.

For the transfer of an A molecule from the phase α richer in A to the phase β poorer in A, the modified entropy change ΔS_A^* , defined analogously to ΔS_p^* in (6), is algebraically smaller (more negative or less positive) than ΔS_A itself, and so is still negative when ΔS_A vanishes at the temperature T_2 .

Where the β phase is very dilute in A it hardly matters to the values of the ΔH and ΔS^* of transfer whether the transfer of the A molecule from the α phase is to the coexisting β phase (where they are then ΔH_A and ΔS_A^*) or to pure B (pure water, say, if β is an aqueous phase). In the latter case the unmodified ΔS of transfer would be infinite. Likewise, if the α phase is nearly pure A it hardly matters to the values of the ΔH and ΔS of transfer whether the transfer of the A molecule to β is from the coexisting α phase (when they are then ΔH_A and ΔS_A) or from pure A, and now in either case there is hardly any difference between ΔS and ΔS^* .

This completes our review of the thermodynamics of hydrophobic hydration. We turn next to microscopic models and to the phenomenon of hydrophobic attraction.

IV. Microscopic models

There are many and diverse microscopic models of solutions of hydrophobes in water (see refs. 9, 19, 21, 29, 35, 40, 77, 78, 98 among many others), but we shall here describe only those we have ourselves been studying, which is a class of lattice models.^{87,99–102}

Fig. 4 is an example in two dimensions with lattice coordination number $Z = 4$, but the same basic model may be in any number of dimensions with a variety of lattice types. Solvent molecules are represented by the larger circles, one at each lattice site. Each may be in any of q (≥ 2) possible orientations or internal states, of which one (state number 1, say) is distinguished from the $q - 1$ others: neighboring solvent molecules interact with an energy w when both are in that special state 1 but with a higher energy u ($> w$) otherwise. Solute molecules are represented by the smaller circles in Fig. 4. They can be accommodated only on the bonds between lattice sites, *i.e.*, between neighboring pairs of solvent molecules, and only then if both solvent molecules of the neighboring pair are in the special state or orientation 1. Thus, accommodation of a solute restricts the possible orientations of the neighboring solvent molecules and at the same time puts that solvent pair in its low-energy configuration. Thus, the model has built into it the basic mechanism of hydrophobicity: the forced accommodation of the solute is energetically favorable but entropically unfavorable.

Lest the models seem more artificial than they are, it should be emphasized that, as in any lattice fluid model,^{97,103} the molecules are not to be thought of as confined to lattice sites or bond centers. One should think of the volume divided into

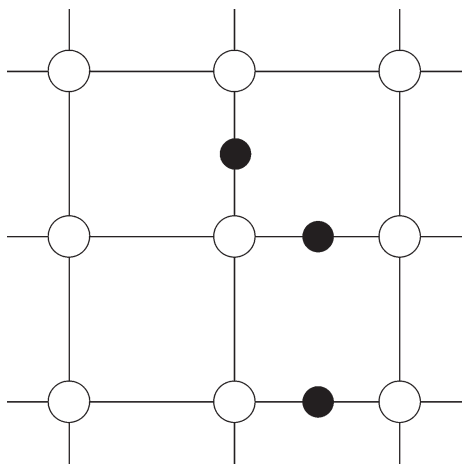


Fig. 4 The lattice model. Large open circles at the lattice sites represent the solvent molecules, small filled circles on the bonds between sites represent the solute molecules.

cells (only as a coordinate system, not with impenetrable walls), so that every molecule has access to any point in the whole volume. The only artificiality is that the interactions between molecules now depend on discrete rather than continuous distance variables.

The two parameters $u - w$ and $q - 1$ are properties of the model solvent alone. The model has a third parameter, v , which is the energy of interaction between an accommodated solute molecule and the two solvent molecules that neighbor it. All three parameters enter into the solubility Σ , defined in (17), while the solvent-mediated part of the potential of mean force between pairs of solutes is determined by the solvent parameters $u - w$ and $q - 1$ alone.

