

Hydrophobic Effect

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The hydrophobic effect refers to the relatively poor solubility of nonpolar substances in water. The effect is seen in the organization of biomolecules such that nonpolar portions are largely sequestered from the aqueous environment. The origin of the effect lies in the response of the three-dimensional hydrogen bonding network of water to different types of solutes.

Hydrophobicity

Hydrophobic (literally, water-fearing) substances are ones that are poorly soluble in water compared with their solubility in nonpolar solvents. For example, the solubility of ethane at 1 atm and 25°C is 0.21 mol L⁻¹ in carbon tetrachloride (Wilhelm and Battino, 1973), but only 1.9 × 10⁻³ mol L⁻¹ in water (Ben-Naim and Marcus, 1984b). In general, ethane equilibrates between nonpolar solvents and water at a molar concentration ratio of about 100:1, and the partitioning of larger nonpolar solutes disfavours water still more strongly. As a result, nonpolar solvents are very effective at extracting nonpolar solutes from water.

The biological interest in hydrophobicity stems from its role in the intramolecular and intermolecular associations of biomolecules. Lipids, with polar head groups and nonpolar tails, assemble into bilayers, with the head groups in contact with water, while the tails are sequestered from water and solvate one another. Proteins, with both polar and nonpolar side-chains, fold with the nonpolar groups largely turned inward so they avoid water. Hydrophobic groups remaining on protein surfaces are often buried in supramolecular assembly, including insertion into membranes, self-assembly into filaments, and docking with other molecules.

Thermodynamics of Transfer

Often solubilities are rationalized in terms of the favourability of interactions between solute and solvent, as compared with solvent–solvent interactions and solute–solute interactions. The maxim that ‘like dissolves like’ is based on the idea that dipole interactions occur only between polar molecules and these are lost when polar molecules are mixed with nonpolar molecules. The expectation then is that immiscibility occurs because the enthalpic disadvantages of mixing prevail over the entropic advantages of mixing so that, overall, the free energy of mixing is unfavourable. Likewise, we expect that transfer of a nonpolar solute from a nonpolar solvent to a polar

solvent will be enthalpically unfavourable owing to the disruption of solvent–solvent dipole interactions.

As it turns out, water is not an ordinary polar solvent, and the foregoing expectations are not generally met for transfer of nonpolar solutes from a nonpolar solvent to water. **Figure 1** shows the thermodynamic results obtained for transfer of ethane from carbon tetrachloride to water when the molar concentrations are the same in the two phases (so that dilution effects make no contribution to the entropy). The term ‘local’ is used when this molar standard is applied because the thermodynamic quantities then correspond to the hypothetical process of transferring the solute from a fixed position in one solvent to a fixed position in the other (Ben-Naim and Marcus, 1984a). At equilibrium the Gibbs free energy change (ΔG) is zero, and the equilibrium concentrations in the water and the organic phase obey the condition described by eqn [1].

$$0 = \Delta G = \Delta G^\circ + RT \ln(c^{\text{water}}/c^{\text{organic}}) \quad [1]$$

The standard free energy change is thus related to the partition coefficient $K_d = (c^{\text{water}}/c^{\text{organic}})$ by eqn [2].

$$\Delta G^\circ = -RT \ln K_d \quad [2]$$

This free energy change includes an enthalpic contribution (ΔH°) and an entropic contribution (ΔS°) in the combination shown in eqn [3].

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad [3]$$

These contributions can be teased apart in two ways. One is to obtain ΔG° for a range of temperatures and obtain ΔS° from the relation $\Delta S^\circ = -\partial\Delta G^\circ/\partial T$. More recently, the development of calorimeters sensitive enough for studies of very dilute solutions has made it possible to measure ΔH° directly.

Figure 1 shows that the transfer of ethane from carbon tetrachloride to water is generally unfavourable ($\Delta G^\circ > 0$). However, it is enthalpically unfavourable ($\Delta H^\circ > 0$) only at relatively high temperatures, while it is entropically unfavourable ($\Delta S^\circ < 0$) in varying degrees throughout the temperature range of liquid water. In fact, both ΔH° and

