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# Correlation between hydrophobic attraction and the free energy of hydrophobic hydration

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We correlate the strength of the solvent-mediated attraction of a pair of hydrophobic solute molecules with the free energy of hydration of a single such molecule. This is done in the framework of a particular model but the results may be more general. When the model parameters are chosen to represent methane as the solute in water it is found that over the relevant temperature range the strength of the attraction, expressed as a multiple of the thermal energy $kT$, increases nearly linearly with increasing hydration free energy expressed in the same units. In the middle of the temperature range studied the strength of the attraction is roughly one-third of the hydration free energy.

## 1. Introduction

The change in enthalpy and the relevant part of the change in entropy accompanying the transfer of a hydrophobic molecule into water are typically both negative. This is a signature of the 'hydrophobic effect'. The enthalpy and entropy of transfer enter the free energy with opposite signs, and the entropic contribution exceeds the enthalpic, so the relevant part of the free energy of transfer is positive—typically several multiples of the thermal energy $kT$, where $k$ is Boltzmann's constant and $T$ is the absolute temperature. The low solubility of the hydrophobe may thus be viewed as a consequence of the large negative entropy of transfer [1–9]. This, in turn, is usually ascribed mainly to structural changes in the water neighbouring the hydrophobic solute: changes such as the forced formation of new hydrogen bonds, the strengthening of those already present, or, more generally, increased restriction of the water molecules' orientations [1–3, 5–10].

The total volume of solvent affected in this way by two such hydrophobic solute molecules, and so the free energy of accommodating them, is less when they are close together than when they are far apart, leading to a solvent-mediated attraction between them [4, 5]. Since this, too, is a manifestation of the unfavourable free energy of hydration we may anticipate some connection between the magnitude of the solvent-mediated attraction between a pair of solutes and the free energy of accommodating an isolated one. The aim of this article is to find a quantitative measure of that connection in a simple model and then express it in as model-independent a way as possible.

In the next section we briefly summarize the thermodynamics of hydrophobic hydration. The ideas and formulas are mostly well known but are collected here for reference. These formulas allow us then in section 3 to derive from experiment the appropriate values to assign to the model parameters when calculating, in the model, the solvent-mediated part of the potential of mean force between pairs of solutes. In section 4 we correlate the strength of the solvent-mediated attraction thus calculated with the hydration free energy, which was our aim. The results are briefly summarized in section 5.

## 2. Thermodynamic preliminaries

If a molecule A is transferred from a phase $\alpha$ to a phase $\beta$ (not necessarily at equilibrium), at fixed pressure [4] and temperature, the Gibbs free-energy change $\Delta G$ that accompanies the transfer is

$$\Delta G = \mu_A^\beta - \mu_A^\alpha, \qquad (1)$$

where $\mu_A^\beta$ and $\mu_A^\alpha$ are the chemical potentials of A in the $\beta$ and $\alpha$ phases, respectively. (Here and below, if the transfer is made with the volumes of the phases fixed instead of at fixed pressure, read Helmholtz instead of Gibbs free energy, energy instead of enthalpy, and constant-volume instead of constant-pressure heat capacity. When both $\alpha$ and $\beta$ are condensed phases

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the distinction is relatively unimportant. When one is a gas, understand constant-volume transfer. The part $\Delta G^*$ of $\Delta G$ which is relevant to hydrophobic hydration is [4]

$$\Delta G^* = \Delta G - kT \ln(c_A^\beta / c_A^\alpha), \qquad (2)$$

where $c_A^\beta$ and $c_A^\alpha$ are the number densities of A in the phases $\beta$ and $\alpha$. This subtracts from $\Delta G$ the part which results merely from the differing concentration of A in the two phases, so that $\Delta G^*$ then reflects only the intrinsic structural and energetic changes accompanying the transfer.

When A is dilute in both phases the whole of the dependence of $\Delta G$ on the concentrations is in $kT \ln(c_A^\beta / c_A^\alpha)$, and $\Delta G^*$ is then independent of $c_A^\beta$ and $c_A^\alpha$. When A is not dilute in both phases there is some additional dependence of $\Delta G$ on those concentrations and that residual dependence is in $\Delta G^*$. This reflects the circumstance that when A is not dilute in both phases the A molecules themselves are a significant part of the environment from or to which the contemplated transfer occurs.