These follow from the expressions^{87,99,100}

$$\Sigma = P_{11}e^{-v/kT} \quad (23)$$

$$W(\mathbf{r}_1, \mathbf{r}_2) = -kT \ln \frac{P(\mathbf{r}_1, \mathbf{r}_2)}{P_{11}^2}, \quad (24)$$

for the first of which it is assumed that the phase that is in equilibrium with the saturated solution is a dilute gas. Here P_{11} is the probability that any neighboring pair of solvent molecules in the pure solvent will both be found to be in the special orientation 1; $P(\mathbf{r}_1, \mathbf{r}_2)$ is the probability that the solvent molecules that are the neighbors of the bonds centered at \mathbf{r}_1 and \mathbf{r}_2 will all be found to be in that special orientation; and $W(\mathbf{r}_1, \mathbf{r}_2)$ is the solvent-mediated part of the potential of mean force between a pair of solute molecules at \mathbf{r}_1 and \mathbf{r}_2 in the infinitely dilute solution; *i.e.*, the potential of mean force from which the direct solute-solute interaction, whatever that might be, has been subtracted. The parameters $u - w$ and $q - 1$ are implicit in P_{11} and $P(\mathbf{r}_1, \mathbf{r}_2)$ while v appears explicitly in (23). The nearest-neighbor pair correlation P_{11} and the pair-pair correlation function $P(\mathbf{r}_1, \mathbf{r}_2)$ are obtained analytically in the one-dimensional version of the model⁹⁹ and with sufficient accuracy by Monte Carlo simulation in two or three dimensions.^{87,100}

For the simulations it is convenient to recognize the equivalence of the model to a related Ising model or one-component lattice gas.¹⁰² With conventional Ising-model notation,^{104,105} the spin-spin interaction-energy parameter J and magnetic field H in the equivalent Ising model are related to $u - w$ and $q - 1$ by

$$J = \frac{1}{4}(u - w), \quad 2H = \frac{1}{2}Z(u - w) - kT \ln(q - 1) \quad (25)$$

where Z is the coordination number of the lattice ($Z = 2$ in one dimension, $Z = 6$ or 8 for the simple cubic or body-centered

cubic lattices, respectively, in three dimensions, *etc.*). In the equivalent one-component lattice gas¹⁰⁶ in which the cells are of volume v_0 , the activity is z , and the near-neighbor interaction energy is $-\varepsilon$, the equivalences are

$$\varepsilon = u - w, \quad v_0 z = 1/(q - 1). \quad (26)$$

The probability P_1 that any given solvent molecule in the hydrophobic-interaction model be in the special state 1 rather than in any of the $q - 1$ other states is equivalently the probability that any given cell in the lattice gas model be occupied rather than empty or that any given spin in the Ising model be in the direction of the field rather than opposed.

The model in any number of dimensions and for any coordination number may be treated in Bethe-Guggenheim approximation^{107,108} as well as by simulation. (For the application of the Bethe-Guggenheim approximation to different lattice models of water and hydrophobic solvation see Besseling and Lyklema³⁵ and Eads.⁷⁸) The approximation is exact on a Bethe lattice (Cayley tree), on which there are no closed loops, so that, as in one dimension, between any two sites there is only a single, unique path. Then $W(\mathbf{r}_1, \mathbf{r}_2)$ may be written $W(r)$, where r is the distance between bond centers measured as a number of lattice steps; and then *via* (24),

$$W(r) = -kT \ln g(r - 1) \quad (r \geq 2) \quad (27)$$

where $g(r)$ is the pair distribution function (radial distribution function) of the equivalent one-component lattice gas in one dimension. For $r = 1$,

$$W(1) = kT \ln y, \quad (28)$$

with y ($0 \leq y \leq 1$) the dimensionless density of the one-component lattice gas. As remarked earlier, this lattice-gas density is also the probability P_1 that any solvent molecule in our original model be in the special state 1. Further, the solubility Σ in our model, *via* (23), is given in Bethe-Guggenheim approximation by

