

A “Universal” Surface Area Correlation for Molecular Hydrophobic Phenomena

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The central tenet of self-assembly in aqueous solution is the existence of stable aggregates in which amphiphilic molecules form unique structures having a hydrophobic core. Although a variety of forces contribute to self-assembly, hydrophobic interactions leading to the formation of this core are thought to play a dominant role.^{1,2} Hydrophobic interactions are generally viewed as a partial reversal of the hydration process and, as such, describe the aggregation of nonpolar solutes, or equivalently, the tendency of nonpolar oligomers to adopt more compact chain conformations in water relative to a nonpolar solvent. An intuitively appealing and computationally expedient method of estimating free energies of hydrophobic hydration is to assume a linear relationship between the free energy, ΔA_{hyd} , and solute surface area:³

$$\Delta A_{\text{hyd}} = \gamma A + b \quad (1)$$

where A is solute surface area, γ is the free energy/surface area coefficient, and b is the free energy of hydration for a point solute ($A = 0$). While this relationship is expected to hold in the limit of macroscopic surfaces, there is no a priori reason that it should hold as well for molecular or mesoscopic surfaces. Experimental vacuum-to-water and oil-to-water transfer free energies of the n -alkanes do indeed exhibit surface area scaling, thus motivating the incorporation of eq 1 into phenomenological models for self-assembly. However, vacuum-to-water transfer free energies of the cycloalkanes fall well below the linear correlation for their n -alkane analogues.⁴ In light of this observation, we ask whether eq 1, optimized to reproduce n -alkane transfer free energies, can predict with quantitative accuracy hydration free energies as a function of chain conformation for these solutes? The answer to our question is “yes” if eq 1 is applied to the cavity or hard-sphere analogues of the n -alkane solutes, that is, excluding contributions to the free energy of hydration from solute–water attractive interactions. That eq 1 is more generally applicable to molecular hydrophobic phenomena for cavities is an important finding, and it implies that the implementation of this simple empirical correlation should be at the level of predicting the thermodynamics of cavity formation in water.

We calculated vacuum-to-water transfer free energies from Monte Carlo simulations of n -alkanes and n -alkane-like cavities

Table 1. Hydration Free Energies of the n -Alkanes Calculated from Simulation^a

solute	ΔA_{hyd} (kcal/mol)		
	experimental values ¹²	OPLS	cavity
methane	1.93	2.62 (0.11)	6.65 (0.15)
ethane	1.77	2.57 (0.12)	9.07 (0.16)
propane	1.98	3.30 (0.13)	11.60 (0.17)
n -butane	2.15	3.51 (0.13)	13.84 (0.18)
n -pentane	2.34	3.69 (0.14)	15.99 (0.19)
n -hexane	2.55	3.92 (0.15)	18.24 (0.20)

^a Numbers in parentheses are statistical uncertainties reported as one standard deviation.

in water at 25 °C and a water density of 0.997 g/cm³. The higher molecular weight alkanes were held fixed in the extended all trans conformation during these simulations. We then calculated changes in the free energy of hydration for conformational transitions connecting the extended all trans conformation to the alternating gauche conformation of n -butane ($t \rightarrow g$), n -pentane ($tt \rightarrow gg'$), and n -hexane ($ttt \rightarrow gg'g$).⁵ Details of the Monte Carlo simulations and the free-energy perturbation techniques used to calculate free energies are given elsewhere.⁶ The n -alkanes are described by standard OPLS united-atom Lennard–Jones (LJ) potential parameters.⁷ Water is modeled using the simple point charge potential.⁸ Cavity–water interactions are modeled using the repulsive portion of the OPLS Lennard–Jones potential:⁹

$$\Phi_{\text{cavity}}(r) = \begin{cases} \Phi_{\text{LJ}}(r) + \epsilon & r \leq 2^{1/6}\sigma \\ 0 & r > 2^{1/6}\sigma \end{cases} \quad (2)$$

where $\Phi_{\text{LJ}}(r)$ is the solute–water LJ potential and σ and ϵ are the LJ diameter and well-depth, respectively. On the basis of recent studies indicating that the molecular surface area gives the most accurate description of hydrophobic interactions between methane pairs in water,¹⁰ we selected the molecular surface in applying eq 1. However, qualitatively similar results are expected for solvent-accessible and van der Waals surfaces. Standard definitions of these surface are given elsewhere.¹¹ The molecular surface area is calculated using a van der Waals radius of 1.9 Å for all methyl and methylene groups and a water probe radius of 1.4 Å.

Vacuum-to-water transfer free energies of the OPLS n -alkanes are reported in Table 1 and plotted as a function of solute molecular surface area in Figure 1. The results for propane through n -hexane are well described by eq 1 with $\gamma = 12.3 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ (Table 2). The transfer free energies for methane and ethane fall somewhat below this line. The corresponding experimental values (Table 1) are systematically lower than the simulation

(5) The letters t and g denote the ideal trans ($\varphi = 180^\circ$) and gauche ($\varphi = \pm 60^\circ$) backbone dihedral conformations, respectively. g' differentiates between the two mirror image gauche conformers, g^+ and g^- , along the same alkane chain.

