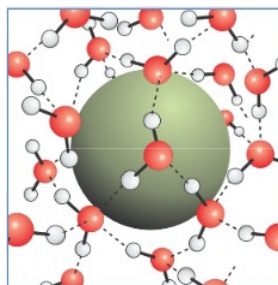


5.2: Hydrophobic Solvation- Solute Size Effect

To create a new interface there are enthalpic and entropic penalties. The influence of each of these factors depends on the size of the solute (R) relative to the scale of hydrogen bonding structure in the liquid (correlation length, ℓ , $\sim 0.5\text{--}1.0\text{ nm}$).

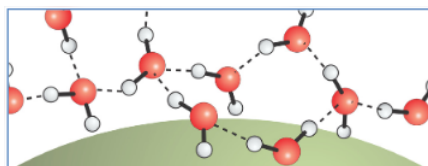
For small solutes ($R < \ell$): Network deformation

The solute can insert itself into the hydrogen bond network without breaking hydrogen bonds. It may strain the HBs ($\Delta H > 0$) and reduce the configurational entropy ($\Delta S < 0$), but the liquid mostly maintains hydrogen bonds intact. We expect the free energy of this process to scale as volume of the solute $\Delta G_{\text{sol}}(R < \ell) \propto R^3$.



For large solutes, $R > \ell$: Creating an interface

The hydrogen bond network can no longer maintain all of its HBs between water molecules. The low energy state involves dangling hydrogen bonds at the surface. One in three surface water molecules has a dangling hydrogen bond, i.e., on average five of six hydrogen bonds of the bulk are maintained at the interface.



We expect ΔG_{sol} to scale as the surface area $\Delta G_{\text{sol}}(R > \ell) \propto R^2$. Of course, large solutes also have a large volume displacement term. Since the system will always seek to minimize the free energy, there will be a point at which the R^3 term grows faster with solute radius than the R^2 term, so large solutes are dominated by the surface term.

Calculating ΔG for Forming a Cavity in Water

Let's investigate the energy required to form cavities in water using a purely thermodynamic approach. To put a large cavity ($R > \ell$) into water, we are creating a new liquid-vapor interface for the cavity. So we can calculate the energy to create a cavity using the surface tension of water. Thermodynamically, the surface tension γ is the energy required to deform a liquid-vapor interface: $\gamma = (\partial U / \partial a)_{N,V,T}$, where a is the surface area. So we can write the change in energy as a result of inserting a spherical cavity into water as the product of the surface tension of water times the surface area of the cavity,

$$U(R) = 4\pi R^2 \gamma$$

In principle, the experimentally determined γ should include entropic and enthalpic contributions to altering the hydrogen bond network at a surface, so we associate this with ΔG_{sol} . For water at 300 K , $\gamma = 72\text{ pN/nm}$. γ varies from 75 pN/nm at 0°C to 60 pN/nm at 100°C .

The surface tension can also be considered a surface energy per unit area: which can also be considered a surface energy, i.e., $\gamma = 72\text{ mJ/m}^2$. To relate this to a molecular scale quantity, we can estimate the surface area per water molecule in a spherical cavity. The molecular volume of bulk water deduced from its density is $3.0 \times 10^{-26}\text{ L/molecule}$, and the corresponding surface area per molecule deduced from geometric arguments is $\sim 10\text{ \AA}^2$. This area allows us to express $\gamma \approx 4.3\text{ kJ/mol}$, which is on the order of the strength of hydrogen bonds in water.

For small cavities ($R < \ell$), the considerations are different since we are not breaking hydrogen bonds. Here we are just constraining the configurational space of the cavity and interface, which should scale as volume. We define

$$\Delta G_{\text{sol}}(R < \ell) = \frac{4\pi R^3}{3} \rho_E$$

where ρ_E is an energy density¹.

$$\rho_E \approx 240 \times 10^{-9} \text{ pJ/nm}^3 = 240 \text{ pN/nm}^{-2}$$

Remembering that $-\partial G/\partial V|_{N,T} = p$, the energy density corresponds to units of pressure with a value $\rho_E = 2.4 \times 10^3$ atm. If we divide ρ_E by the molarity of water (55M), then we find it can be expressed as 4.4 kJ/mol , similar to the surface free energy value deduced.

So combining the surface and volume terms we write

$$\Delta G_{\text{sol}}(R) = 4\pi\gamma R^2 + \frac{4}{3}\pi R^3 \rho_E$$

Alternatively, we can define an effective length scale (radius) for the scaling of this interaction

$$\frac{\Delta G_{\text{sol}}}{k_B T} = \left(\frac{R}{R_{\text{surf}}}\right)^2 + \left(\frac{R}{R_V}\right)^3 \quad R_{\text{surf}} = \sqrt{\frac{k_B T}{4\pi\gamma}} \quad R_V = \left(\frac{3k_B T}{4\pi\rho_E}\right)^{1/3}$$

where $R_{\text{surf}} = 0.067 \text{ nm}$ and $R_V = 1.6 \text{ nm}$ at 300 K . We can assess the crossover from volume-dominated to area-dominated hydrophobic solvation effects by setting these terms equal and finding that this occurs when $R = 3\gamma/\rho_E = 0.9 \text{ nm}$. The figure below illustrates this behavior and compares it with results of MD simulations of a sphere in water.