$$\Sigma = y^2 g(1) e^{-v/kT}. \quad (29)$$

In this approximation, the lattice-gas $g(r)$ and density y required in (27)–(29) are expressible in terms of the solvent parameters $u - w$ and $q - 1$ of the hydrophobic-interaction model by

$$g(r) = 1 + \left(\frac{1}{y} - 1\right) \left(\frac{Q - 1}{Q + 1}\right)^r \quad (r \geq 1) \quad (30)$$

$$\frac{1}{y} - 1 = \frac{1 + \alpha}{\alpha(1 + c\alpha)} \quad (31)$$

where

$$Q = \sqrt{1 + 4(c - 1)(1 - y)} \quad (32)$$

$$c = e^{(u-w)/kT} \quad (33)$$

$$\left(\frac{1 + c\alpha}{1 + \alpha}\right)^{Z-1} = (q - 1)\alpha, \quad (34)$$

with Z again the coordination number of the lattice. The lattice-gas density y is thus given parametrically (parameter α) in terms of the model parameters $q - 1$ and $u - w$ (and Z and the temperature T) by (31) and (34), with c defined by (33).

With $Z = 2$ the Bethe-Guggenheim approximation becomes the exact one-dimensional version of the model.⁹⁹ In the limit $Z \rightarrow \infty$ and $u - w \rightarrow 0$ with fixed $\phi = Z(u - w)$ it becomes the mean-field approximation, in which $g(r) \equiv 1$ for all $r \geq 1$ and for which y is given implicitly in terms of $q - 1$ and ϕ by $q - 1 = (1/y - 1)\exp(y\phi/kT)$.

One object in the study of these models is to find a connection between the free energy of hydrophobic hydration (ΔF_V^*

or ΔG_p^* , Section III), and the solvent-mediated part, $W(\mathbf{r}_1, \mathbf{r}_2)$, of the potential of mean force between hydrophobic solutes. To this end we choose the parameters $u - w$ and $q - 1$ to match the experimental solubility Σ of methane as closely as possible over the 60° temperature interval $273 \text{ K} \leq T \leq 333 \text{ K}$, and then with these values of the parameters calculate W .

We continue to define $\phi = Z(u - w)$. In Fig. 5 we show the nearly perfect fit to the experimental Σ obtained with the model in Bethe–Guggenheim approximation with $Z = 8$ and the model parameters

$$\phi/k = 1008 \text{ K}, \quad q - 1 = 6.16, \quad v/k = 464.3 \text{ K}. \quad (35)$$

The corresponding plot when the properties of the model on the body-centered cubic lattice ($Z = 8$) are obtained by Monte Carlo simulation⁸⁷ and the solubility then fit with the parameter values

$$\phi/k = 1026 \text{ K}, \quad q - 1 = 6.7, \quad v/k = 406.7 \text{ K}. \quad (36)$$

is almost indistinguishable from that in Fig. 5.

It is noteworthy that the parameter values in (35) and (36), where $Z = 8$ in both, are not very different. It should also be noted that it is not a forgone conclusion that the experimental Σ even over this restricted temperature range could have been fit by these three-parameter functions. Only the two parameters $u - w$ and $q - 1$ occur in the factor P_{11} in (23), so the slope and curvature and thus the whole shape of a plot of $-kT \ln \Sigma$ as a function of T have to be fit by those alone, while the third parameter, v , corresponds merely to a constant displacement of such a plot without a change in its shape. In Bethe–Guggenheim approximation the fit is better the greater the coordination number Z , and so, although already nearly perfect at $Z = 8$, is even better in mean-field approximation ($Z \rightarrow \infty$), where the fit is with the parameter values

$$\phi/k = 912.4 \text{ K}, \quad q - 1 = 4.95, \quad v/k = 498.2 \text{ K}; \quad (37)$$

while the fit is poorest, although still acceptable, in one dimension ($Z = 2$).⁸⁷