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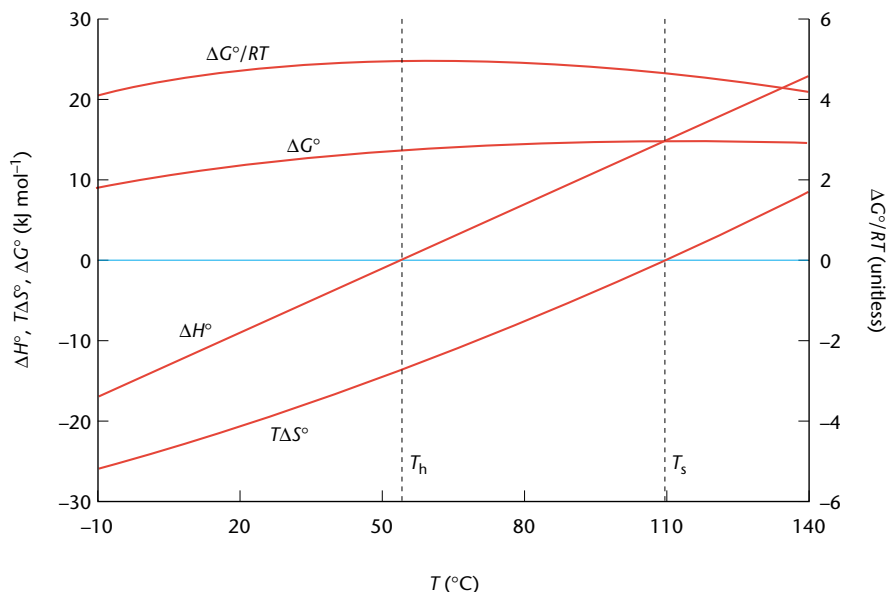


Figure 1 The thermodynamics of transfer of ethane from carbon tetrachloride to water. T_h and T_s represent the temperatures at which ΔH° and ΔS° of transfer are zero, respectively. At T_s , ΔG° is at its maximum, and at T_h , $\Delta G^\circ/RT$ is at its maximum and the partition coefficient $K_d = \exp(-\Delta G^\circ/RT)$ is at its minimum.

ΔS° are strongly temperature dependent, indicating that transfer is accompanied by a large change in the constant pressure heat capacity ΔC_p . Nevertheless, ΔG° only varies weakly with temperature, indicating that the changes in ΔH° and ΔS° are largely compensating. This occurs because ΔC_p appears in both $\partial\Delta H^\circ/\partial T = \Delta C_p$ and $\partial(T\Delta S^\circ)/\partial T = \Delta S^\circ + \Delta C_p$, so this large contribution cancels in the full temperature dependence of ΔG° , as shown in eqn [4].

$$\frac{\partial\Delta G^\circ}{\partial T} = \frac{\partial\Delta H^\circ}{\partial T} - \frac{\partial(T\Delta S^\circ)}{\partial T} = -\Delta S^\circ \quad [4]$$

The interesting feature in the temperature dependence of ΔG° is the curvature. This also reflects the large change in the heat capacity through the relationship shown in eqn [5].

$$\Delta C_p = \frac{\partial\Delta H^\circ}{\partial T} = T \frac{\partial\Delta S^\circ}{\partial T} = -T \frac{\partial^2\Delta G^\circ}{\partial T^2} \quad [5]$$

The positive value of ΔC_p upon transfer from organic to aqueous solution produces a maximum in ΔG° when $\partial\Delta G^\circ/\partial T = -\Delta S^\circ = 0$. This temperature is designated T_s . The positive value of ΔC_p also generates a maximum in $\Delta G^\circ/RT = -\ln K_d$ because when $\partial(\Delta G^\circ/RT)/\partial T = -(\Delta H^\circ/T^2) = 0$, the second derivative must be less than zero, as shown in eqn [6].

$$\frac{\partial^2(\Delta G^\circ/RT)}{\partial T^2} = \frac{\Delta H^\circ}{T^3} - \frac{\Delta C_p}{T^2} < 0 \quad [6]$$

Thus, the partitioning is most hydrophobic (i.e., K_d is the smallest) when $\Delta H^\circ = 0$. At this temperature, designated

T_h , the hydrophobicity is driven entirely by the unfavourable entropy change ($\Delta S^\circ < 0$).

Thermodynamics of Solvation

Interpretation of the thermodynamics of transfer between two solvents is complicated because it involves changes in both of the solvents. Therefore it is desirable to consider dissolution in each phase separately from a solvent-free reference state. **Figure 2** shows the relationships between these processes. Here o and w represent the solute dissolved in organic solvent and water, respectively, while g , l and s represent the gaseous, liquid and solid states of pure solute. Thus the horizontal line represents the transfer between solvents discussed above, the vertical lines represent the condensation–vaporization and freezing–melting transitions of pure solute, and the oblique lines represent the dissolution of solute. Clearly the thermodynamic functions for transfer can be parsed as differences between the thermodynamic functions for dissolution in the two solvents. Using the notation $\delta X = X_b - X_a$, these relationships can be summarized as in eqn [7].

