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Hydrophobic Effect on Chain Folding. The Trans to Gauche Isomerization of *n*-Butane in Water[†]

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Abstract: A Monte Carlo simulation in *n*-butane dissolved in water shows that at 300 K water induces a dramatic shift in the conformational equilibrium of *n*-butane from what is observed in either the gas phase or in non-hydrogen-bonded liquids; however, at 333 K, this strong solvent effect disappears.

Introduction

The common view of hydrophobic interaction is based on a simple picture. Because nonpolar species are relatively insoluble in water, it is assumed that there are thermodynamic forces in aqueous solution that will drive two such species together to a much greater extent than would be the case if these solute molecules were dissolved in a nonassociated, nonpolar solvent. It is not difficult to see where the driving force arises. It is well known that the entropy of solution of simple nonpolar solutes in water is negative (e.g., $\Delta S^\circ \simeq -30.2$ eu). Most of this entropic change springs from a restructuring of the water surrounding the solute molecule—a restructuring that leads to greater order in the solvent in close proximity to the solute. Thus, since two nonpolar molecules in contact will order fewer solvent molecules than when they are apart, the entropy change on bringing two solute molecules together should be positive, and should thereby lower the free energy of the solution. From this follows the clustering alluded to above. In two recent publications[1,2] we showed, in agreement with an earlier prediction,[6] that this may not be the case for inert gas solutes, A (= Ne, Ar, Xe). It was found that there are two relatively stable minima in the potential of mean force, $W_{AA}(r)$ for the A–A pair. In one position the two A atoms are nearly in contact, whereas in the other position a water molecule sits somewhere between the two A particles. The maximum in $W_{AA}(r)$, separating these two minima, represents the barrier to removing an internal water molecule. In both configurations the water maintains a linear hydrogen bonded network and is more ordered in the neighborhood of the two spheres except possibly when they are separated by the distance corresponding to the free energy barrier.

When a chain molecule is dissolved in a liquid, the equilibrium between its various possible conformational states is likely to be shifted from what is found in the gas phase.[3] When chain molecules containing nonpolar groups are dissolved in nonpolar solvents, the shift is not expected to be large.[4,5] When these same molecules are dissolved in water, the hydrophobic interaction is expected to have a large effect on the conformational states observed, and thereby on chain folding.[6,7]

The *n*-butane molecule is perhaps the simplest molecule consisting of nonpolar groups with only one conformational degree of freedom. We have already studied this molecule dissolved in "CCl_4" by computer simulation and observed a shift in the gauche to trans equilibrium. It is of considerable interest to compare these solvent effects in a "classical" liquid to those in water. Because the separation between the methyl end groups in both the trans and gauche states is too small to permit the intrusion of water between them, we do not expect to observe any deviation from the intuitive expectation that the hydrophobic interaction will shift the equilibrium to the gauche state. However, longer chain molecules will permit waters to intrude between their end groups, so that our previous observations[1,2] with regard to the second minimum in the potential of mean force in A–A may play an important role in chain folding. This question will be addressed in the future.

To better understand the effects of water on the conformations of chain molecules consisting of nonpolar groups we have performed two Monte Carlo simulations of a model of *n*-butane dissolved in a model of liquid water (the ST2 model) at 300 and 333 K at a water density of 1 g/cm^3. In this model, the *n*-butane is flexible; that is, there are bond bending and bond stretching modes in addition to changes in the dihedral angle. In addition to shifting the conformational equilibrium, the solvent can also distort the molecule, and both of these effects are studied here.

