

Models of the Hydrophobic Attraction*

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Some recently proposed models of hydrophobic attraction, equivalent to the Ising model of ferromagnetism, are described and their properties reviewed. They are such that the accommodation of a hydrophobic solute in the solvent is energetically favorable but even more unfavorable entropically, which is believed to be the basic mechanism of hydrophobicity in water solution. The effective attraction between pairs of solute molecules as mediated by the solvent is calculated, as is the deviation from additivity in the interactions among three or more. The very low solubilities of the solutes in the model solvents are also calculated. In a different model, based on a phenomenological free energy leading to a closed-loop solubility curve in the temperature-composition plane, one finds the same very great increase in heat capacity on dissolving a hydrophobic solute as is found in experiment.

Key words: lattice model, solution, solvation, solubility, thermodynamics

When a hydrophobic solute such as a hydrocarbon molecule dissolves in water, both the energy and entropy decrease; that is, the dissolution is energetically favorable but entropically unfavorable. It is on balance so unfavorable that the solubility is very low. The net increase in free energy when two such solute molecules are accommodated in the solvent is less when they are close together than when they are far apart, with the consequence that there is an effective, solvent-mediated attraction between them. This is the hydrophobic attraction, which is of importance in many areas of physical chemistry and biochemistry [1–12]. It is closely related to the solvation force as calculated in the beautiful paper by Evans and Stecki [13].

Lattice model: To illustrate this mechanism [14], we adapted a one-dimensional lattice model originally proposed as a student exercise in statistical mechanics by Ben-Naim [15]. At each site is a molecule that can be in any of q different states or take on any of q different orientations. Only nearest neighbors interact, which they do with energy w if both are in a special one of the q states and with energy $u > w$ otherwise. In our adaptation of the model we take those molecules to constitute the solvent and we then add a second species as a solute to the model solvent. The solute molecules are only allowed to occupy interstitial sites, with a finite energy v , but then only if the two

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solvent molecules between which the solute is to be accommodated are both in that special orientation in which their own interaction energy is the lower energy w rather than the higher energy u . In this way the energetic contribution to the free energy of solvation is the favorable $-(u-w)$, while the entropic contribution is the unfavorable $kT\ln(q-1)$, where k and T are the Boltzmann constant and the absolute temperature, respectively.

Specifically,

$$\Delta F = -(u-w) + kT\ln(q-1) \quad (1)$$

is the cost in free energy of forcing a solvent molecule to be in its special orientation when a specified one of its neighbors is already in that orientation. The solute is hydrophobic when $\Delta F > 0$. It is an immediate consequence of (1) that the hydrophobic effect is stronger at higher temperatures than at lower. This agrees with experiment.

The properties of this one-dimensional model are found analytically [14]. Let P_{11} be the probability, **in the pure solvent**, that the molecules at a given pair of neighboring sites be both in their special orientation, and let $P(r)$ be the probability that the molecules at two such pairs of sites be all in that special orientation when the distance (measured as a multiple of the lattice spacing) between the first pair of neighbors and the second is r . Then, independently of the solvent-solute interaction energy v , the solvent-mediated part, $W(r)$, of the potential of mean force between pairs of **solute** molecules in the model solvent is found from the potential-distribution theory [16] to be

$$W(r) = -kT \ln \frac{P(r)}{P_{11}^2} \quad (2)$$

This is the effective interaction between solutes over and above whatever direct interaction there may be between them. That $W(r)$ is a property of the **solvent** is in accord with earlier ideas [7].

For this one-dimensional model the two probabilities $P(r)$ and P_{11} are found by transfer-matrix methods [17], with the result that

$$W(r) = -kT \ln \left[1 + \frac{1+Q}{1-Q} \left(\frac{1-S}{1+S} \right)^{r-1} \right] \quad (3)$$

where

$$Q = \frac{x-1}{\sqrt{(x-1)^2 + 4x/c}} \quad (4)$$

$$S = \sqrt{1 - \frac{4x}{(1+x)^2} \left(1 - \frac{1}{c}\right)} \quad (5)$$

$$c = e^{(u-w)/kT}, \quad x = \frac{q-1}{c} \quad (6)$$

The range (exponential decay length) ξ of the potential W is, according to (3),

$$\xi = \frac{1}{\ln \frac{1+S}{1-S}} \quad (7)$$

Typically, ΔF in (1) is much less than either $u-w$ or $kT \ln(q-1)$ separately, which are themselves much greater than kT , with the result that $c \gg x$. We then have

$$\xi \simeq kT/\Delta F \quad (8)$$

The numerator in (8) increases with increasing T at the rate k , while the denominator, according to (1), increases with T at the much greater rate $k \ln(q-1)$, so while the strength of the hydrophobic interaction, measured by ΔF , increases with increasing T , its range, ξ , decreases with increasing T . These conclusions are clear in Figs. 1 and 2, which show the potential $W(r)$ (in units of k) and the corresponding attractive force $-W'(r)/k$ (in units of k and the lattice spacing), as functions of r , for the three temperatures 275, 300, and 348 K, having chosen for the parameters the values $(u-w)/k = 3000$ K and $q-1 = 110\,000$.