Correspondingly, the relevant part $\Delta S^*$ of the entropy change $\Delta S$ that accompanies the transfer is

$$\Delta S^* = \Delta S + k \ln(c_A^\beta / c_A^\alpha) = -\partial \Delta G^* / \partial T, \qquad (3)$$

the temperature differentiation being at fixed pressure (or volume) and composition. This $\Delta S^*$, like $\Delta G^*$, is independent of $c_A^\beta$ and $c_A^\alpha$ when both phases are dilute in A, but otherwise not. The associated enthalpy and constant-pressure heat capacity of transfer, $\Delta H$ and $\Delta C_p$, are

$$\Delta H = \Delta G + T \Delta S = \Delta G^* + T \Delta S^*, \qquad (4)$$

$$\Delta C_p = \partial \Delta H / \partial T = T \partial \Delta S / \partial T = T \partial \Delta S^* / \partial T, \quad (5)$$

and are also independent of $c_A^\beta$ and $c_A^\alpha$ when both phases are dilute in A.

When the $\alpha$ and $\beta$ phases are at equilibrium with respect to the transfer of A the associated $\Delta G = 0$, and then from (2),

$$\Delta G^* = -kT \ln \Sigma \quad \text{(equilibrium transfer)}, \qquad (6)$$

where

$$\Sigma = (c_A^\beta / c_A^\alpha)_{\text{eq}}, \qquad (7)$$

the ratio of the number densities of A in the two phases at equilibrium. This $\Sigma$ is the partition coefficient of A between the two phases at equilibrium. When the phases are dilute in A it is independent of the separate values of $c_A^\beta$ and $c_A^\alpha$, but otherwise not. When $\alpha$ is a dilute gas and $\beta$ a dilute solution of A it is the Ostwald absorption coefficient.

Table 1. $\Delta G^*/kT$, $\Delta S^*/k$, $\Delta H/kT$, and $\Delta C_p/k$ for $CH_4$ and $n$-$C_4H_{10}$ at 300 K.

| Solute | $\Delta G^*/kT$ | $\Delta S^*/k$ | $\Delta H/kT$ | $\Delta C_p/k$ |
|---|---|---|---|---|
| $CH_4$ | 3.4 | $-7.5$ | $-4.1$ | 29 |
| $n$-$C_4H_{10}$ | 3.6 | $-12.5$ | $-8.9$ | 36 |

Our interest here is in the case where both phases are dilute in A. From equations (3)–(6), the dimensionless $\Delta G^*/kT$, $\Delta S^*/k$, $\Delta H/kT$ and $\Delta C_p/k$ may then be obtained from the equilibrium partition coefficient or Ostwald absorption coefficient $\Sigma$ by

$$\Delta G^*/kT = -\ln \Sigma, \qquad (8)$$

$$\Delta S^*/k = \partial(T \ln \Sigma) / \partial T, \qquad (9)$$

$$\Delta H/kT = T \partial(\ln \Sigma) / \partial T, \qquad (10)$$

$$\Delta C_p/k = T \partial^2(T \ln \Sigma) / \partial T^2. \qquad (11)$$

These quantities are now, in this dilute case, all independent of the concentrations of A in the two phases, and indeed are independent of whether the transfer of the molecule of A from $\alpha$ to $\beta$ occurs at equilibrium or not. The significance of equations (8)–(11) is that they relate these now invariant quantities to the experimentally measurable equilibrium $\Sigma$ and its temperature dependence.

In table 1 we present as illustration the values of these quantities at $T = 300$ K for $CH_4$ and $n$-$C_4H_{10}$ as calculated with equations (8)–(11) from the smoothed experimental Ostwald absorption coefficients given by Battino [11]. We see the characteristically negative $\Delta S^*$ and $\Delta H$, positive $\Delta G^*$, and large and positive $\Delta C_p$ [7, 8, 12]. We see also that $\Delta H$ and $T \Delta S^*$ largely cancel in $\Delta G^*$, leaving $\Delta G^*$ smaller in absolute value than either. The hydration free energies of $CH_4$ and $n$-$C_4H_{10}$ are about the same at this temperature (an example of the frequently remarked 'enthalpy–entropy compensation' [13–15]), but the other quantities are greater in absolute value for $n$-$C_4H_{10}$ than for $CH_4$.

There is a vast literature of attempts to account for these numbers by microscopic theory and simulation. Numerous references to both the older and more recent literature may be found in the authoritative review by Pratt [16].