We find that at 300 K water induces a *dramatic* change in the conformation of *n*-butane from its gas phase structure. $S(\phi)$, the probability distribution of the dihedral angle, consists of a small trans peak and two large gauche peaks, indicating a large shift from trans to gauche conformations (cf. Figure 1a). The change in $S(\phi)$ from its gas phase value, $S^{(0)}(\phi)$, is found to be much larger than predicted by a simple two cavity model of *n*-butane,[6] and it is rather striking compared to what happens in ordinary solvents such as CCl_4.[5] The equilibrium const. K (= % gauche/% trans) for the trans–gauche equilibrium is found to be 330% larger in water than in the gas phase ($K^{(0)} = 0.54$). In contrast, ordinary solvents such as CCl_4 are found to shift K by less than 50% from the gas phase value.[5] Thus, at 300 K water provides a large thermodynamic driving force toward the folded state (gauche state). This effect is considerably larger than that observed in non-hydrogen-bonded model solvents, an observation consistent with expectations based on the intuitive view of the hydrophobic interaction. In this study, electrostatic interactions between the solute and solvent are entirely ignored. It is worth noting that from a purely electrostatic viewpoint a polar solvent such as water is expected to stabilize the conformation of molecules like 1,2-dibromoethane with large dipoles relative to those with small dipoles so that electrostatic effects should shift the equilibrium even further to the gauche state.

Given the large solvent effect at 300 K, it is of extreme interest to determine what happens at a higher temperature where the water structure is softened. A Monte Carlo simulation at 333 K shows that the dramatic effect observed at 333 K disappears completely. The change in $S(\phi)$ from its gas-phase value at 333 K is small but in the direction of increasing the trans population (cf. Figure 3a). The equilibrium constant, K (= % gauche/% trans) at 333 K for the trans–gauche equilibrium is found to be 0.41 ± 0.11, a value which appears to be smaller than the gas phase value of 0.61.

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Molecular Model

The system consists of 121 ST2 water molecules[8] and one primitive *n*-butane in a periodic cell such that the density of the water is 1 g/cm^3 and the temperature is 300 K. The water molecules interact with each other through the ST2 potential. The primitive *n*-butane molecule[5,9] consists of four overlapping methylene spheres of Lennard-Jones diameter $\sigma_{\mathrm{Me}} = 3.92$ Å (the L-J diameter of methane) with centers arranged at the vertices of the three C–C σ bonds. Each of these methylene sites interacts with the center of each water molecule through a Lennard-Jones 12–6 potential with parameters ($\sigma_{\mathrm{MeW}} = 3.36$ Å, $\epsilon_{\mathrm{MeW}} = 201$ K); chosen to make the experimental and theoretical[6] Henry's law constant equal for methane water solution at 298 K.

The intramolecular potential of *n*-butane is taken to be

$$V_{\mathrm{M}} = V_{\mathrm{b}}(\phi) + \frac{1}{2}k_{\mathrm{b}} \sum_{i=1}^{3}(b_i - b_0)^2 + \frac{1}{2}k_\theta \sum_{\alpha=1}^{2}(\cos\theta_\alpha - \cos\theta_0)^2 \tag{1}$$

where $\{b_i,\theta_\alpha\}$ are respectively the bond lengths and angles indicated and ϕ is the dihedral angle between the planes containing carbon atoms 1,2,3 and 2,3,4, respectively. The second and third terms in eq 1 specify a local harmonic model for bond stretching and an anharmonic model for bond bending. The force constants are taken to be $k_\theta = 1.8 \times 10^5$ J/mol, $k_{\mathrm{b}} = 3.5 \times 10^7$ J/mol^2 mol, and the equilibrium bond lengths and bond angles are taken to be $b_0 = 1.53$A and $\theta_0 = 109°\ 28'$. These are the values used by Helfand and Weber in their stochastic dynamic studies of *n*-alkanes and used subsequently by us in our study of isomerization dynamics in liquids by full molecular dynamics. At 300 K, this model allows for gas-phase *n*-butane bond bending amplitudes $102° \lesssim \theta \lesssim 117°$ and bond stretching amplitudes 1.52 Å $\lesssim b \lesssim 1.54$ Å.