The solubility of the hydrophobic solute in the model solvent is given by the dimensionless quantity Σ ,

$$\Sigma = P_{11} e^{-v/kT} \quad (9)$$

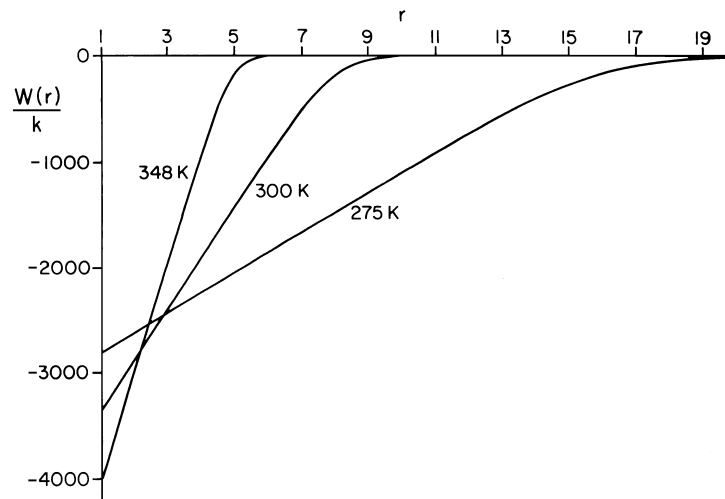


Figure 1. Solvent-mediated potential of mean force between a pair of solute molecules, in units of the Boltzmann constant, as a function of the distance r between molecules, in units of the lattice spacing.

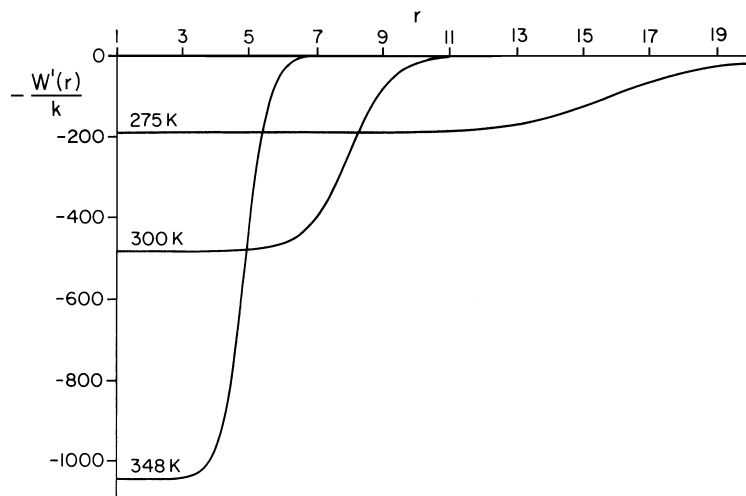


Figure 2. Solvent-mediated mean force between pairs of solute molecules.

where now the solute-solvent interaction parameter v enters. The probability P_{11} , as determined from the model's transfer matrix, is

$$P_{11} = \{-(x-1)(c-1) + \frac{1}{2}[(x-1)c + 2][x + 1 + (x-1)/Q]\}^{-1} \quad (10)$$

with x , c , and Q as defined in (4) and (6). Again with $c \gg x$, the solubility Σ becomes

$$\Sigma \simeq \frac{e^{-v/kT}}{(x-1)^2 c} \quad (11)$$

This decreases with increasing T at low temperatures and continues decreasing if $v < u-w$; but if $v > u-w$, after initially decreasing with increasing T , the solubility reaches a minimum and then increases. The decrease is a manifestation of the increasing strength of the hydrophobic effect with increasing temperature, while the subsequent increase in the solubility, when it occurs, is the more common effect of temperature ultimately manifesting itself. Such variations with temperature of the solubility of hydrophobic solutes in water are as observed in experiment and in simulations [18].

Two and three dimensional versions of this model have also been studied [19]. The problem is then no longer analytically soluble, but $W(r)$ and Σ are still given by (2) and (9), while the required probabilities $P(r)$ and P_{11} are obtained by Monte Carlo simulation. The results are qualitatively similar to those in the one-dimensional version of the model, although now $W(r)$ has some small oscillations, reflecting the greater geometrical complexity of the lattice in the higher dimensions. Such oscillations are seen also in models in which the solvent is modeled more realistically [7, 11].