$$\Delta_o^w = \left\{ \begin{array}{l} \Delta_g^w + \Delta_o^g = \Delta_g^w - \Delta_o^g \\ \Delta_l^w + \Delta_o^l = \Delta_l^w - \Delta_o^l \\ \Delta_s^w + \Delta_o^s = \Delta_s^w - \Delta_o^s \end{array} \right\} \quad [7]$$

As a matter of convenience, the reference state for experiments is chosen as the state in which the pure solute is stable under ambient conditions. Translation of

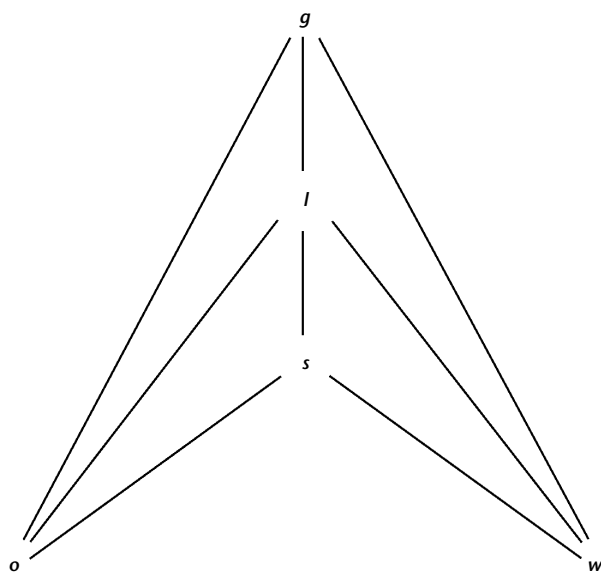


Figure 2 Relationships between the transfer of solute between solvents and the dissolution of pure solute in these solvents. *o* and *w* represent the solute dissolved in organic solvent and water, respectively, while *g*, *l* and *s* represent the gaseous, liquid and solid states of pure solute.

thermodynamic functions to other reference states can then be made by using the thermodynamic functions for the condensation–vaporization and freezing–melting transitions. It is also common to assume that nonpolar liquids are all pretty much alike. In this case, ~ 0 , which gives the expedient result that \sim .

For purposes of interpretation, the most advantageous reference state is the gaseous state. In dilute gases, there are no interactions between the molecules, and for simple molecules the internal degrees of freedom can be assumed to be similar to those that will occur in solution. ‘Solvation’ refers specifically to dissolution from the gaseous state, and we wish to compare solvation in nonpolar solvents with solvation in water. **Table 1** shows such a comparison for

ethane, again using the molar concentration standard (for the gas phase as well as the solutions). It is clear that the various nonpolar solvents show similar behaviour and water is the anomalous solvent. A great deal of attention has therefore focused on understanding hydration (i.e. solvation in water). However, before we focus on water we should note that the nonpolar solvents all show a favourable enthalpy of solvation that presumably reflects attractive dispersion forces, and an unfavourable entropy of solvation that presumably reflects the formation of cavities to accommodate the solute molecules. Overall, the solvation of ethane in nonpolar solvents is favourable ($\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ < 0$) at 25°C. The mystery in the case of hydrophobic hydration is: (1) the more favourable enthalpy and the much less favourable entropy, such that hydration overall is unfavourable ($\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ > 0$); and (2) the relatively large heat capacity, such that there are large temperature dependencies in the enthalpy and entropy which are largely compensating.

Thermodynamics of Hydration

While the hydration of nonpolar molecules like ethane and propane is unfavourable, the hydration of polar molecules is favourable, and a comparison is instructive. **Table 2** shows thermodynamic data for two groups of molecules. The members of each group are isoelectronic. The differences are in the replacement of a methyl group by a hydroxyl group or an amino group. The data show that substitution of a polar group for a methyl group has no significant effect on the entropy of hydration. Rather, it has a major effect on the enthalpy of hydration and the heat capacity of hydration, making the enthalpy change much more favourable and the heat capacity change less dramatic. Between the two groups of molecules, the difference is one methylene unit. Comparison between the two groups shows that all three thermodynamic

Table 1 Local thermodynamic functions for solvation of ethane in water and nonpolar solvents at 25°C

Solvent	ΔH° (kJ mol ⁻¹)	$T\Delta S^\circ$ (kJ mol ⁻¹)	ΔC_p (J mol ⁻¹ K ⁻¹)
Water	-17.46 ^a	-25.14 ^a	272.6 ^b
CCl ₄ ^c	-9.82	-5.66	10.5
Benzene ^c	-7.85	-4.33	12
Acetone ^c	-7.34	-4.44	-17.7
Methyl acetate ^c	-7.05	-4.13	-19.9

^a From Ben-Naim and Marcus (1984b).

^b From Naghibi *et al.* (1987).