The first term, $V_{\mathrm{b}}(\phi)$ in eq 1 represents the potential of the reactive degree of freedom, ϕ. This is taken to be the tristable Scott–Scheraga potential,[10] as modified by Ryckaert and Bellemans,[9] and is plotted in Figure 2. Because of the barriers, a Monte Carlo run starting with the molecule in either the trans or gauche state (the minima) would converge slowly due to the infrequent passage of the system over the barrier. To guarantee rapid convergence importance[5,11,12] sampling techniques are used. We devise a reference potential that gives rapid and almost uniform sampling in the full space of ϕ except in the physically inaccesible cis configurations where there is a high internal barrier in $V_{\mathrm{b}}(\phi)$. The details of the method are reported in a long paper in which we study the hydrophobic hydration around *n*-butane in different conformational states.[13] It is sufficient to say here that after equilibration, the system is simulated by Monte Carlo for 21 000 passes. Each pass consists of an attempted move for each water molecule, and 121 attempted moves of the *n*-butane molecule. The cooridinates used for butane are the three center of mass coordinates, the Euler angles[14] specifying the bond $\vec{b}_1$, and polar coordinates (bond length, azimuthal, and polar angles) of each succeeding bond relative to the preceeding bond vector as Z axis. Each move of the butane consisted of choosing one of the 12 coordinates at random and attempting a move. The water molecules were moved by Metropolis Monte Carlo with Euler angles. Thus the run consisted of 2.54×10^6 butane configurations and 2.54×10^6 water configurations. The acceptance ratio for water moves was 30% and for the butane moves it was 45%. In the data analysis, the dihedral angle domain, $-\pi \leq \phi \leq \pi$, was divided into 50 equal bins, $\Delta\phi = 7.2°$. In the 300 K system, 20 000 passes were divided into 4 equal blocks, and the number of counts accumulated in the symmetrized angular bins for each block allows determination of the average value of the distribution function, $S(\phi)$, its standard deviation, $\sigma(\phi)$, and the error bars $\pm\ \sigma(\phi)/3^{1/2}$, whereas in the 333 K system, 16 000 passeswere divided into 4 equal blocks.

Table I

	temp, K	X_{t}	X_{g}	$K = X_{\mathrm{g}}/X_{\mathrm{t}}$
water[a]	300	0.30 ± 0.08	0.70 ± 0.08	2.3 ± 0.9
gas[b]	300	0.65	0.35	0.54
CCl_4[c]	300	0.59 ± 0.01	0.41 ± 0.01	0.70 ± 0.03
water[a]	333	0.71 ± 0.06	0.29 ± 0.06	0.41 ± 0.11
gas[b]	333	0.62	0.38	0.61

[a] Results of this simulation. [b] Exact results using $s^{(0)}(\phi) = ce^{-\beta V_{\mathrm{b}}(\phi)}$. [c] Results from ref 5 corrected for flexible molecule.

Results and Discussion

The frequency distribution of conformations of *n*-butane is given by the normalized distribution function, $S(\phi)$, of the dihedral angle. Figure 1a gives a comparison between $S(\phi)$ for *n*-butane in water at 300 K and for *n*-butane in an ideal gas at the same temperature. In the gas phase the trans peak is higher than the gauche peaks, whereas in water the gauche peaks are larger than the trans peak. Integration of these peaks gives the mole fractions listed in Table I. Equilibrium constants for the trans to gauche reaction are also given in Table I. The gas phase value is $K^{(0)} = 0.54$, whereas the water value is $K = 2.3$. This represents a 330% change in the equilibrium constant from the gas phase, a change representing an enormous shift of the equilibrium to the gauche (or folded) state. Ordinary solvents such as CCl_4 also shift the equilibrium to the gauche state but by a much smaller amount[5] (50%). For comparison the results of CCl_4 simulation are given in Figure 1b and also in Table I. In water there is clearly a very large thermodynamic driving force to the gauche state.

The situation is entirely different at 333 K. Figure 3a gives a comparison between $S(\phi)$ for *n*-butane in water and in an ideal gas at this temperature. It is clear that the solvent effect is relatively small and shifts the equilibrium slightly to the trans conformation over what is found in the gas at 333 K. The mole fractions and equilibrium constant are given in Table I. Thus, at 333 K, the strong hydrophobic effect observed at 300 K disappears.