## 3. Model

Any model in which the forced accommodation of a solute in a solvent is energetically favourable but even more unfavourable entropically could in principle provide a theoretical framework within which to study the connection between hydrophobic attraction and hydrophobic hydration. We do so here with a lattice model introduced previously and studied in one-, two- and three-dimensional versions [17, 18].
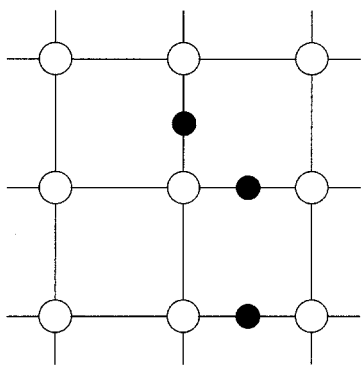
Figure 1. Lattice model, with large open circles at the lattice sites representing solvent molecules and small filled circles on bonds between sites representing solute molecules.

The model is pictured schematically in figure 1. Each lattice site is occupied by a solvent molecule, each of which may be in any of $q > 1$ internal states or orientations. Solute molecules may be present only on the bonds between lattice sites, at most one on any bond, and then only if the two solvent molecules at the sites joined by that bond are both in a special one—say, state number 1—of the $q$ possible states. Neighbouring solvent molecules that are both in that special state interact with each other with interaction energy $w$; neighbouring solvent molecules that are not both in that special state interact with each other with energy $u > w$; and an accommodated solute on the bond between two solvent sites interacts with them with interaction energy $v$. The parameters of the model are then $q - 1 > 0$, $u - w > 0$ and $v$. Accommodating a solute molecule thus forces the two neighbouring solvent molecules into energetically favourable but restricted (each to one out of the $q$) orientations.

The model solvent characterized by the parameters $q - 1$ and $u - w$ is equivalent to an Ising spin model on the underlying lattice or to the corresponding one-component lattice gas. If $J$ is the spin–spin interaction energy parameter and $H$ is the external magnetic field, in standard Ising-model notation, then at temperature $T$ and on a lattice of coordination number $Z$ these are related to $u - w$ and $q - 1$ by [19]

$$J = \tfrac{1}{4}(u - w), \quad 2H = \tfrac{1}{2}Z(u - w) - kT \ln(q - 1). \quad (12)$$

For the equivalent one-component lattice gas, in which the volume is divided into cells of volume $v_0$, each centred at one site of the lattice, and in which molecules in neighbouring cells interact with energy $-\varepsilon$, the correspondence is

$$\varepsilon = u - w, \quad v_0 z = 1/(q - 1), \quad (13)$$

where $z$ is the thermodynamic activity of the gas. With this mapping the fraction $P_1$ of solvent molecules in the

model solvent that are in the special state number 1 at equilibrium, in the absence of solutes, is the same as the fraction of occupied cells in the underlying one-component lattice gas, or equivalently the fraction of $\uparrow$ spins (the direction of the field) in the Ising model.

To assign physically realistic values of the parameters $q - 1$, $u - w$ and $v$ in the model solution we choose them to reproduce as closely as possible the experimental values of the Ostwald absorption coefficient $\Sigma$ for methane in water in the temperature interval $273\,\text{K} \leqslant T \leqslant 328$ or $333\,\text{K}$. The Ostwald coefficient $\Sigma$ of methane goes through a minimum at around $350\,\text{K}$, where the transfer enthalpy $\Delta H$ (but not $\Delta S^*$) then changes sign [8]. Such solubility minima are characteristic of most hydrocarbons [20]. With the appropriate values of the parameters $q - 1$, $u - w$ and $v$ the present model is capable of yielding a $\Sigma$ with a minimum as a function of $T$, but then $\Sigma$ itself is much too low to match that of methane [17]. In neither the one- nor the three-dimensional version of the model have we found it possible to fit both the magnitude of $\Sigma$ appropriate to methane and the temperature minimum, which is the reason we restrict the fitting to the interval $273\,\text{K} \leqslant T \leqslant 328$ or $333\,\text{K}$.

For this model, in any number of dimensions, $\Sigma$ is given by [17, 18]

$$\Sigma = P_{11} \exp\left(-v/kT\right), \quad (14)$$

where $P_{11}$ is the probability that a pair of neighbouring molecules in the model pure solvent be both in the special orientation 1. In the underlying Ising model, with the transcriptions (12), it is the probability that the spins at a pair of neighbouring sites be both $\uparrow$. In the equivalent one-component lattice–gas model, with the transcriptions (13), it is the probability that the cells centred at a pair of neighbouring sites be both occupied.

