

T-12

Theoretical Chemistry & Molecular Physics

Molecular Theory of Hydrophobic Effects

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“No one has yet proposed a quantitative theory of aqueous solutions of non-electrolytes, and such solutions will probably be the last to be understood fully.”¹

Hydrophobic and hydrophilic are categories of solvation effects in aqueous solutions. Classical ions such as Na^+ or polar molecules such as NH_3 are hydrophilic solutes. In contrast, the interactions of hydrophobic solutes or groups with water molecules do not display classic electrostatic or specific chemical interactions. Primitive hydrophobic solutes are inert gases and simple hydrocarbons that are sparingly soluble in water. However, protein molecular structure, function, and aggregation motivate study of hydrophobic effects because of the widely-held view that hydrophobic interactions drive protein folding. An important aspect of this puzzle is that it now appears common for proteins to unfold upon appropriate supercooling of the aqueous system.

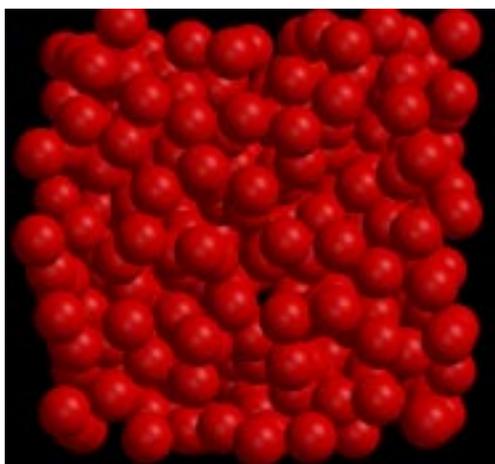


Figure 1: Configuration of 343 water molecules (periodic boundary conditions) drawn from a canonical ensemble with $T = 300\text{K}$ and $\rho = 1.0\text{g}/\text{cm}^3$ —only the oxygen atoms are shown.

Another important part of the puzzle is that hydrophobic effects seem to be largely independent of the molecular details of solute-solvent interactions within broad families. This emphasizes the utility of studying

primitive hydrophobic effects first. It is helpful to identify the minimum model that shows the interesting behavior and only after that to include other features actually present in specific cases.

Beginning therefore with hard core interactions between rigid solutes and water molecules, we note that the desired free energies may be connected to the *insertion probability*, p_0 :

$$\Delta\mu = -kT \ln p_0.$$

p_0 is the probability that a volume v , that a solute molecule would exclude to solvent molecules, is observed to have no solvent occupants when the solute is absent. In some cases p_0 can be calculated directly by simulation techniques. During the course of its thermal motion the solvent (e.g., Figure 1) presents void volumes (Figure 2). p_0 is the average fractional free volume accessible to a hard solute.

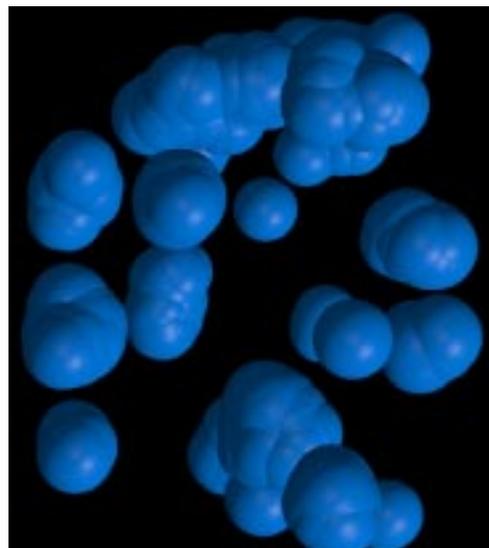


Figure 2: Successful insertions of spheres of radius 1.5\AA in a water configuration such as that shown in Figure 1.

