The hydrophobic effect in a simple isotropic water-like model: Monte Carlo study

Matej Huš and Tomaz Urbic^{a)}

Chair of Physical Chemistry, Department of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

(Received 5 February 2014; accepted 25 March 2014; published online 14 April 2014)

Using Monte Carlo computer simulations, we show that a simple isotropic water-like model with two characteristic lengths can reproduce the hydrophobic effect and the solvation properties of small and large non-polar solutes. Influence of temperature, pressure, and solute size on the thermodynamic properties of apolar solute solvation in a water model was systematically studied, showing two different solvation regimes. Small particles can fit into the cavities around the solvent particles, inducing additional order in the system and lowering the overall entropy. Large particles force the solvent to disrupt their network, increasing the entropy of the system. At low temperatures, the ordering effect of small solutes is very pronounced. Above the cross-over temperature, which strongly depends on the solute size, the entropy change becomes strictly positive. Pressure dependence was also investigated, showing a “cross-over pressure” where the entropy and enthalpy of solvation are the lowest. These results suggest two fundamentally different solvation mechanisms, as observed experimentally in water and computationally in various water-like models. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4870514>]

I. INTRODUCTION

Water has many distinct properties^{1–4} that differentiate it from other solvents.^{5,6} Among the most important anomalies of pure water are the following: high boiling and freezing points, a temperature of maximum density in the liquid phase, a minimum in the isothermal compressibility, and a large heat capacity. Due to the ubiquity of water in life and its tremendous importance in biological processes^{7,8} and technological implications, those anomalous properties have been targets of considerable research effort.^{9–13} Several models have been devised to describe water, ranging from simple isotropic potentials,^{14–20} simple angle dependent potentials,^{21,22} and point-charge models,^{23–27} to ultimately complex polarizable models.^{28–30} However, complexity is not the necessary condition for the appearance of anomalies. It has been shown that even isotropic soft-core potentials can correctly describe water anomalies, such as density maximum.^{15,31}

Of particular importance are solvation processes in water. Hydration of apolar solutes is an important driving force for protein folding, ligand binding, micelle formation, and many other processes. Apolar solutes generally do not dissolve in water but instead clump together. The interactions responsible for this behavior are collectively called the hydrophobic interaction or the hydrophobic effect.^{32–34} The hydrophobic effect in water is characterized by a positive free energy of solvation for apolar solutes and a temperature of minimum solubility (TMS). At low temperatures, transfer of a hydrophobic particle from vacuum to water is accompanied by a decrease of entropy. This effect is so strong that the process is endergonic despite the negative enthalpy change. Another recognizable feature of the hydrophobic interaction is a large

positive heat capacity of transfer. The hydrophobic effect can also be studied by analyzing the potential of mean force (PMF) and the solute-solute pair distribution function (PDF). It has been known for a long time that PMF between two solute particles must display two local minima, corresponding to the contact configuration (CC) and solvent-separated configuration (SSC), respectively.^{35–37} Hydrophobic effect is strongly dependent on temperature,^{38,39} pressure,^{40,41} solute size and concentration,⁴² solvent polarizability,⁴³ and interactions in the solution.⁴⁴ In this paper, we show how a fairly simple model describes the temperature, pressure, and solute size dependence of the hydrophobic effect. The continuous shouldered well (CSW) model we use has previously been shown to accurately describe pure water and solvation of small apolar particles, such as noble gases and small hydrocarbons.^{5,31,45–47}

This paper is organized in the following way. In Sec. II, we detail the model used to describe interactions involving the solute and the solvent. We provide the computational details and simulation description in Sec. III. Results are presented and discussed in Sec. IV, followed by a conclusion in Sec. V.