In the one-dimensional version of the model, $P_{11}$ is known explicitly [17]:

$$P_{11} = \frac{1/c}{\begin{array}{c} -(x-1)[1-(1/c)] + \tfrac{1}{2}[x - 1 + (2/c)] \\ \times [x + 1 + [(x-1)^2 + (4x/c)]^{1/2}] \end{array}}, \quad (15)$$

where

$$x = \frac{q-1}{c}, \quad c = \exp\left[(u - w)/kT\right]. \quad (16)$$

The best fit of $-T \ln \Sigma$ from (14)–(16) to the experimental $-T \ln \Sigma$ for $273\,\text{K} \leqslant T \leqslant 328\,\text{K}$ is with the parameter values

$$q - 1 = 16.35, \quad (u - w)/k = 664.14\,\text{K}, \quad v/k = 265.51\,\text{K}. \quad (17)$$
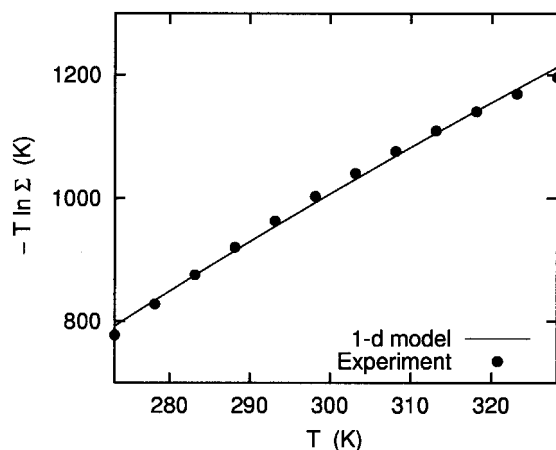
The fit is shown in figure 2.

Figure 2. Fit of $-T \ln \Sigma$ of the one-dimensional lattice model to the experimental values for methane, with the parameter values in (17).
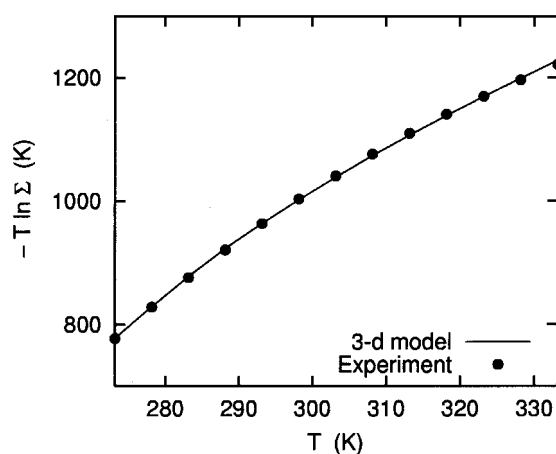


Figure 3. Fit of $-T \ln \Sigma$ of the three-dimensional (bcc) lattice model to the experimental values for methane, with the parameter values in (18).

For the three-dimensional version of the model, Monte Carlo simulations were performed on the equivalent Ising model on a bcc (body-centred cubic) lattice (coordination number $Z = 8$) with periodic boundary conditions. Following Barkema and Widom [18], a modified Bortz–Kalos–Lebowitz [21] scheme was used so that the detailed balance condition was strictly satisfied for any system size and the acceptance ratio could be kept high at any thermodynamic state. In order to determine appropriate values for the parameters, simulations were performed systematically for various trial values of $\ln(q-1)$ and $u - w$ on a lattice of $N = 2 \times 50^3 = 250\,000$ sites. Then, simulations with fixed $\ln(q-1)$ and $u - w$ were performed at various $T$ on a lattice of $N = 2 \times 26^3 = 35\,152$ sites to obtain the correlation functions. For the latter simulations, equilibrium properties at each temperature were obtained from averages over 5 sets of independent simulations of 10 000 steps each, where a single step is defined as $N$ trial moves.