^c Derived from the data of Horiuti (1931).

Table 2 Local thermodynamic functions for hydration of polar and nonpolar molecules at 25°C

Solute	ΔH° (kJ mol ⁻¹) ^a	$T\Delta S^\circ$ (kJ mol ⁻¹) ^a	ΔC_p (J mol ⁻¹ K ⁻¹)
CH ₃ -CH ₃	-17.46	-25.14	251 ^b , 272.6 ^c
CH ₃ -OH	-42.89	-21.58	114 ^b , 158.3 ^d
CH ₃ -NH ₂	-42.97	-23.85	105 ^b
CH ₃ -CH ₂ -CH ₃	-20.19	-28.39	295 ^b , 319 ^c
CH ₃ -CH ₂ -OH	-50.42	-29.32	195 ^b
CH ₃ -CH ₂ -NH ₂	-52.31	-33.46	

^a From Ben-Naim and Marcus (1984b).

^b From Cabani *et al.* (1981).

^c From Naghibi *et al.* (1987).

^d From Makhatadze and Privavlov (1990).

functions are accentuated by the addition of a methylene (-CH₂-) group.

More quantitative additivity analyses have been carried out on much larger bodies of data with similar results. The general conclusion is that polar and nonpolar groups make similar contributions to the entropy of hydration and distinctive contributions to the enthalpy and heat capacity of hydration. In fact, the contributions of polar and nonpolar groups to the heat capacity of hydration are of opposite sign. A complete account of hydration must allow for both the similarities and the differences between polar and nonpolar solutes.

Physical Features of Water

One of the remarkable features of water is that it forms a liquid under ambient conditions. The simple hydrides of the nonmetals (XH_n) are small molecules, isoelectronic with the nearest noble gas in the periodic table. Except for water, all form gases under standard conditions. Water is also the only one that has more than one hydrogen bond donor and more than one hydrogen bond acceptor on each molecule. As a result, water is unique among the simple non-metal hydrides in being able to form a three-dimensional hydrogen bonded network. (NH₃, with only one hydrogen bond acceptor per molecule, and HF, with only one hydrogen bond donor per molecule, can only form hydrogen bonded chains.)

Figure 3 shows the 3D network of water when all the hydrogen bonds are straight and of equal length, corresponding to ice I at low temperature. It is a relatively open, low-density structure. At higher temperatures and pressures, the bonds can deform, leading to structures with higher densities. Thus, with increasing temperature the density increases to a maximum at 4°C (after which thermal motion causes the density to decrease again as in

normal liquids), and at high pressures one obtains different forms of ice (ice II, III, etc.). A picture of water that focuses on the bending and stretching of the hydrogen bonds is known as the Random Network Model (Sceats and Rice, 1980). An older picture of variations in water structure conceived of several discrete states. However, the broad, temperature-dependent bands for the OH stretch in Raman and IR spectra of water are more consistent with a continuum of hydrogen bonding states.

3D hydrogen-bonded networks are also formed by some larger molecules, such as hydrazine (H₂N-NH₂) and ethylene glycol (HO-CH₂-CH₂-OH). As shown in **Table 3**, the network liquids (marked with asterisks) are highly cohesive (high boiling point, high surface tension, and small thermal expansion coefficient) compared with isoelectronic species with fewer hydrogen bond donors and acceptors per molecule. **Table 3** also shows that the strength of a 3D network also makes a liquid relatively incompressible.

The relevance of networks to solvation is illustrated in **Tables 4** and **5**. As a nonpolar molecule, argon is much less readily solvated (larger ΔG°) by the network-forming solvents (marked with asterisks) than by isoelectronic solvents without networks (see **Table 4**). The notable difference between the various network-forming solvents is in the distribution of the unfavourable free energy between the enthalpy and the entropy. However, the variations in these contributions are compensating so that the overall free energies are similar. This behaviour is reminiscent of the compensation seen when water is heated. In fact, as shown in **Table 5**, the entropic and enthalpic contributions to argon solvation in ethylene glycol at 25°C are remarkably similar to those in water at 85°C, and the entropic and enthalpic contributions to argon solvation in hydrazine at 25°C are very similar to those in water at about 145°C (at a pressure high enough to maintain a liquid phase).