II. THE MODEL

We use the CSW potential, originally proposed by Franzese,¹⁵ to model an anomalous water-like fluid as the solvent. Particles of the solvent interact pair-wise with the potential function as

$$U(r) = \frac{U_R}{1 + \exp(\Delta(r - R_R)/a)} - U_A \exp\left(-\frac{(r - R_A)^2}{2\delta_A^2}\right) + U_A \left(\frac{a}{r}\right)^{24}. \quad (1)$$

^{a)}Electronic mail: tomaz.urbic@fkk.uni-lj.si

This potential can be thought to consist of three constituent parts: a steep repulsive wall, a soft repulsive shoulder of height U_R , and an attractive Gaussian well of depth U_A and width $2\delta_A\sqrt{2\ln 2}$. R_R and R_A are the repulsive shoulder radius and the location of the potential minimum, respectively, and a determines the diameter of particles.

The parameters of the model were kept unchanged from the original papers^{15,45,46} and our previous studies^{31,47,48} to allow for a better comparison of results: $U_R/U_A = 2$, $R_R/a = 1.6$, $R_A/a = 2$, $(\delta_A/a)^2 = 0.1$, $\Delta = 15$.

Interactions between apolar solutes were modeled with a modified Lennard-Jones potential. To ensure that its behavior in the repulsive range corresponds to that of the CSW potential ($U \propto r^{-24}$), the following potential function was used for solute-solute and solute-solvent interactions:

$$U = \frac{4}{3} \cdot 2^{\frac{2}{3}} \epsilon \left[\left(\frac{\sigma}{r} \right)^{24} - \left(\frac{\sigma}{r} \right)^6 \right]. \quad (2)$$

$$U_{LJ} = \begin{cases} \infty; & \text{for } r < \sigma_{LJ} - \sigma_{tr} \\ \frac{4}{3} \cdot 2^{\frac{2}{3}} \epsilon_{LJ} \left[\left(\frac{\sigma_{tr}}{r - (\sigma_{LJ} - \sigma_{tr})} \right)^{24} - \left(\frac{\sigma_{tr}}{r - (\sigma_{LJ} - \sigma_{tr})} \right)^6 \right]; & \text{for } r \geq \sigma_{LJ} - \sigma_{tr} \end{cases}. \quad (5)$$

See Figure 1 for the CSW potential, the normal LJ potential ($\sigma_{LJ}/a = 1.0$), and its shifted version ($\sigma_{LJ}/a = 2.5$).

III. METHODS

We carried out Monte Carlo simulations under the constant number of particles, pressure, and temperature (NPT ensemble)⁵¹ with minimum image convention to minimize the surface effects. When dealing with small solutes ($\sigma_{LJ}/a \leq 2.0$), it was found that 300 solvent particles suffice for the system-size effects to be negligible. For larger solutes, twice as many solvent particles were simulated.

Each simulation was equilibrated for 100 000 cycles. In one cycle, a move of each particle and one change of volume was attempted. The maximum particle displacement per move

FIG. 1. Distance dependence of potentials; solvent-solvent interaction is plotted with solid line; solute-solute interactions are plotted with dashed line for $\sigma_{LJ} = 1.0$ and dotted line for $\sigma_{LJ} = 2.5$.

For solute-solute interaction, the well depth was set to $\epsilon_{LJ}/U_A = 0.10$ to describe a weakly interacting apolar particle, while the solute size σ_{LJ} varied.

For solvent-solute interactions, modified Lorentz-Berthelot^{49,50} mixing rules were used:

$$\epsilon_{mix} = \epsilon_{LJ}, \quad (3)$$

$$\sigma_{mix} = \frac{\sigma_{LJ} + a}{2}. \quad (4)$$

In a typical Lennard-Jones potential, the width of the attraction well grows as the solute size (σ_{LJ}) increases. This behavior is warranted when modeling solute-solute interactions but is physically unjustified for solvent-solute interactions. To circumvent this problem and keep its width characteristic of $\sigma/a = 1.0$ in the latter case, we shifted the potential above $\sigma_{tr}/a = 1.0$

and the maximum volume change were dynamically adjusted to yield a 50% acceptance ratio. Those values were then kept constant throughout ten simulation runs of 1 000 000 cycles, when statistics were sampled.