The required $P_{11}$, hence also $\Sigma$, from (14), was obtained in the simulations. The parameter values that best fit the experimental $-T \ln \Sigma$ for methane over the interval $273\,\mathrm{K} \leqslant T \leqslant 333\,\mathrm{K}$ were

$$q - 1 = 6.7, \quad (u - w)/k = 128.3\,\mathrm{K}, \quad v/k = 406.7\,\mathrm{K}. \tag{18}$$

The fit is shown in figure 3. Over this temperature interval the fit is nearly perfect, unlike in the one-dimensional case in figure 2.

The probability $P_1$ that a solvent molecule be in its special orientation (or that a spin in the underlying Ising model be $\uparrow$ or that a cell in the one-component lattice

gas be occupied) is also known analytically for the one-dimensional version of the model [22]:

$$P_1 = \frac{1}{2}\left[1 - \frac{x^{1/2} - 1/x^{1/2}}{[(x^{1/2} - 1/x^{1/2})^2 + 4/c]^{1/2}}\right] \tag{19}$$

with $x$ and $c$ as in (16). With the $q - 1$ and $(u - w)/k$ in (17), one finds that $P_1$ varies from 0.24 to 0.13 as $T$ varies from 273 to 333 K. From the simulations on the bcc lattice, with the $q - 1$ and $(u - w)/k$ in (18), one finds that $P_1$ varies from 0.47 to 0.26 over that same temperature interval, and so over that interval is twice as great as in one dimension.

In figure 4 is a sketch of the $T$, $P_1$ coexistence curve for the bcc model and the locus of states for which the simulations were done. It is seen that this locus lies well outside the region of phase separation. With the value of $(u - w)/k$ in (18) and the relation $J = (u - w)/4$ from (12), one finds the critical temperature in the bcc model [23] to be $T_c = 205\,\mathrm{K}$.

## 4. Hydrophobic attraction

With what are now realistic values of the model parameters as found in the preceding section, we here calculate the solvent-mediated part, $W(r)$, of the potential of mean force between pairs of solute molecules in the model. This is the potential of mean force from which the direct solute–solute interaction potential has been subtracted. For both the one-dimensional model and the three-dimensional bcc model we take $r$ to be in units of the closest possible distance between two solutes, so that $r = 1$ at that distance.

In this model $W(r)$ depends only on the parameters $u - w$ and $q - 1$; it is independent of the solute–solvent interaction-energy parameter $v$. This is in accord with
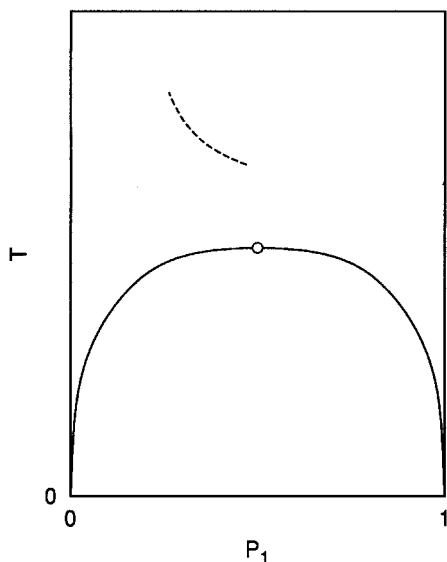
Figure 4. Sketch of the $T$, $P_1$ coexistence curve for the bcc model (solid curve), together with the locus of states for which the simulations were done (dashed curve).
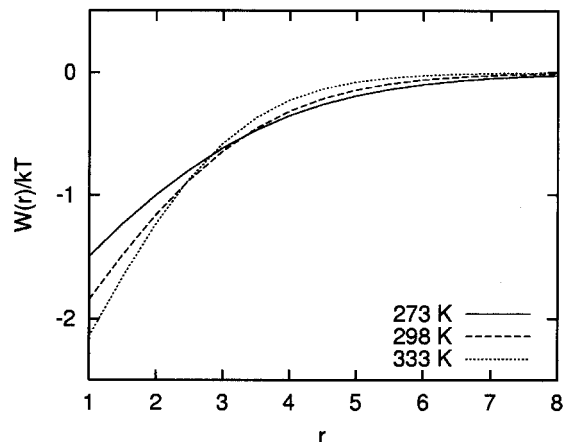