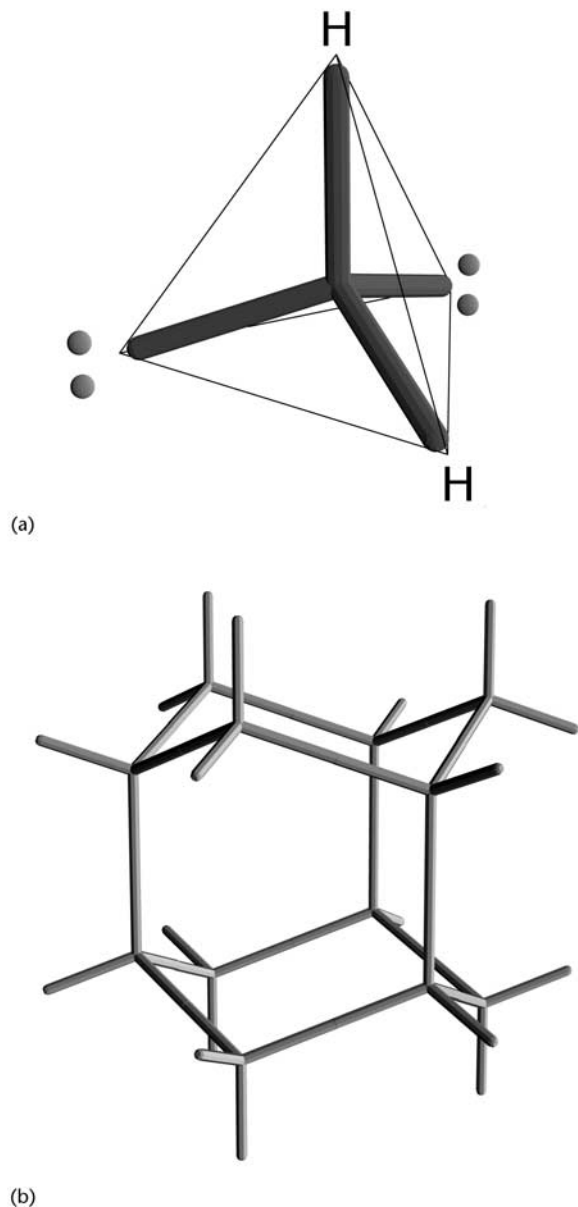


Figure 3 Representation of a single water molecule and the structure of ice I. (a) Water's two hydrogen atoms and two electron pairs are oriented tetrahedrally. (b) In ice I, the tetrahedra are oriented so each water molecule is hydrogen bonded to its four neighbours.

Mechanism of Hydration

The favourable solvent–solvent interactions in solvents that form 3D hydrogen bonding networks are highly directional. Therefore, it can be expected that if solute–solvent interactions are too weak to compete with solvent–solvent hydrogen bonds, then the solvent will orient itself around the solute in such a way as to minimize the loss or

distortion of solvent–solvent hydrogen bonds. The result can be imagined as a hydrogen-bonded cage around the solute, a ‘clathrate’ structure approximating the structures found in the crystalline hydrates of nonpolar solutes.

Figure 4 compares the ways that water molecules can be expected to arrange themselves around different types of solutes. Remember that experimental studies indicate that ΔS° is similar for hydration of polar and nonpolar groups at room temperature. On the other hand, ΔH° and ΔC_p are different: for nonpolar solutes, weaker solute–solvent attractions result in a less favourable ΔH° , while a more constrained hydrogen-bonding arrangement increases the opportunities for stretching and bending to absorb energy with increasing temperature (a positive ΔC_p).

Certain features of the water in the hydration shell around a hydrophobic solute have been measured by sensitive experimental probes. In particular, changes in ^2H NMR relaxation when xenon or benzene are dissolved in D_2O indicate slower rotational motion of the water (Haselmeier *et al.*, 1995; Nakahara *et al.*, 1996). Interestingly, the opposite occurs when the more polar phenol is added to water. Neutron diffraction with isotope substitution has also been used to study hydrophobic hydration. For methane, the coincidence of the first peak in the H and O distributions around the solute indicate that the water molecules are oriented tangentially to the solute surface (de Jong *et al.*, 1997). This orientation (which is illustrated in **Figure 4a**) has the virtue of maximizing the possibility for hydrogen bonds with other water molecules. Tangentially oriented water molecules have also been observed in computer simulations of hydrophobic hydration. Furthermore, analysis of the hydrogen bond lengths and hydrogen bond angles obtained in such simulations (using the Random Network Model) find a positive ΔC_p for hydration of nonpolar solutes and a negative ΔC_p of hydration for polar solutes, consistent with experiments (Madan and Sharp, 1997).

In computer simulations, different parts of individual water molecules are assigned interactions such that bulk water properties are mimicked as closely as possible. However, a number of attempts have been made to make a more direct connection between the distinctive physical properties of bulk water and the characteristics of hydrophobic hydration. These efforts focus on the process of cavity formation since water–solute interactions are weak for nonpolar solutes. One approach emphasizes the size and packing of water molecules. In this analysis, the water molecules are considered as hard spheres. These spheres model the short-range repulsions between water molecules, but the attractions (dispersive, polar and hydrogen bonding) are ‘turned off’. The probability that a solute-size cavity will be vacated in such a collection of spheres can be calculated accurately using Scaled Particle Theory. The probability is lower (corresponding to lower entropy) when the solvent particles are closely packed and when the sizes of the individual solvent particles is small.