An interesting recent development [20] has been the demonstration that these lattice models are equivalent to an Ising model on the same lattice. The spin-spin inter-

action-energy parameter J and magnetic field H in the equivalent Ising model are related to the present parameters $u-w$ and $q-1$ by

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

where Z is the coordination number of the lattice. Here, $H > 0$ favors the special orientation of the solvent molecules in the solution model and $H < 0$ any of the remaining $q-1$ orientations. When $kT \ln(q-1) > (1/2)Z(u-w) \gg kT$, as in the numerical illustration above, almost none of the solvent molecules are in the special orientation. In one dimension, where $Z=2$, we have the identification $2H = -\Delta F$. The potentials of mean force $W(r)$ in the lattice hydrophobic-interaction models are directly transcribable from the spin-spin correlation functions of the Ising model. Such transcription has also been exploited [21] in obtaining potentials of mean force for decorated-lattice-gas models that are likewise equivalent to underlying Ising models.

The general potential of mean force among n solute particles has also been calculated analytically in the one-dimensional version of the model [22] and is found to be the sum of the pair potentials between nearest neighbors only. Thus, for example, the potential among three, $W(r_{12}, r_{23})$, where r_{ij} is the distance between solute molecules i and j and $r_{13} = r_{12} + r_{23}$, is the sum of the two pair potentials $W(r_{12}) + W(r_{23})$. The specifically three-body part of the total $W(r_{12}, r_{23})$, *i.e.*, the difference between it and the sum of the three pair potentials $W(r_{12}) + W(r_{23}) + W(r_{13})$, is then $-W(r_{13})$. This illustrates the deviation from additivity of hydrophobic interactions.

Phenomenological model with closed-loop solubility curve: In Fig. 3 is a schematic representation of a closed-loop solubility curve in the temperature-composition plane of a binary (A,B) liquid mixture at fixed pressure. It has been noted (see, for example, the brief remark in [11]) that the lower critical solution point is a manifestation of the hydrophobic effect. For states on the lower part of the curve, the mutual solubility of A and B decreases with increasing temperature. If component B is water then the decreasing solubility of A with increasing temperature is one of the signatures of the hydrophobic effect, as noted in the preceding section.

In addition, if at fixed temperature and pressure a molecule of A from the relatively A-rich phase is transferred to the relatively B-rich phase with which it is in equilibrium, and if this occurs in an equilibrium state on the lower part of the curve, where the solubility of A in B is decreasing with increasing T , then the entropy and enthalpy changes ΔS and $\Delta H (= T\Delta S)$ accompanying the transfer are both negative, which again is characteristic of the hydrophobic effect. [When one subtracts from this entropy of transfer the ideal $k \ln(x_A^\alpha / x_A^\beta)$, where x_A^α is x_A in the A-rich phase **from** which the transfer is made and x_A^β is x_A in the coexisting B-rich phase **to** which it is made, the result, which is the part of the entropy of transfer that is due only to the accompanying structural changes in the phases, is then even more negative.] By contrast, when such a transfer occurs in states on the upper part of the curve, ΔS and ΔH are both positive. The sign change occurs at some temperature between that at which

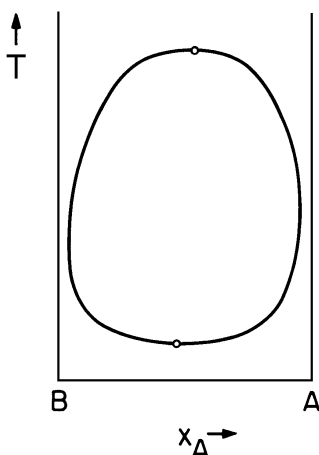


Figure 3. Closed-loop solubility curve in the temperature-composition plane at fixed pressure, for a mixture of species A and B.

$dx_A/dT = 0$ on the left-hand branch of the coexistence curve and that at which $dx_A/dT = 0$ on the right-hand branch. When in a theoretical model those two temperatures are the same by symmetry, the sign change occurs at that common temperature, which is also where the coexistence curve is at its widest.

It is also frequently noted that the partial molar heat capacity with respect to solute concentration of a dilute aqueous solution of a hydrophobe is characteristically large and positive, in contrast with that for a non-hydrophobic solute [12,23–32]. We have studied a model based on a phenomenological free energy that leads to a closed-loop solubility curve such as that in Fig. 3, and with this model have calculated the difference between the partial molecular heat capacity of A at infinite dilution in B and the heat capacity per molecule of pure A, as a function of the temperature [33].