We note in (35)–(37) that the model parameter v is positive. One must make a distinction between the interaction energy between solute and solvent, which here is v , and the energy or enthalpy change ΔE_v or ΔH_p of the whole system that accompanies the forced accommodation of the solute. The latter are negative here, as well as in reality, because they follow from the experimental Σ , which we have fit nearly exactly with the parameter values in (35)–(37). But we note also in (35)–(37) that ϕ , which is $Z(u - w)$, is greater than v ; so the favorable energy and enthalpy of hydration is a consequence of the

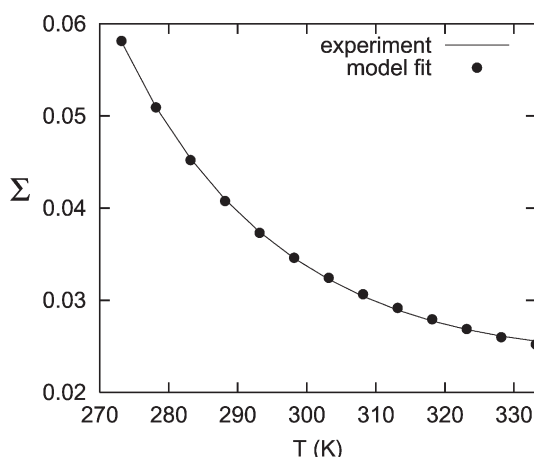


Fig. 5 Fit of the model Σ in Bethe–Guggenheim approximation with $Z = 8$ to the experimental Σ for methane. The points are the theoretical values with the parameters given in (35); the curve is from Battino's interpolation formula fitting the experimental results.¹

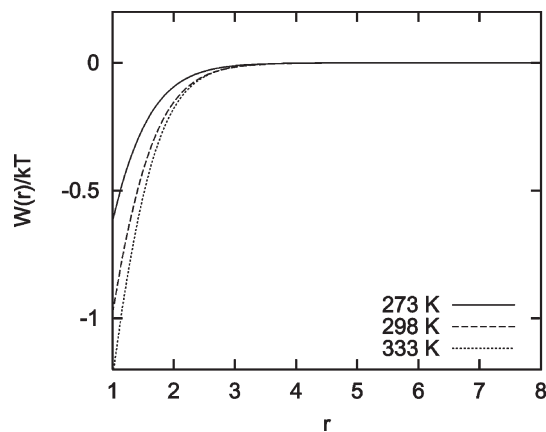


Fig. 6 $W(r)/kT$ for the model in Bethe–Guggenheim approximation with $Z = 8$.

energetically favorable change in the solvent–solvent interaction that accompanies the dissolution of the solute, which overweighs what *in this model* (not necessarily in reality) is the unfavorable solute–solvent interaction.

With the parameters in (35) or (36) that fit the experimental Σ , one may now calculate the solvent-mediated part of the potential of mean force, W , between methane molecules in the infinitely dilute solution. This follows from (24) in general for the models of this class, or in particular from (27) and (28) with (30)–(34) in Bethe–Guggenheim approximation. In Fig. 6 we show $W(r)/kT$ in this approximation with $Z = 8$, as a function of r at each of the three temperatures 273 K, 298 K, and 333 K. These curves are strongly reminiscent of the theoretical curves in Marčelja *et al.*,¹⁷ although those are indexed by solute size rather than temperature. In Fig. 7, from ref. 87, we show the corresponding results from the Monte Carlo simulations of the model on the body-centered cubic lattice. In the latter plot $W(\mathbf{r}_1, \mathbf{r}_2)$ is again called $W(r)$, with r again in multiples of the shortest distance between bond centers, but this shortest distance is now the fraction $1/\sqrt{3} = 0.577 \dots$ of the bond length itself. In both figures, then, “ $r = 1$ ” is the closest the centers of two hydrophobic molecules may come if both molecules are imagined located at the lattice's bond centers.