A good measure of the solvent effect is given by the cavity distribution function[5,6]

$$y(\phi) = cS(\phi)e^{+\beta V_{\mathrm{b}}(\phi)} \tag{2}$$

where c is a normalization constant. $y(\phi)$ is the normalized distribution function of ϕ for a fictitious butane molecule dissolved in water in which the intramolecular potential is independent of ϕ; that is, there is no barrier to internal rotation. In an ideal gas $y(\phi)$ would be uniform, but because of solvent effects which favor certain molecular conformations over others, $y(\phi)$ will be nonuniform. $y(\phi)$ thus gives a measure of the pure solvent effect. The cavity function $y(\phi)$ for *n*-butane in water at 300 K is shown in Figure 1c and for that at 333 K in Figure 3b. This shows that in the absence of the intramolecular potential, $V_{\mathrm{b}}(\phi)$, water at 300 K strongly pushes *n*-butane into the cis state, and water at 333 K slightly shifts *n*-butane into the trans state and cis state relative to the gas phase.

It is often useful to discuss solvent effects in terms of the potential of mean force, $W(\phi)$ $(= -kT \ln S(\phi)/S(0))$. This represents the reversible work required to change *n*-butane from its trans conformation ($\phi = 0$) to a conformation with dihedral angle ϕ in the solvent. In a constant volume ensemble, as simulated here, $W(\phi)$, is the Helmholtz free energy change and contains contributions from the energy and entropy changes attendant on this change of conformation. $W(\phi)$ can be decomposed into two terms

$$W(\phi) = V_{\mathrm{b}}(\phi) + \Delta W(\phi) \tag{3}$$

where $V_{\mathrm{b}}(\phi)$ is the intramolecular dihedral potential and $\Delta W(\phi)$ $(= -kT \ln y(\phi)/y(0))$ is the solvent–solute contribution.

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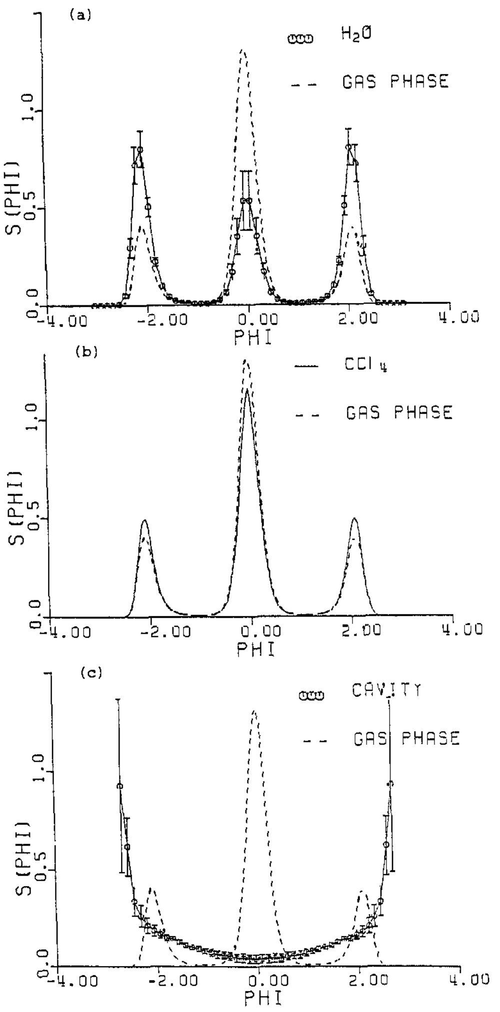

Figure 1. (a) The normalized and symmetrized distribution function of the dihedral angle of *n*-butane, $s(\phi)$: in H_2O (O) and in the gas phase (---) at 300 K. (b) The distribution function of the dihedral angle of *n*-butane, $s(\phi)$: in liquid CCl_4 (—) and in the gas phase (---). (c) The normalized and symmetrized cavity distribution function, $y(\phi)$ (cf. eq 2) in water (O) compared with the normalized distribution function in the gas phase (---) at 300 K.