Our model Gibbs free energy $G(T,p,N_A,N_B)$ as a function of temperature T , pressure p , and the numbers of molecules N_A and N_B is

$$G(T,p,N_A,N_B) = N_A (\mu_A^\circ + kT \ln x_A + \omega x_B^2) + N_B (\mu_B^\circ + kT \ln x_B + \omega x_A^2) \quad (13)$$

where $\mu_A^\circ = \mu_A^\circ(T,p)$ and $\mu_B^\circ = \mu_B^\circ(T,p)$ are the chemical potentials of pure A and B, where $x_A = N_A/(N_A + N_B)$ and $x_B = N_B/(N_A + N_B)$ are the mole fractions, and where $\omega = \omega(T,p)$, at any fixed p , is a function of T that depends on three (in principle pressure-dependent) parameters θ , T_U , and T_L ,

$$\omega = \frac{1}{2} \frac{kT}{\theta + (1 - 4\theta)[(T - T_m)/(T_U - T_L)]^2} \quad (14)$$

with

$$T_m = \frac{1}{2} (T_U + T_L) \quad (15)$$

With $0 < \theta < 1/4$ this implies a closed-loop coexistence curve such as that in Fig. 3, with T_U and T_L the temperatures of the upper and lower critical points.

The difference between the partial molecular constant-pressure heat capacity $(\partial C_p / \partial N_A)_{T,p,N_B}$ of A at infinite dilution in B, and the constant-pressure heat capacity per molecule c_p^A of pure A, is readily calculated from (13)–(15). This difference, divided by the Boltzmann constant k so that it is dimensionless, and with the parameter values

$$\theta = 0.15, T_U = 425 \text{ K}, T_L = 300 \text{ K}, \quad (16)$$

is plotted as a function of T over the range $275 \text{ K} < T < 450 \text{ K}$ in Fig. 4. With this value of θ the compositions of the coexisting phases at the coexistence curve's widest part, which occurs at $T = T_m = 362.5 \text{ K}$, are $x_A = 0.954$ and $x_B = 0.046$ in the A-rich phase and **vice versa** in the B-rich phase. The mutual solubility at this temperature is thus 4.6%.

The plotted heat capacity difference has a very high maximum, approximately 150 k , at $T \approx 368 \text{ K}$, just a little above T_m . It is large and positive wherever the mutual solubility is low but not where it is high. We have not specified the pressure dependence of any of the quantities in our phenomenological model. It is observed in experiment that a closed-loop solubility curve usually becomes smaller, *i.e.*, that the mutual solubility of A and B increases, with increasing pressure [34]. Our present results imply that the heat capacity anomaly should then also decrease with increasing pressure, eventually disappearing entirely. This is in accord with what has been observed in molecular dynamics simulations [32].

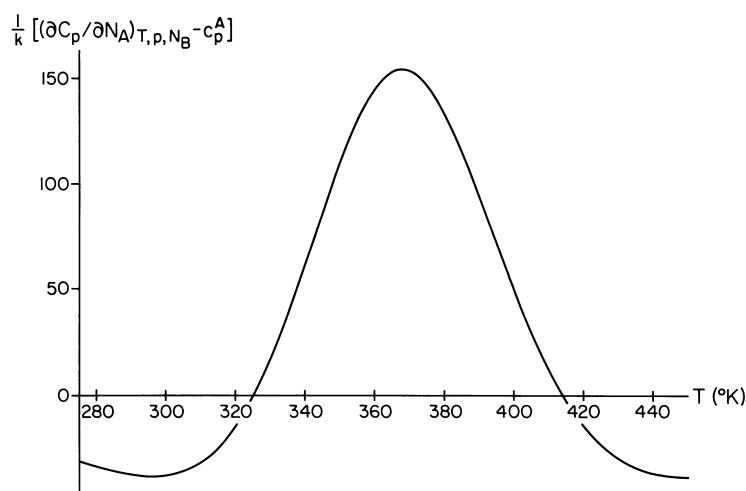


Figure 4. Difference between the partial molecular constant-pressure heat capacity of A at infinite dilution in B and the constant-pressure heat capacity per molecule of pure A, as a function of the temperature.

With the same model one may also calculate the limiting entropy difference Δs^* defined by

$$\Delta s^* = \lim_{x_A' \rightarrow 0} [\Delta s - k \ln (1/x_A')], \quad (17)$$

where Δs is the entropy of isothermal transfer of an A molecule from pure A to a B-rich solution in which $x_A = x_A'$. The heat capacity difference that is plotted in Fig. 4 in units of k is also $T d\Delta s^*/dT$, or $\lim \partial\Delta s/\partial \ln T$. With the same values of the parameters as in that figure, Δs^* is negative at temperatures below 370 K, as a manifestation of the hydrophobic effect, and positive above. Thus, the heat capacity anomaly is greatest not where the hydrophobic effect is greatest but near where it vanishes, and where the previously hydrophobic solute becomes hydrophilic.

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