Not visible in Fig. 6 on the scale of that plot, and scarcely visible in Fig. 7, is the crossing of the curves for the various temperatures: the higher the temperature the stronger the hydrophobic attraction as measured by $-W(1)$ but the shorter is its range as measured by its rate of decay as $r \rightarrow \infty$. For the body-centered cubic lattice, and generally in three dimensions

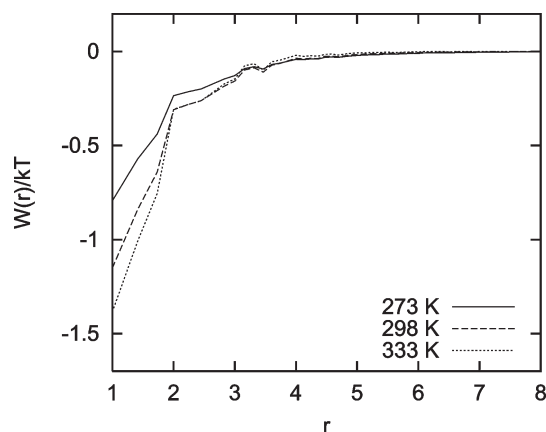


Fig. 7 $W(r)/kT$ by Monte Carlo simulation of the model on the body-centered cubic lattice.

with the direct interactions of short range, $W(r)$ decays proportionally to $(1/r)\exp(-r/\xi)$, and in Bethe–Guggenheim approximation proportionally to $\exp(-r/\xi)$, where the decay lengths ξ decrease with increasing temperature. This may not be an important feature of hydrophobic forces, however, because $W(r)$ is already so small when the curves cross: the three curves in Fig. 6 taken in pairs cross at $r = 2.7, 4.0$, and 5.9 .

This attraction, which is largely entropic in origin, has been termed the “hydrophobic bond”.^{3,6} In both figures it is seen that the strength of the attraction, $-W(1)$, is only about kT . The direct van der Waals attraction between pairs of solutes at this distance is only about 15 or 20% of the solvent-mediated attraction,^{19,109} so the total is still only about kT . This means, for example, that of the “hydrophobic bonds” in the native structure of a protein, at any moment approximately the fraction $1/(1+e) \cong 1/4$ of them are “broken”. This may be important for the dynamical functioning of the protein.¹¹⁰

This has illustrated the calculation of the strength $-W(1)$ of the hydrophobic attraction in the model, using parameters that closely fit the experimental Σ ; or, equivalently, from (16), that fit the experimental hydration free energy ΔF_V^* or ΔG_p^* . Fig. 8 now shows how $W(1)/kT$ varies with $\Delta G_p^*/kT$. Shown are the Bethe–Guggenheim approximation with $Z = 2, 3, 8$, and ∞ ($Z = 2$ is the one-dimensional model and $Z = \infty$ the mean-field approximation), and the results of the simulation on the body-centered cubic lattice. We see a steady progression with Z . Over this restricted temperature range all the plots are nearly linear: almost exactly linear from the simulations but with slight positive curvature for $Z = 2$ and 3 and slight negative curvature for $Z = 8$ and ∞ in the Bethe–Guggenheim approximation. They are nearly parallel with a common slope near -0.7 .

These plots answer the question, at least for this class of models, of how the strength of the solvent-mediated attraction between a pair of hydrophobic solute molecules depends on the hydration free energy of a single one; *i.e.*, they are a quantitative answer to the question implicit in Fig. 2. We note again that the hydrophobic effect, *i.e.*, $\Delta G_p^* > 0$ and $W(1) < 0$, becomes stronger with increasing temperature. We also see again that $-W(1)$ is only about kT , while ΔG_p^* , from the figure or from Table 1, is about $3kT$. One can understand why $-W(1) < \Delta G_p^*$.⁸⁷ Suppose in Fig. 2 that the volume of solvent structurally and energetically affected by the presence of an isolated solute molecule is v_1 and that the total volume so affected by a closely spaced pair of solute molecules is v_2 .

