provides a working mechanism for the latter.

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Supplementary Material Available: Experimental details, a listing of spectral data, and the ^{13}C NMR spectrum for 2-anthrylboronic acid (2 pages). Ordering information is given on any current masthead page.

Entropy of Association of Methane in Water: A New Molecular Dynamics Computer Simulation

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Hydrophobic interactions are important in clathrate–hydrate formation, protein folding, micelle formation, and other fields.[1-9] Entropy should play a major role in the interaction of hydrophobic solutes, just as it dominates the thermodynamics of hydrophobic solvation. Theoretical and computer studies have calculated the free energy of association of hydrophobic solutes,[10-17] yet none have evaluated directly the role of entropy. We present here a computer simulation of the entropy of association of two methane-like molecules in aqueous solution. The entropic contribution to the free energy of association is attractive at short separations, when the solutes are in contact.

The free energy of association of two methane molecules in water at 25 °C is shown in Figure 1a, together with the potential energy used to model the methane–methane interaction. This free energy, or potential of mean force (PMF), is calculated using a traditional thermodynamic integration technique.[18] Two distinct minima are evident in the PMF, and the contact minimum is significantly deeper than the solvent-separated minimum. The position of the solvent-separated minimum is in conflict with a recent discussion of solvent-induced interactions by Ben-Naim[19] and will be examined later.[20] The SPC model[21] is used for water, and a united atom approximation for the two methane molecules. The methane–methane (MM) and methane–oxygen (MO) interactions are pairwise additive, spherically symmetric Lennard-Jones potentials, with parameters $\sigma_{MM} = 3.73$ Å, $\epsilon_{MM} = 0.2931$ kcal mol^{-1}, $\sigma_{MO} = 3.4475$ Å, and $\epsilon_{MO} = 0.2134$ kcal mol^{-1}.

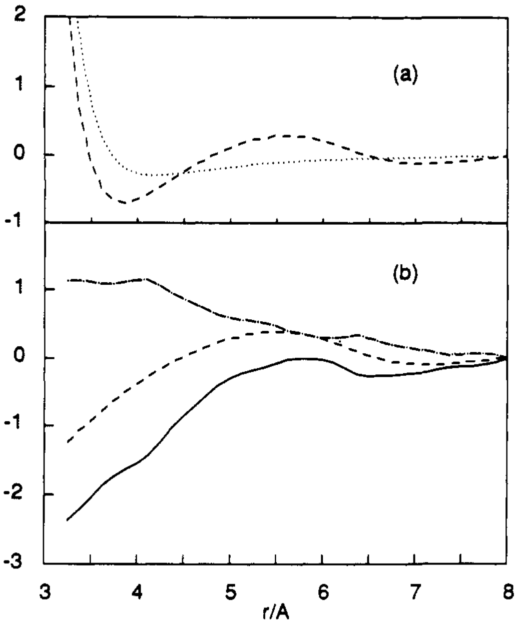

Figure 1. (a) Methane–methane potential of mean force (dashed line) and potential energy (dotted line), in kcal mol^{-1}. (b) Solvent contribution to the potential of mean force (dashed line); entropy of association, $-TS(r)$ (solid line); and configurational energy of association (dot-dashed line).

Subtracting the methane–methane potential energy from the PMF yields the so-called "indirect"[6] (solvent) contribution to the PMF, displayed as the dashed line in Figure 1b, along with its energetic and entropic components. Unlike the full PMF, the "indirect" component is purely attractive at short separations.

Our new result is the entropy of association, $-TS(r)$, the solid line displayed in Figure 1b, calculated from an equation introduced below. Our central result is that *the entropy causes an attraction between the solutes* at separations less than approximately 5.5 Å. Experiments by Pollack and others[22] document that the entropy of hydration for hydrophobic solutes is unfavorable, presumably due to increased solvent ordering around the solutes. Hence solvating two solutes in contact (where their solvation shells are shared) should be favored entropically over solvating each solute individually.[1,7] The data of Figure 1b are, to our knowledge, the first direct confirmation of this hypothesis.

Our data predict that as the temperature increases, (i) the magnitude of the attraction at short separations increases and (ii) the contact well in the PMF becomes deeper. The latter conclusion disagrees with the temperature dependence of the PMF for hard spheres in water calculated by Pratt and Chandler,[10] probably due to a different choice of the interaction potentials.[20] Our result is in qualitative agreement with the single-point (1.533 Å) experimental estimate of Yaacobi and Ben-Naim[23] of the entropy of association for methane.

The energy of association is determined by subtracting the entropy of association from the free energy (PMF). The energy (dot-dashed line in Figure 1b) is slightly repulsive at short range.