Table 3 Normal boiling point (T_b), surface tension (γ), cubic thermal expansion coefficient (α) and isothermal compressibility (κ) for solvents with* and without 3D hydrogen bonding networks^a

Solvent	T_b (°C)	γ (mN m ⁻¹) ^b	$\alpha \times 10^3$ (°C ⁻¹) ^c	$\kappa \times 10^4$ (mPa ⁻¹) ^c
* H ₂ O	100	71.99	0.206	4.591
* H ₂ N–NH ₂	114	66.39		
CH ₃ –OH	65	22.07	1.49	12.14
* HO–CH ₂ –CH ₂ –OH	197	47.99	0.626	3.64
CH ₃ –CH ₂ –CH ₂ –OH	97	23.32	1.22 ^d	8.43 ^d
Cyclohexane	81	24.65	1.15	11.30

^a From Lide (1998).^b At 25°C.^c At 20°C unless otherwise indicated.^d At 0°C.**Table 4** Local thermodynamic functions for solvation of argon at 25°C in solvents with* and without a 3D hydrogen bonding network

Solvent	ΔG° (kJ mol ⁻¹)	ΔH° (kJ mol ⁻¹)	$T\Delta S^\circ$ (kJ mol ⁻¹)
* D ₂ O ^a	8.19	-12.26	-19.54
* H ₂ O ^a	8.37	-11.0	-18.34
* HO–CH ₂ –CH ₂ –OH ^b	11.12	1.04	-10.08
CH ₃ –CH ₂ –CH ₂ –OH ^c	0.67	0.07	-0.61
* H ₂ N–NH ₂ ^c	11.55	10.39	-1.16
CH ₃ –OH ^e	1.97	0.80	-1.17
Cyclohexane ^d	2.73	0.67	-2.04
<i>n</i> -Hexane ^e	1.86	-1.31	-3.17

^a Ben-Naim (1987).^b From Ben-Naim (1968).^c Chang *et al.* (1968).^d Clever *et al.* (1957).^e Abraham (1982).

Since water molecules are unusually small, the entropy of cavity formation in water is unusually unfavourable. This result is mitigated only partially by the relatively open structure (loose packing) of water. If attractions between water molecules were 'turned on', then the energy and entropy of the system would be lower as molecules take advantage of favourable interactions. However, to the extent that these effects are compensating, the free energy will not be much affected. Thus the free energy of cavity formation can be approximated by the hard sphere model, although the enthalpy and entropy cannot. In this model, variations in the free energy of cavity formation with

temperature come entirely from variations in the density of water, and this free energy change is least favourable at 4°C where the density of water is the greatest.

Another approach to modelling cavity formation relates it to the distribution of molecules in bulk water. A full description of the structure of a fluid can be given as a series of particle distribution functions of increasing order: the single-particle distribution corresponds simply to the concentration of water molecules, the two-particle correlation function gives the distribution of particles around a given particle and is directly related to the isothermal compressibility, the three-particle correlation function

Table 5 Local thermodynamic functions for solvation of argon in solvents with 3D hydrogen bonding networks

Solvent	$T(^{\circ}\text{C})$	ΔG° (kJ mol ⁻¹)	ΔH° (kJ mol ⁻¹)	$T\Delta S^{\circ}$ (kJ mol ⁻¹)
* H ₂ O ^a	25	8.37	-11.0	-18.34
* H ₂ O ^a	85	10.74	1.00	-10.1
* Ethylene glycol ^b	25	11.12	1.04	-10.08
* H ₂ O ^a	145	11.39	10.95	-1.02
* Hydrazine ^c	25	11.55	10.39	-1.16

^a From Ben-Naim (1987), using the heat capacity data as needed.

^b From Ben-Naim (1968).

^c Chang *et al.* (1968).