To describe the insertion probability *theoretically*,² we recognize p_0 as the $k = 0$ member of a distribution p_k of the numbers of solvent centers in the observation volume v , *i.e.*, within the surface outlining the solute excluded volume. We construct and maximize an information entropy.

$$\eta = - \sum_{k \geq 0} p_k \ln p_k$$

subject to the known information. Moments $m_k = \langle n^k \rangle$ are the typically considered information. It has been found

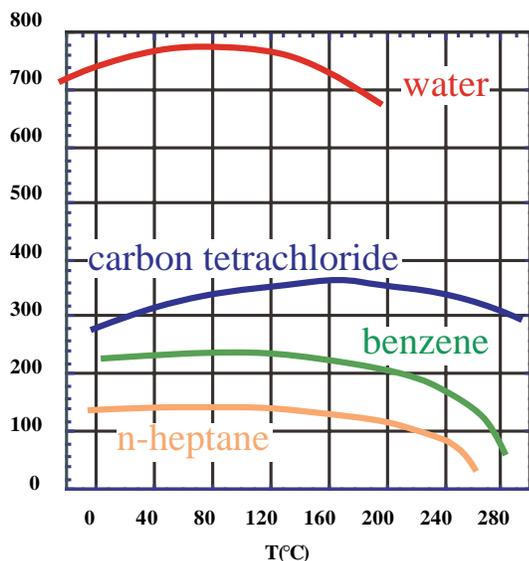


Figure 3: $T\rho_{sat}(T)^2$ [Kg^2/cm^6] for several solvents along their liquid-gas coexistence curve.¹

that the experimentally available moments m_0 , m_1 , and m_2 describe primitive hydrophobic effects accurately. A remarkable feature of this information theory model is that it provides an explanation of a puzzling hydrophobic phenomenon known as entropy convergence:³ along the water saturation curve, hydration free energies of inert gases show a maximum at about the same temperature. Similarly, hydrophobic contributions to protein folding extracted from calorimetry also show this maximum. The solvation entropy is nearly zero in this temperature region, nearly independently of the detailed nature of the hydrophobic solute. So hydrophobic entropies for many solutes converge at a common temperature. Why is this?

A continuous gaussian distribution reliably approximates the two moment information model, exhibits the entropy convergence, and produces

$$\Delta\mu \approx kT\rho_{sat}(T)^2 v^2 / 2 \langle \delta n^2 \rangle + kT \ln(2\pi \langle \delta n^2 \rangle)$$

as an explicit result for the excess chemical potential. $\rho_{sat}(T)$, the solvent density along the vapor saturation curve, decreases with increasing temperature along the saturation curve and $T\rho_{sat}(T)^2$ shows a maximum (Figure 3). But for water $\langle \delta n^2 \rangle$ along the saturation curve outside the critical region is relatively insensitive to temperature. Thus, the maximum in the hydration free energies derives principally from the solute independent maximum in $T\rho_{sat}(T)^2$ relatively uninfluenced by temperature variations of $\langle \delta n^2 \rangle$.

The isothermal compressibility β_T is the thermodynamic parameter that reflects $\langle \delta n^2 \rangle$. Water is less compressible than organic solvents; β_T displays a minimum and thus weak temperature dependence within the temperature range of interest (Figure 4).

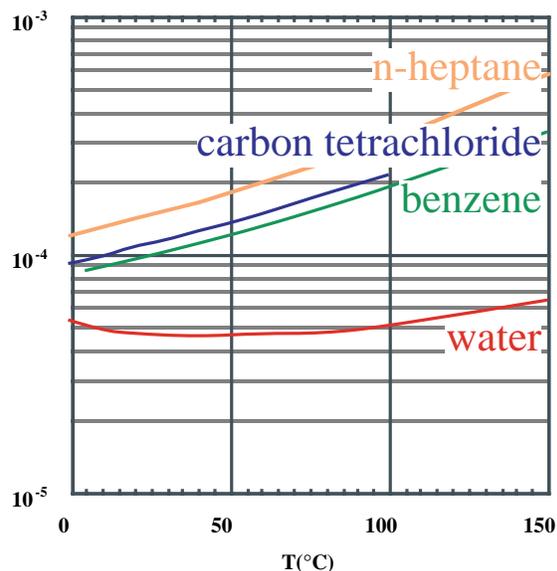


Figure 4: Isothermal compressibilities, β_T [bar^{-1}], of several solvents along their liquid-gas coexistence curve.¹

In conclusion, hydrophobic effects are entropic contributions associated with solution impurities without classic electrostatic or chemical interactions with the solvent. Recent theories have transplanted statistical and geometric concepts associated with packing in the hard sphere fluid to more general solution environments. Similar concepts have found use in studies of polymeric glasses.

References

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3. Garde, S.; Hummer, G.; Garcia, A. E.; Paulaitis, M. E.; Pratt, L. R. *Phys. Rev. Letts.* 1996, **77**, 4966.

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