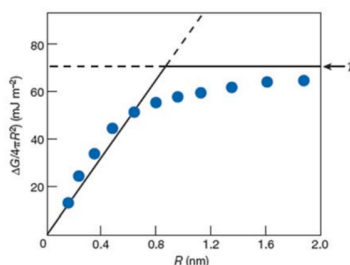


Figure 2 | Solvation free energy, ΔG , for a spherical cavity in water as a function of the cavity size. The results are for ambient conditions (room temperature and 1 atm pressure). The circles show the results of detailed microscopic calculations². The liquid-vapour surface tension is shown by γ . The solid lines show the approximate scaling behaviour of $\Delta G/4\pi R^2$ for small R , and the asymptotic behaviour for large R . This approach can be used to infer the typical length characterizing the crossover behaviour, but not the quantitative behaviour of ΔG in the crossover regime.

Reprinted by permission from Macmillan Publishers Ltd: D. Chandler, Nature **437**, 640–647 (2005). Copyright 2005.

An alternate approach to describing the molar free energy of solvation for a hydrophobic sphere of radius r equates it with the probability of finding a cavity of radius r :

$$\begin{aligned} \Delta G &= -k_B T \ln P(r) \\ P(r) &= \frac{e^{-U(r)/k_B T}}{\int_0^\infty e^{-U(r)/k_B T} dr} = \frac{\exp\left[\frac{-4\pi\gamma r^2}{k_B T}\right]}{\frac{1}{2} \sqrt{\frac{k_B T}{4\gamma}}} \\ &= \frac{2}{\sqrt{\pi} R_{\text{surf}}} \exp[-r^2/R_{\text{surf}}^2] \end{aligned}$$

This leads to an expression much like we previously described for large cavities. It is instructive to determine for water @ 300 K :

$$\langle r \rangle = \int_0^\infty dr r P(r) = \pi^{-1/2} R_{\text{surf}} = \frac{1}{2\pi} \left(\frac{k_B T}{\gamma}\right)^{1/2} = 0.038 \text{ nm}$$

This is very small, but agrees well with simulations. (There is not much free volume in water!) However, when you repeat this to find the variance in the size of the cavities $\delta r = (\langle r^2 \rangle - \langle r \rangle^2)^{1/2}$, we find $\delta r = 0.028 \text{ nm}$. So the fluctuations in size are of the same scale as the average and therefore quite large in a relative sense, but still less than the size of a water molecule.

Simulations give the equilibrium distribution of cavities in water

$$\Delta\mu^0 = -k_B T \ln(P)$$

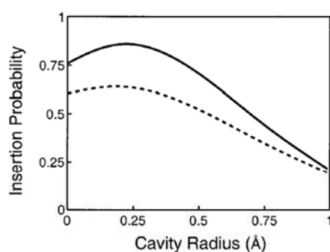


Figure 9. Free volume distributions from molecular dynamics simulations of a simple liquid, *n*-hexane (dashed line), and water (solid line). The probability of finding a cavity of a given radius is plotted. Water has more small cavities (<1 Å) than *n*-hexane. Data adapted from G. Hummer et al., *J. Phys. Chem. B* **1998**, *102*, 10 475.

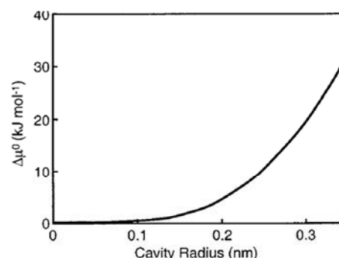


Figure 10. Free energy cost of creating a cavity, from molecular simulations. Data adapted from Hummer, G., et al. *J. Phys. Chem. B* **1998**, *102*, 10 475.

Reprinted with permission from N. T. Southall, K. A. Dill and A. D. J. Haymet, *J. Phys. Chem. B* **106**, 521–533 (2002). Copyright 2002 American Chemical Society.

1. D. Chandler, Interfaces and the driving force of hydrophobic assembly, *Nature* **437**, 640–647 (2005).

This page titled [5.2: Hydrophobic Solvation- Solute Size Effect](#) is shared under a [CC BY-NC-SA 4.0](#) license and was authored, remixed, and/or curated by [Andrei Tokmakoff](#) via [source content](#) that was edited to the style and standards of the LibreTexts platform.