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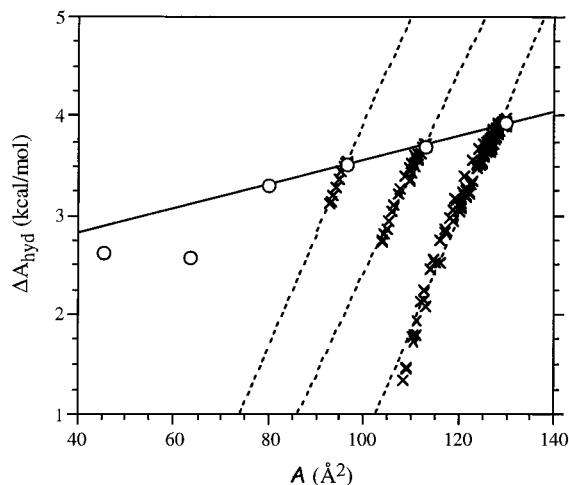


Figure 1. Hydration free energies of OPLS *n*-alkanes plotted as a function of alkane molecular surface area: ○, “exact” (simulation values) vacuum-to-water transfer free energies of methane through *n*-hexane; and ×, conformation-dependent transfer free energies of *n*-butane, *n*-pentane, and *n*-hexane (from left to right) calculated by adding to their respective vacuum-to-water transfer free energies, the change in the free energy of hydration for conformations along reaction paths connecting the extended all trans conformations to the alternating gauche conformations of *n*-butane (*t*→*g*), *n*-pentane (*tt*→*gg'*), and *n*-hexane (*ttt*→*gg'g*).⁵ The solid and dashed lines are fits to eq 1.

results and fit a linear correlation that is simply shifted vertically with $\gamma = 11.6 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ (Table 2). The conformational free energies of hydration of OPLS *n*-butane, *n*-pentane, and *n*-hexane are also plotted in Figure 1. The values of γ obtained from fits of these free energies of hydration to eq 1 are essentially the same for all three solutes and an order of magnitude greater than the value derived from the transfer free energies (Table 2).

Vacuum-to-water transfer free energies of the *n*-alkane-like cavities are also reported in Table 1 and plotted as a function of solute molecular surface area in Figure 2. These results are well described by eq 1 with $\gamma = 138 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ (Table 2). Interestingly, this linear fit of cavity transfer free energies, when extrapolated to zero surface area, yields a free energy of hydration close to the scaled-particle theory value for a point solute in water:¹³

$$\Delta A_{\text{hyd}}(A = 0) = 0.45 \pm 0.15 \text{ kcal/mol} \approx -kT \ln(1 - \pi \rho_w \sigma_w^3/6) = 0.29 \text{ kcal/mol} \quad (3)$$

where ρ_w and σ_w are the density of water and the radius of a single water molecule, respectively. Also plotted in Figure 2 are the free energies of hydration for the all trans to alternating gauche conformational rearrangements of *n*-butane-, *n*-pentane-, and *n*-hexane-like cavities in water. Both the conformational free energies of hydration and vacuum-to-water transfer free energies for these cavities are described with quantitative accuracy using a single linear correlation with $\gamma = 139 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ (Table 2).

The “universal” correlation for cavity free energies of hydration independent of conformation is in stark contrast to the results in Figure 1 for the OPLS *n*-alkanes. These results lead to our

Table 2. Parameters in Equation 1 Obtained from Linear Fits of Transfer and Conformational Free Energies for the *n*-Alkanes in Water^a

solute	γ (cal/mol \AA^2)	b (kcal/mol)
transfer free energies		
OPLS alkanes	12.3 (1.6)	2.32 (0.17)
experimental values	11.6	1.04
alkane cavities	138 (1)	0.45 (0.15)
conformational equilibria		
OPLS alkanes	110 (10)	
alkane cavities	139 (7)	

^a Numbers in parentheses are statistical uncertainties reported as one standard deviation.

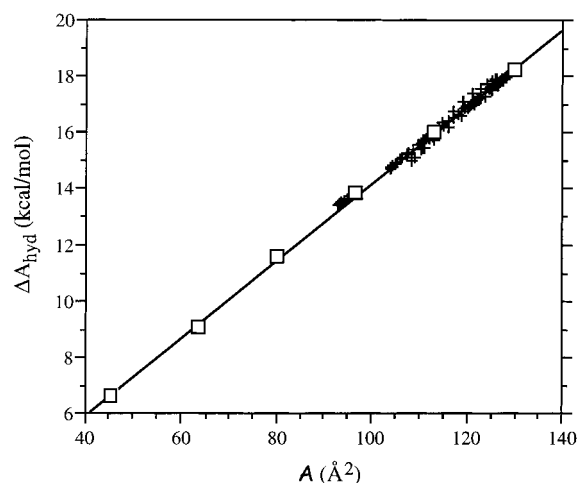


Figure 2. Hydration free energies of *n*-alkane-like cavities plotted as a function of cavity molecular surface area: □, vacuum-to-water transfer free energies of the cavity solutes; and ×, conformation-dependent transfer free energies of *n*-butane-, *n*-pentane-, and *n*-hexane-like cavities. The solid line is the fit of eq 1 to all free energies.

conclusion that the most general application of eq 1 is at the level of describing the thermodynamics of cavity formation in water. Moreover, the “universal” value of γ is close to the average value obtained for the conformational free energies of hydration of the OPLS *n*-alkanes in water, suggesting that solvent-mediated contributions to the conformational equilibria of nonpolar molecular solutes in water are dominated by the thermodynamics of cavity formation in water.¹⁴ As such, the conformation dependence of the free energy of hydration is described by eq 1 applied to cavities having conformations that define the equilibria of interest. That conformational equilibria of nonpolar solutes in water are in large part independent of solute–water attractive interactions is further exemplified by considering the simple hypothetical process of bringing a pair of methane molecules infinitely far apart in water into perfect overlap. From first-order perturbation theory,⁹ solute–water attractive interactions are equivalent for both configurations, while the reversible work for the process is dominated by excluded volume interactions.

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