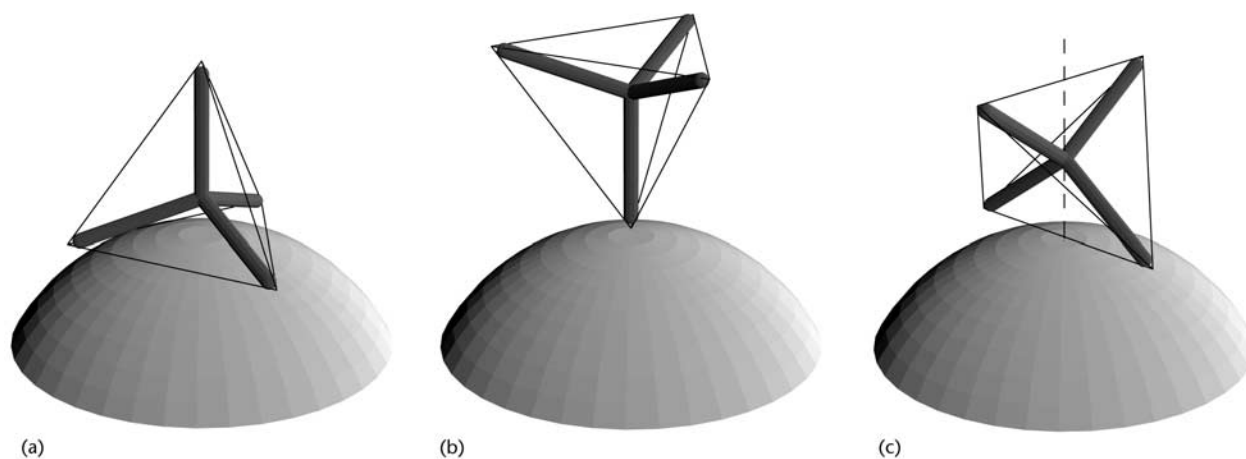


Figure 4 Favourable orientations of water at the surface of a solute that is (a) nonpolar, (b) hydrogen bonding, and (c) polar but not hydrogen bonding (the dashed line indicates the dipole axis).

gives the distribution of particles around a given pair of particles, and so on. Since the correlation functions express the probabilities of different spacings between particles, they are related to the energies of the most favourable orientations at different spacings. Thus, the correlation functions contain information on how water molecules form cavities, including how they arrange themselves around the cavities. As it turns out, a good estimate of the free energy of cavity formation in water can be made without going beyond the two-particle correlation function. In particular, a good description of hydrophobic hydration can be had from Information Theory by maximizing the entropy subject to the constraint of matching just the concentration and the

isothermal compressibility of bulk water (Hummer *et al.*, 1998).

The foregoing experimental and theoretical results include recent insights into hydrophobic hydration made possible by advances in experimental and theoretical methods. This remains an active field and further progress is expected.

Hydrophobic Interactions

So far, we have considered the transfer of solute from one macroscopic phase to another. However, when hydro-

phobic molecules sequester themselves from water, they initially come together in small aggregates. The question then arises as to how intervening water affects the interactions between individual solute molecules. Of course, the effect depends on distance. At long distances, the molecules do not influence one another. As they approach more closely, their hydration shells begin to overlap and the preferred orientations of water molecules around the two centres conflict. This frustration is thermodynamically unfavourable. At still shorter distances, water molecules begin to be squeezed out between the two solute molecules. Their release to join bulk water is favourable. Thus hydrophobic interactions (as the effective, water-mediated interactions between nonpolar solutes are called) are repulsive at medium range and attractive at short range.

Protein Folding

Although protein folding is driven by the hydrophobic effect, the details are a good deal more complicated than removing nonpolar groups from water (i.e. reducing the exposure of water to nonpolar groups). In proteins, the nonpolar groups are attached to polar groups – not only may neighbouring residues be polar, but the peptide backbone is also invariably polar. Thus protein folding involves the removal of polar groups from water, as well as nonpolar groups. This has two consequences. One is that the sequestering of polar groups makes its own distinctive contribution to ΔH° , ΔS° and ΔC_p of folding. Another is that interactions between polar groups (e.g. hydrogen bonding along the backbone and ion pair formation between oppositely charged side-chains) lend specificity to folding and cause a solid-like structure to be formed (which is why protein structures are amenable to elucidation by diffraction methods). This solidification makes its own contribution to the thermodynamics of folding (see **Figure 2**). As a result of these effects, T_h and T_s for protein folding are both close to physiological temperatures. Thus the native fold is most favoured over the denatured state near physiological temperature, with ‘cold denaturation’ occurring at lower temperatures and ‘heat denaturation’ occurring at higher temperatures.

References

- Abraham MH (1982) Free energies, enthalpies, and entropies of solution of gaseous nonpolar nonelectrolytes in water and nonaqueous solvents. The hydrophobic effect. *Journal of the American Chemical Society* **104**: 2085–2094.
- Ben-Naim A (1968) Solubility and thermodynamics of solution of argon in the water–ethylene glycol system. *Journal of Physical Chemistry* **72**: 2998–3001.
- Ben-Naim A (1987) *Solvation Thermodynamics*. New York: Plenum Press.