Thermodynamics of solvation was evaluated with three methods. First, the most straightforward way to obtain the free energy (ΔG), enthalpy (ΔH), entropy ($T\Delta S$), and heat capacity change (ΔC_p) is the Widom's insertion method. A ghost solute particle is randomly inserted into the simulation box and its interactions with every other particle are calculated. From a weighted average of those interaction values, a complete panel of thermodynamic quantities can be obtained as⁵²

$$\Delta G = -\beta^{-1} \ln [\langle V \rangle_N^{-1} \langle V \exp(-\beta U) \rangle_N], \quad (6)$$

$$\Delta H = \frac{\langle H_{N+1} \exp(-\beta U) \rangle_N}{\langle \exp(-\beta U) \rangle_N} - \langle H_N \rangle_N, \quad (7)$$

$$k_B T^2 \Delta C_p = \frac{\langle H_{N+1}^2 \exp(-\beta U) \rangle_N}{\langle \exp(-\beta U) \rangle_N} - \frac{\langle H_{N+1} \exp(-\beta U) \rangle_N^2}{\langle \exp(-\beta U) \rangle_N^2} - \langle H_N^2 \rangle_N + \langle H_N \rangle_N^2, \quad (8)$$

$$\Delta V = \frac{\langle V \exp(-\beta U) \rangle_N}{\langle \exp(-\beta U) \rangle_N} - \langle V \rangle_N, \quad (9)$$

where $\beta = (k_B T)^{-1}$ (k_B is the Boltzmann constant). Angle brackets $\langle \dots \rangle_N$ denote averages throughout the run over all insertions in the system, consisting of N particles. U is the interaction of a ghost particle with the system and $H_{N+1} = H_N + U$ represents the enthalpy of the system with the ghost particle. $\langle H_N \rangle_N$ and $\langle H_N^2 \rangle_N$ stand for average enthalpy

and average of squared enthalpy, respectively, of the system without the ghost particle.

For an infinitely long simulation where the whole phase space is sampled, the Widom's insertion method yields useful results regardless of the particle size, temperature, and density. In practice, however, when the probability of a successful insertion (measured as sufficiently favorable $-\beta U$) decreases, the method fails.

To avoid these problems, free energy perturbation (FEP) method was used.⁵³ A solute of size σ_1 is fixed at the center of the simulation box, interacting normally with solvent particles (U_1) during the equilibration and sampling phases of the simulation. Once per cycle, the current configuration is frozen and the solute particle is temporarily replaced with a

solute particle of size σ_2 . Its interaction with solute particles is calculated (U_2). If the free energy of transfer for the first solute is known (in our case from Widom's insertion method), the free energy for the solvation of the larger solute can be calculated, as follows:

$$\Delta G_2 = \Delta G_1 + \left(-k_B T \ln \left(\exp \left(-\frac{U_2 - U_1}{k_B T} \right) \right) \right). \quad (10)$$

It is also possible to obtain the free energy of solvation via thermodynamic integration. A solute particle is slowly introduced into the system by turning on its interaction with the solvent through the increase of the parameter λ in the following potential:

$$U_{LJ} = \frac{4}{3} \cdot 2^{\frac{2}{3}} \epsilon_{LJ} \lambda^n \left[\frac{1}{\left(\alpha(1-\lambda)^m + \left(\frac{r}{\sigma_{LJ}} \right)^{12} \right)^2} - \frac{1}{\left(\alpha(1-\lambda)^m + \left(\frac{r}{\sigma_{LJ}} \right)^3 \right)^2} \right]. \quad (11)$$