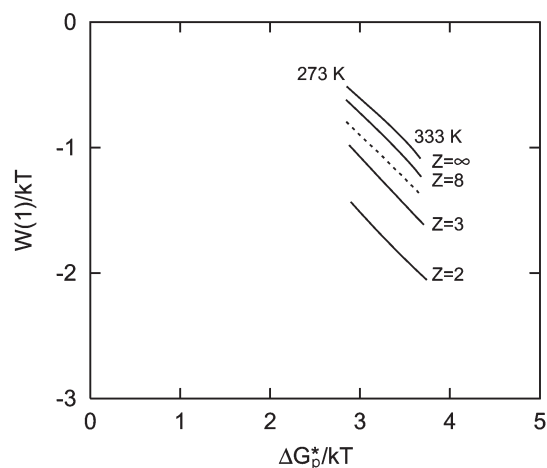


Fig. 8 Variation of $W(1)/kT$ with $\Delta G_p^*/kT$; $-W(1)$ is the strength of the hydrophobic attraction between a pair of solute molecules while ΔG_p^* is the hydration free energy of a single one. The solid curves are the Bethe–Guggenheim approximation with the indicated coordination numbers Z ; the dashed curve is the result of Monte Carlo simulation of the model on the body-centered cubic lattice, for which $Z = 8$.

Let the resulting unfavorable free-energy density in those affected regions be some $f > 0$. Then $\Delta G_p^* = v_1 f > 0$; while the solvent-mediated potential energy, $W(1)$ in the notation of our model, is $W(1) = (v_2 - 2v_1)f$, which is negative (attractive) because $v_2 < 2v_1$. But also $v_2 > v_1$, so $v_2 - 2v_1 > -v_1$; *i.e.*, $-W(1) < \Delta G_p^*$. In this argument we have assumed that the free energy density (what we have called f) in the lens-shaped overlap region and in the non-overlap region are not very different.

A related argument allows one to guess the sign of the three-body contribution to the hydrophobic attraction. This is the subject of the next section.

V. Three-body potential

In an analysis of the one-dimensional version of this lattice model¹⁰¹ it was found that the solvent-mediated part of the potential of mean force among n solute molecules on the bonds centered at x_1, x_2, \dots, x_n with $x_1 < x_2 < \dots < x_n$ is the sum of the pair potentials between nearest neighbors only:

$$W(r_{12}, r_{23}, \dots, r_{n-1,n}) = W(r_{12}) + W(r_{23}) + \dots + W(r_{n-1,n}) \quad (38)$$

where $r_{12} = x_2 - x_1$, *etc.* With three solute molecules at x_1, x_2, x_3 , this is

$$W(r_{12}, r_{23}) = W(r_{12}) + W(r_{23}). \quad (39)$$

This is greater than the sum of the three pair potentials,

$$W(r_{12}, r_{23}) - W(r_{12}) - W(r_{23}) - W(r_{13}) = -W(r_{13}) > 0 \quad (40)$$

because the pair potential $W(r)$ is negative (attractive); *i.e.*, the three-body contribution to the energy of interaction of three such solute molecules is positive: the three-body force is repulsive.

One may guess that the same will be true in near linear configurations of three hydrophobic solutes in two or three dimensions as well, while an extension of the argument at the end of Section IV indicates that it may also be true in triangular configurations of the three. An equilateral configuration of three is shown schematically in Fig. 9. The volume of solvent affected by the presence of a single solute molecule is called u_1 ; it is the same as what was called v_1 in the argument at the end of Section IV. The volume of the lens-shaped region of overlap of two such regions is u_2 , previously called $2v_1 - v_2$. The volume of the curvilinear region of triple overlap is u_3 .