Figure 5. $W(r)/kT$ for the one-dimensional model, as functions of $r$ at three temperatures.
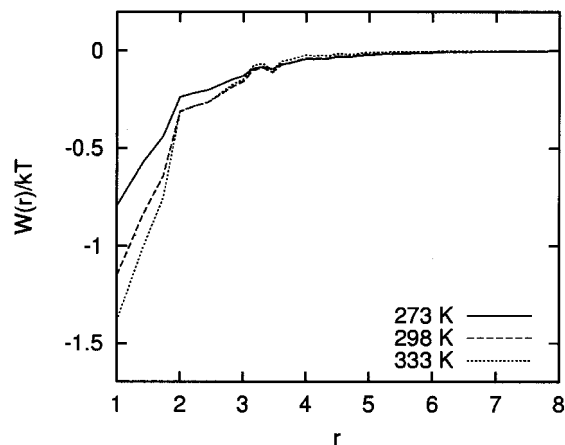


Figure 6. $W(r)/kT$ for the three-dimensional model, as functions of $r$ at three temperatures.

what Pratt and Chandler found in their pioneering study [24].

The potential $W(r)$ in these lattice models is given by [17, 18]

$$W(r) = -kT \ln\left[P(r)/P_{11}^2\right], \qquad (20)$$

where $P_{11}$ is as defined just below equation (14), and where $P(r)$ is the probability that two bonds, the centres of which are a distance $r$ apart, be both available to accommodate a solute; i.e. that the solvent molecules at the pairs of lattice sites connected by those bonds be all in the special orientation 1. In the one-dimensional model $P(r)$ and $P_{11}$ are known analytically [17]. In figure 5, $W(r)/kT$ is shown as a function of $r$ for each of the three temperatures 273, 298 and 333 K, with the parameters $u - w$ and $q - 1$ in (17). For the three-dimensional bcc model $P(r)$ and $P_{11}$ are obtained in the simulations. In figure 6, $W(r)/kT$ is shown as a function of $r$ at those same three temperatures, with the parameters $u - w$ and $q - 1$ in (18).

With these values of the parameters and at these temperatures $W(r)$ in the three-dimensional model is seen to have practically reached its limiting value of 0 at $r = 4$ or 5. In one dimension $W(r)$ decays at long distances proportionally to $\exp(-r/\xi)$ and in three dimensions proportionally to $(1/r)\exp(-r/\xi)$ [25], with exponential decay lengths $\xi$ that depend on the parameters $u - w$ and $q - 1$ and on the temperature. For the one-dimensional model $\xi$ is known analytically [17]:

$$\xi = \frac{1}{\ln\dfrac{1 + S}{1 - S}}, \qquad (21)$$

where

$$S = \left[1 - \frac{4x}{(1 + x)^2}\left(1 - \frac{1}{c}\right)\right]^{1/2} \qquad (22)$$

with $x$ and $c$ as defined in (16). With the values of $u - w$ and $q - 1$ in (17) one finds $\xi = 1.403$, 1.120 and 0.887 at the respective temperatures 273, 298 and 333 K. That $\xi$ decreases with increasing temperature, so that $W(r)$ becomes shorter ranged as $T$ increases, was remarked on before [17, 18], and is also apparent here in figure 5 from the crossing of the curves. The decreasing range of $W(r)$ with increasing $T$ is also apparent in figure 6 for the three-dimensional model.

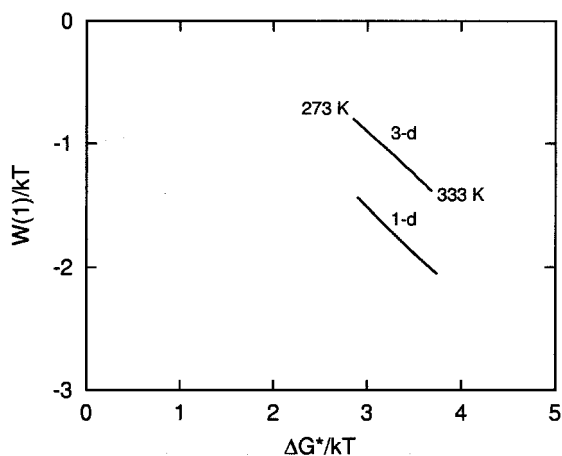The main aim of this study is to find how $W(1)$, which we take as the measure of the strength of the

Figure 7.   $W(1)/kT$ versus $\Delta G^*/kT$ in the temperature interval $273\,\mathrm{K} \leqslant T \leqslant 333\,\mathrm{K}$. The upper curve is for the three-dimensional model, the lower one for the one-dimensional model.

solvent-mediated attraction between solute molecules, is correlated with $\Delta G^*$, the hydration free energy of an isolated solute molecule as defined in equation (2) and related to the Ostwald coefficient $\Sigma$ by equation (6). Except for a factor of the Boltzmann constant $k$, the required $\Delta G^*$ is then the $-T \ln \Sigma$ which is plotted for the one- and three-dimensional models in figures 2 and 3, respectively.