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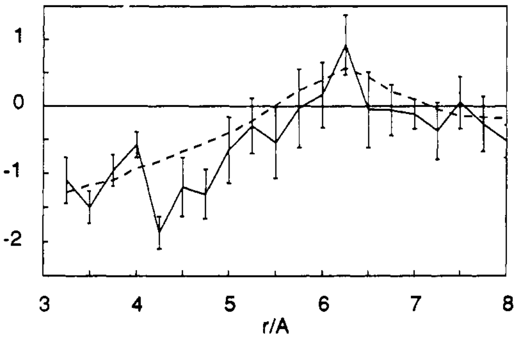

Figure 2. Negative derivatives of the potential of mean force (dashed line) and its entropic component (solid line), in kcal mol^{-1} Å^{-1}. Error bars correspond to 1 standard deviation.

Again this is in qualitative agreement with the estimate of Yaacobi and Ben-Naim.[23] The noise in the data is too great to determine which of the entropic and energetic effects is larger in the solvent-separated region of the PMF.

Our formula for calculating the entropic contribution to the free energy of association is straightforward. To our knowledge, a calculated PMF between two solutes has never before been decomposed directly into its energetic and entropic components either by theory or by computer simulation. The entropic component is

$$-TS(r) = -TS(r_0) + \frac{1}{kT}\int_{r_0}^{r} \mathrm{d}R\left[\left\langle E\frac{\partial E}{\partial R}\right\rangle_R - \langle E\rangle_R\left\langle\frac{\partial E}{\partial R}\right\rangle_R\right] \quad (1)$$

where $TS(r_0)$ is an additive constant, E is the total configurational energy, and $\langle ...\rangle_R$ denotes the ensemble average with the solute–solute separation fixed at R. We set both $-TS(r)$ and the free energy of association to 0 at 8.0-Å separation. Similar formulas have been published,[18,24] but apparently not used to calculate the entropy of association.

Our MD calculations simulate a periodically replicated collection of 106 SPC water molecules and two methane molecules at 1.0 g cm^{-3} and 25 °C, using the program SOLVENT 1.0,[25] described elsewhere. The PMF and entropy of association are calculated for solute separations between 3.25 and 8.00 Å. The total simulation time is approximately 60 ns. The simulations measure directly the *derivatives* of the quantities plotted in Figure 1b. The negative derivatives of the free energy (i.e., the solvent averaged force) and its entropic component ($-kT^{-1}$ times the integrand in eq 1) are shown in Figure 2. Uncertainties ($\pm\sigma$) are displayed for the entropy derivative, while the average uncertainty for the mean force is 0.05 kcal mol^{-1} Å^{-1}.

The entropy contribution in Figure 2 is clearly negative for separations shorter than 5.5 Å. This provides statistical validation of our central result, that entropy drives the hydrophobic solutes together. A rather small (108 molecule) system is simulated here due to the large statistical uncertainty in the entropy calculation. Alternative methods of calculation provide no improvement in accuracy. The "direct" method of calculating the configurational energy of the system as a function of solute separation shows a large uncertainty which grows with the system size. Differencing of PMFs at different temperatures is equally inefficient. System size effects on the free energy have been determined and are found to be minimal.[20] Further applications of this technique are underway.

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Coherence Transfer Involving Quadrupolar Nuclei in Solids: ^{27}Al $\leftrightarrow$ ^{31}P Cross-Polarization NMR in the Molecular Sieve VPI-5

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During the last 15 years there have been significant advances in solid-state chemistry and materials research which derive directly from the application of high-resolution solid-state NMR spectroscopy.[1] Typically a dilute spin-$^1/_2$ nucleus such as ^{13}C is observed, while interactions from protons are removed by dipolar decoupling and the carbon chemical shift anisotropy is averaged using magic-angle spinning (MAS). A spectrum with sharp lines is then observed which is similar to that obtained from the same material in the liquid state or dissolved in solution.[2] Problems inherent in the study of dilute nuclei, namely, the low signal-to-noise ratio, are overcome by cross-polarization of spin magnetization from an abundant spin reservoir such as protons.[3]

Historically, cross-polarization has been used to transfer spin coherence from abundant spins to a dilute spin system. Protons (^{1}H) have been used almost exclusively as the source of strong nuclear polarization for cross-polarization experiments, although there have been some examples where other abundant nuclei such as ^{19}F have been used.[4,5] Another notable exception is found in the studies of Schaefer and co-workers involving magnetization transfer between ^{13}C and ^{15}N in isotopically enriched materials.[6,7]

For quadrupolar nuclei with nonintegral spins such as ^{11}B, ^{17}O, and ^{27}Al, the second-order quadrupolar broadening of the readily observed central ($+^1/_2 \leftrightarrow -^1/_2$) transition is not completely averaged by MAS.[8-10] The NMR lines from quadrupolar spins are shifted and distorted in single-axis spinning experiments, but the recently introduced techniques of dynamic-angle spinning[11,12] and double rotation[13] can achieve averaging of these resonances. Very few examples exist of cross-polarization experiments involving quadrupolar nuclei, and they all involve magnetization transfer from protons *to* quadrupolar nuclei.[14-22] Recently, a description

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