- Ben-Naim A and Marcus Y (1984a) Solubility and thermodynamics of solution of xenon in liquid *n*-alkanes. *Journal of Chemical Physics* **80**: 4438–4440.
- Ben-Naim A and Marcus Y (1984b) Solvation thermodynamics of nonionic solutes. *Journal of Chemical Physics* **81**: 2016–2027.
- Cabani S, Gianni P, Mollica B and Lepori L (1981) Group contributions to the thermodynamic properties of non-ionic organic solutes in dilute aqueous solution. *Journal of Solution Chemistry* **10**: 563–595.
- Chang ET, Gokcen NA and Poston TM (1968) Thermodynamic properties of gases in propellants. II. Solubilities of helium, nitrogen, and argon gas in hydrazine, methylhydrazine, and unsymmetrical dimethylhydrazine. *Journal of Physical Chemistry* **72**: 638–642.
- Clever HL, Battino R, Saylor JH and Gross PM (1957) The solubility of helium, neon, argon, and krypton in some hydrocarbon solvents. *Journal of Physical Chemistry* **61**: 1078–1082.
- de Jong PHK, Wilson JE, Neilson GW and Buckingham AD (1997) Hydrophobic hydration of methane. *Molecular Physics* **91**: 99–103.
- Haselmeier R, Holz M, Marbach W and Weingärtner H (1995) Water dynamics near a dissolved noble gas. First direct experimental evidence for a retardation effect. *Journal of Physical Chemistry* **99**: 2243–2246.
- Horiuti J (1931) On the solubility of gas and coefficient of dilatation by absorption. *Scientific Papers of the Institute of Physical and Chemical Research* **17**:(341) 125.
- Hummer G, Garde S, García AE, Paulaitis ME and Pratt LR (1998) Hydrophobic effects on a molecular scale. *Journal of Physical Chemistry B* **102**: 10469–10482.
- Lide DR (ed.) (1998) *CRC Handbook of Chemistry and Physics*. Boca Raton, FL: CRC Press.
- Madan B and Sharp K (1997) Molecular origin of hydration heat capacity changes of hydrophobic solutes: perturbation of water structure around alkanes. *Journal of Physical Chemistry B* **101**: 11237–11242.
- Makhatadze GI and Privavlov PL (1990) Heat capacity of proteins I. Partial molar heat capacity of individual amino acid residues in aqueous solution: hydration effects. *Journal of Molecular Biology* **213**: 375–384.
- Naghbi H, Dec SF and Gill SJ (1987) Heats of solution of ethane and propane in water from 0 to 50°C. *Journal of Physical Chemistry* **91**: 245–248.
- Nakahara M, Wakai C, Yoshimoto Y and Matubasasi N (1996) Dynamics of hydrophobic hydration of benzene. *Journal of Physical Chemistry* **100**: 1345–1349.
- Sceats MG and Rice SA (1980) The enthalpy and heat capacity of liquid water and the ice polymorphs from a random network model. *Journal of Chemical Physics* **72**: 3248–3259.
- Wilhelm E and Battino R (1973) Thermodynamic functions of the solubilities of gases in liquids at 25°C. *Chemical Reviews* **73**: 1–9.

Further Reading

- Ben-Naim A (1987) *Solvation Thermodynamics*. New York: Plenum Press.
- Blokzijl W and Engberts JBFN (1993) Hydrophobic effects. Opinions and facts. *Angewandte Chemie–International Edition in English* **32**: 1545–1579.
- Hummer G, Garde S, García AE, Paulaitis ME and Pratt LR (1998) Hydrophobic effects on a molecular scale. *Journal of Physical Chemistry B* **102**: 10469–10482.
- Keener CR, Fullerton GD, Cameron IL and Xiong J (1995) Solution nonideality related to solute molecular characteristics of amino acids. *Biophysical Journal* **68**: 291–302.

- Madan B and Sharp K (1997) Molecular origin of hydration heat capacity changes of hydrophobic solutes: perturbation of water structure around alkanes. *Journal of Physical Chemistry B* **101**: 11237–11242.
- Oas TG and Toone EJ (1997) Thermodynamic solvent isotope effects and molecular hydrophobicity. *Advances in Biophysical Chemistry* **6**: 1–52.
- Pollack GL (1991) Why gases dissolve in liquids. *Science* **251**: 1323–1330.
- Ragone R and Colonna G (1994) The role of conditional hydration on the thermodynamics of protein folding. *Journal of the American Chemical Society* **116**: 2677–2678.
- Schellman JA (1997) Temperature, stability and the hydrophobic interaction. *Biophysical Journal* **73**: 2960–2964.
- Tanford C (1980) *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*. New York: John Wiley & Sons.