We set $m = n = 2$ and $\alpha = 0.5$. Notice that for $\lambda = 0$ the potential function equals 0 and for $\lambda = 1$ it simplifies to the aforementioned modified Lennard-Jones potential. We average the derivative of the solute-solvent potential with respect to λ and the volume for every value of λ . The free energy for transfer of a solute particle into the solution is given by

$$\Delta G = \int_{\lambda=0}^{\lambda=1} \frac{\partial U_{LJ}}{\partial \lambda} d\lambda + \ln \frac{V_{(\lambda=1.0)}}{V_{(\lambda=0.0)}}. \quad (12)$$

Enthalpy of solvation is calculated via the Gibbs-Helmholtz equation

$$\left(\frac{\partial \frac{\Delta G}{T}}{\partial T} \right)_p = -\frac{\Delta H}{T^2}. \quad (13)$$

Entropy of solvation is obtained from $T\Delta S = \Delta H - \Delta G$. To check if the methods give consistent results, we calculated thermodynamics of solvation at $T^* = 1.0$ and $p^* = 0.10$ for various solutes size using these methods. As shown in Figure 2, symbols of different colors coincide, meaning that values obtained from different methods differ less than the statistical uncertainty.

IV. RESULTS AND DISCUSSION

All presented results are reported in dimensionless reduced units in terms of the solvent diameter and the depth of its attractive well, as $T^* = k_B T / U_A$, $\rho^* = \rho a^3$, and $p^* = p a^3 / U_A$.

A. Temperature dependence

Figure 3 shows how the transfer free energy, transfer enthalpy, transfer entropy, transfer heat capacity, and volume change at infinite dilution depend on temperature for three

sizes of solute ($\sigma/a = 0.5, 1.0, 2.5$). For each solute, there is a pronounced maximum in the free energy of transfer, corresponding to the TMS. As the solute size grows, this maximum shifts towards lower temperatures, just as in more complex water models.⁵⁴ Entropy and enthalpy of solvation rise monotonically with increasing temperature and start to deflect in the supercritical region (above $T^* = 1.13^{31}$). The mechanism of solvation arguably changes as the solute size increases, since the cross-over temperature of zero entropy (T_S) decreases with the solute size (see Sec. IV B and Figure 6).

At high temperatures, the process is primarily enthalpically driven. Introduction of a solute disrupts the system and increases its entropy. However, the process is not favorable due to large enthalpic penalty. At lower temperatures, the entropy of the system actually decreases as the introduction of the solute causes the solvent particles to assume a more

FIG. 2. Calculated transfer thermodynamics, i.e., ΔG^* (diamonds), ΔH^* (circles), and $T\Delta S^*$ (triangles), for different methods is plotted with black for Widom insertion method; blue for free energy perturbation; and magenta for thermodynamic integration. (Note that we plot the inverse hyperbolic sine versus logarithm in order to represent positive and negative values across several orders of magnitude.)

FIG. 3. Calculated temperature trends of transfer thermodynamics for modified LJ solutes of various sizes, as indicated in the figure.

ordered configuration. Smaller solutes introduce a greater amount of order as they squeeze more easily into the cavities between solvent molecules, resulting in greater entropy decrease. For larger solutes, this effect is less pronounced as they generally do not fit in the cavities. The enthalpy of solvation for small solutes is actually slightly favorable, but the effect is too small to influence solubility at lower temperatures.

Heat capacity is only slightly dependent on temperature. The volume change of transfer shows a temperature minimum around the TMS. These findings are in excellent agreement with the experimental results for solvation of small non-polar molecules.^{55–58}

Hydrophobic effect can be characterized by several physical quantities. Besides the TMS, the comparison of solute-solute radial distribution function (RDF), $g_{ss}(r)$, is perhaps the most illustrative. Figure 4 shows this RDF across the temperature range of a liquid phase for large solutes ($\sigma/a = 2.5$) at near infinite dilution. As the solution gets warmer, the first peak in RDF increases as the solubility decreases and solute

particles clump together. Upon further increase of temperature, the trend reverses and the peak starts to diminish. PMF, obtained as $-k_B T \ln g(r)$, changes monotonically with temperature. However, it displays a typical behavior of two minima. The first one corresponds to the contact configuration ($r/a = 2.5$) and the second one to the solvent separated configuration ($r/a = 2.5 + 1.0$). Between we found a so-called desolvation peak,⁵⁹ where the system is particularly unstable.