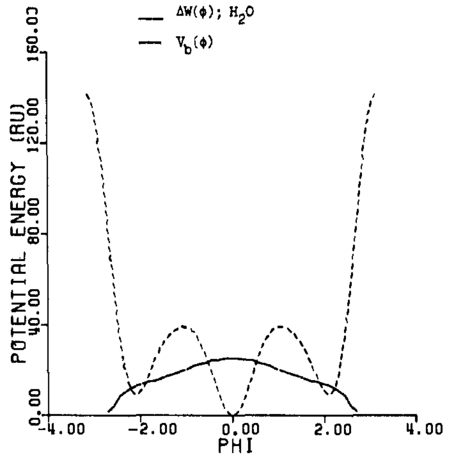

Figure 2. The solvent–solute part of the potential of mean force, $\Delta W(\phi)$ (cf. eq 3) in water (—) compared to the intramolecular dihedral angle potential $V_b(\phi)$ (---) for $T = 300$ K.

Figure 2 shows a comparison between $V_b(\phi)$ and $\Delta W(\phi)$, the solvent–solute part of the potential of mean force in H_2O at 300 K. The central peak shows that the solvent–solute free energy is lower in the cis state than the trans state. It is clear from this figure that the solvent contribution, $\Delta W(\phi)$ opposes the intramolecular potential and drives the system to the gauche state.

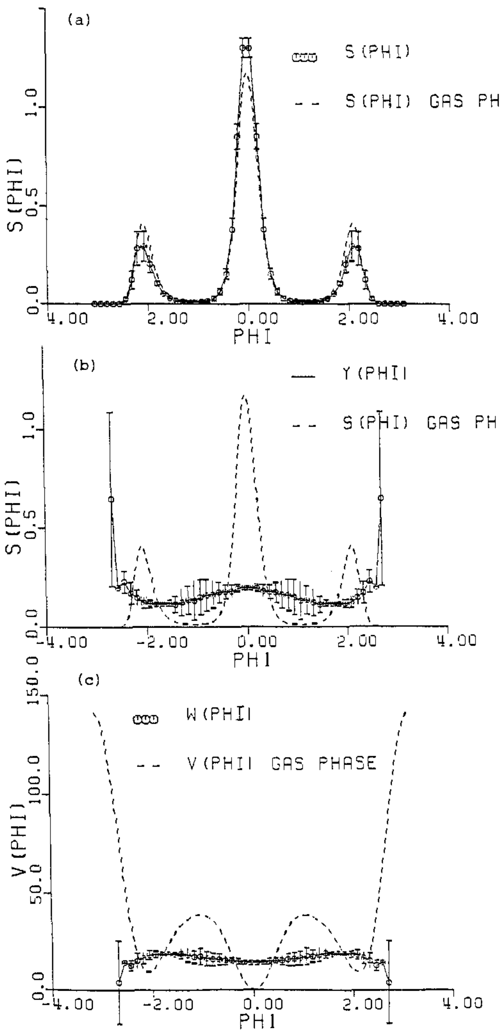

Figure 3. (a) The normalized and symmetrized distribution function of the dihedral angle of *n*-butane, $s(\phi)$: in H_2O (O) and in the gas phase (---) at 333 K. (b) The normalized and symmetrized cavity distribution function, $y(\phi)$ (cf. eq 2) in water (O) compared with the normalized distribution function in the gas phase (---) at 333 K. (c) The solvent–solute part of the potential of mean force, $\Delta W(\phi)$ (cf. eq 3) in water (—) compared to the intramolecular dihedral angle potential $V_b(\phi)$ (---) for $T = 333$ K.

Figure 3c gives this comparison for the system at 333 K.

Finally, we have studied the effect of the solvent on the bond lengths and bond angles. It is found that in H_2O at 300 K the mean bond bending angle is $\bar{\theta} = 108.7°$ and the mean bond length is $\bar{b} = 1.50$. This should be compared to $\theta_0 = 109°28'$ and $b_0 = 1.53$ Å. Detailed discussion of the distribution function function of these quantities will be presented in a detailed account of this study.[13] The radial distribution of oxygen atoms and hydrogen atoms around *n*-butane in its different isomeric states will also be discussed there. It is sufficient to say that unlike what happens in CCl_4, there is a very dramatic change in the structure of water around the butane when it changes conformation.

In conclusion, there is a very significant hydrophobic effect on the conformational properties of *n*-butane at 300 K. This dramatic solvent effect disappears at 333 K.

Note Added in Proof: While this paper was in press we received a preprint in which related material was presented.[15]

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Registry No. Butane, 106-97-8.

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