In figure 7, $W(1)/kT$ is shown plotted against $\Delta G^*/kT$ over the temperature interval $273\,\mathrm{K} \leqslant T \leqslant 333\,\mathrm{K}$ for the one- and three-dimensional models. These are nearly linear over this temperature range, and for the two models are nearly parallel. Both the strength of the attraction $-W(1)$ and the hydration free energy $\Delta G^*$ increase with increasing temperature, so $W(1)$ becomes more negative with increasing $\Delta G^*$, as seen in the figure. For given $\Delta G^*$, the attraction $-W(1)$ is stronger in the one-dimensional model. In the three-dimensional model, the nearly linear relation between $-W(1)/kT$ and $\Delta G^*/kT$ is

$$-W(1)/kT = -1.2 + 0.7\Delta G^*/kT. \qquad (23)$$

At $T = 300\,\mathrm{K}$, the strength $-W(1)$ of the attraction in the three-dimensional model is about one-third of $\Delta G^*$ at that temperature. It is understandable that $-W(1)$ should be less than $\Delta G^*$. As remarked in section 1, an isolated solute molecule adversely (i.e. with an increase in free energy) affects some volume of surrounding solvent, while the total volume so affected by two solute molecules that are close together is less than the sum of the two separate volumes. Suppose the volume so affected by a single solute molecule is $v_1$, that by a pair of solutes close together is $v_2$, and that there is some unfavourable free-energy density $f > 0$. Then the

magnitude of the solvent-mediated attraction between the two solute molecules is $f(2v_1 - v_2) > 0$. This is the analogue of $-W(1)$, while $fv_1$ is the analogue of $\Delta G^*$. But, while $v_2$ is less than $2v_1$, it is greater than $v_1$. Thus, $2v_1 - v_2 < v_1$, so $-W(1) < \Delta G^*$. This is seen to be true for both curves in figure 7.

It is remarked in the literature [24, 26, 27] that the methane–methane potential of mean force in water (including the direct methane–methane interaction) has both a 'contact' minimum and, at larger distances, a much shallower 'solvent-separated' minimum. From simulations of realistic models by Smith and Haymet [26] and Garde *et al.* [27] we may estimate the solvent-mediated contributions to these minima at $298\,\mathrm{K}$ to be $-0.5$ or $-0.8\,\mathrm{kcal\,mol}^{-1}$ at the contact minimum, and $-0.1\,\mathrm{kcal\,mol}^{-1}$ at the solvent-separated minimum. Dividing these by $RT$, with $R$ the gas constant, yields the dimensionless $-0.8$ or $-1.4$, and $-0.2$, respectively. The results are markedly dependent on the assumed interaction potentials [26]. Since in the present model '$r = 1$' is the closest a pair of solute molecules may come, our $W(1)$ may reasonably be taken to correspond to the contact minimum. At $298\,\mathrm{K}$ in the three-dimensional version of the model, $W(1)/kT = -1.2$, which is thus in the range of values found with realistic potentials.

## 5.   Summary

The strength $-W(1)$ of the solvent-mediated attraction between a pair of hydrophobic solute molecules in water is correlated with the hydration free energy $\Delta G^*$ of an isolated solute, via a lattice model that incorporates the major mechanism of hydrophobicity. The correlation is displayed in figure 7. The model parameters were chosen to reproduce the solubility of methane in water over the temperature interval $273\,\mathrm{K}$ to $328$ or $333\,\mathrm{K}$. Both $-W(1)/kT$ and $\Delta G^*/kT$ increase with increasing temperature and over that temperature range do so nearly linearly with each other; the approximate linear relation is in equation (23). At $T = 300\,\mathrm{K}$, $-W(1)$ in the three-dimensional version of the model is about one-third of $\Delta G^*$. An argument is given that explains why $-W(1)$ should be less than $\Delta G^*$. It is remarked that $-W(1)$ in the lattice model may reasonably be identified with the solvent-mediated part of the 'contact' minimum in the potential of mean force between a pair of solute molecules.

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