The total volume of solvent affected by the presence of the solutes in this configuration is $3u_1 - 3u_2 + u_3$. But with W_1, W_2 , and W_3 the one-, two-, and three-body effective potentials, the total excess free energy due to the presence of the three solute molecules is $3W_1 + 3W_2 + W_3$, because there are three distinct single bodies, three distinct pairs, and one triple. The

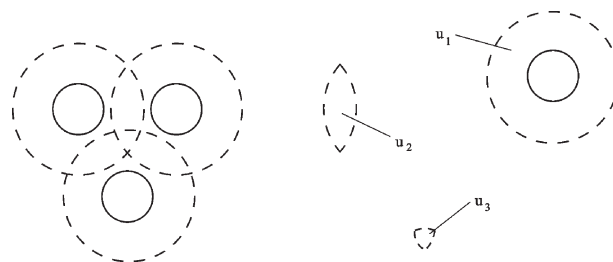


Fig. 9 Three solute molecules in an equilateral configuration. The volume of solvent affected by the presence of a single solute molecule is u_1 , the volume of the lens-shaped region of overlap of two such regions is u_2 , and the volume of the curvilinear region of triple overlap is u_3 .

one-body potential W_1 is the earlier hydration free energy ΔG_p^* , which was v_1f , now called u_1f ; the pair potential W_2 is what was earlier called $W(1)$, the effective potential between a closely spaced pair of solutes, which was $(v_2 - 2v_1)f$, now called $-u_2f$. Thus, the three-body potential W_3 , which is our present object, is here seen to be $W_3 = u_3f$, which is positive. Thus, in this configuration, as in the linear configuration in the one-dimensional model, the three-body force is repulsive, which is what we wished to determine.

But for application to real hydrophobic interactions this argument can be no more than suggestive; it is not a substitute for detailed calculation with realistic models.^{53,76}

VI. Summary and conclusions

The basic result of the thermodynamics as outlined in Section II and illustrated in Section III is contained in eqns. (18)–(22), where the thermodynamics of transfer of a hydrophobic molecule into water are seen to follow from measurements of the equilibrium partition coefficient or Ostwald absorption coefficient. That the suitably defined free energy of transfer [denoted with an asterisk in eqns. (3) and (4)] is positive and equal to a few multiples of the thermal energy kT , and that the energy (or enthalpy) and suitably defined entropy of transfer are both negative, are characteristic of, and essentially define, hydrophobic solutes. Hydrophobicity increases with increasing temperature, reflecting the corresponding decrease in solubility.

Many of the features of the hydrophobic effect are realistically rendered by the lattice model described in Section IV. The model was designed to make the accommodation of a solute in the solvent energetically favorable but entropically unfavorable, and thus to incorporate the basic mechanism of hydrophobicity as revealed by the thermodynamics. Once the parameters in the model are chosen to reproduce the experimentally measured solubility of methane and its temperature dependence in the temperature interval 273 to 333 K, the model leads to a realistic picture of the solvent-mediated part, $W(r)$, of the potential of mean force between a pair of solute molecules as a function of their separation r . It is found that “ $W(1)$ ”, the potential at close approach of the pair, is negative, which is the hydrophobic attraction, and becomes more negative with increasing temperature, in accord with the conclusion from the thermodynamic analysis that hydrophobicity increases with increasing temperature. The strength $-W(1)$ of the hydrophobic attraction increases nearly linearly with the free energy of hydrophobic hydration, but is less than the latter: only about kT as compared with about $3kT$. That the solvent-mediated attraction is as small as kT means that hydrophobic “bonds” are easily “broken”, which may have implications for dynamical effects in protein structure.

It is remarked in Section V that in the one-dimensional version of the lattice model the three-body force in the solvent-mediated interaction among hydrophobic solutes is always repulsive. A simple argument is presented according to which that may still be so in various configurations in two and three dimensions as well; but one is warned that the argument, while suggestive, is not definitive.

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