B. Size dependence

Figure 5 shows the solute-solvent ($g_{sw}(r)$) and solute-solute ($g_{ss}(r)$) radial distribution functions at $T^* = 1.0$ and $p^* = 0.100$ for infinite dilution of several solutes of different size. With an increase of the solute diameter, solvation is improved, which manifests as a higher first peak in solute-solvent particles RDF and an accompanying, albeit much less pronounced decrease in the solute-solute RDF. This happens for sizes up to $\sigma/a = 1.5$, where solute particles can still fit in

FIG. 4. (a) and (b) Solute-solute pair correlation function $g_{ss}(r)$ for different temperatures. The first peak of solute-solute pair distribution function becomes stronger, signifying the agglomeration of hydrophobic solutes. After reaching the maximum value around $T^* = 0.75$, any further increase of temperature drives the particles apart. (c) PMF changes monotonically with temperature.

the cavities between the solvent molecules. Larger solute particles, however, tend to destroy the configuration of solvent molecules. Solvation becomes less favorable, which shows up as a decrease of first peak in the solute-solvent RDF and an increase of the first peak for solute-solute RDF. The same behavior is encountered when using Jagla potential or cavity equation of state (C-EoS) for water.⁶⁰ A different solvation mechanism for small and large particles is proposed as an explanation for this behavior.

Further explanation of this behavior is in Figure 6. For smaller solutes, the solvation is primarily entropically driven. The entropy change is negative for smaller solutes because they actually allow the solvent to attain a cage-like ordered structure around the solute. We describe the “lack

of solvation” as entropically driven because the unfavorable entropy decrease is an order of magnitude larger than the net gain from the favorable enthalpy contribution to Gibbs free energy. Larger solutes, however, do not fit in those cavities and disrupt the local environment, increasing the entropy. This phenomenon is strongly temperature-dependent, disappearing altogether at high temperature when addition of the solute particles always increases the entropy. For smaller solutes, the free energy of solvation scales with their volume. Above the cross-over size for each temperature, the free energy of solvation depends on the surface size of the solute and approaches a limit. It has been shown that this limit corresponds to the surface tension.⁶¹ For smaller solutes, the free energy of solvation per surface size increases with

FIG. 5. Solvent-solute (left) and solute-solute (right) pair distribution functions at infinite dilution for various solute sizes, as indicated in the figure at $T^* = 1.0$ and $p^* = 0.100$.

FIG. 6. As the size of hydrophobic particles increases, the mechanism of hydrophobic solvation changes. For small particles ($1 \leq \sigma \leq 2$), the free energy of solvation scales with volume (upper left) and increases with temperature, whereas for larger particles it scales with surface (upper right) and decreases with temperature. In the intermediate range, there is a clearly observable cross-over between the mechanisms. Solvation of larger particles is entropically favored, while smaller particles actually decrease the entropy of solvent molecules.

temperature, while for larger solutes, it decreases. Such cross-over is typical of water-like liquids and generally absent in normal (e.g., Lennard-Jones) liquids.⁶⁰

We can quantify different solvation mechanisms by the cross-over temperature (T_S), where the sign of the entropy of solvation flips (see the left panel of Figure 7). Above $T^* = 1.27$, entropy of solvation for solute of any size is positive. At lower temperatures, the entropy of solvation of smaller solutes is negative. This is decisive proof of two distinct and competing solvation mechanisms. It has been shown that for large radii the excess chemical for a hard sphere ($\Delta G/\sigma^2$) in water corresponds to the surface tension of water.⁶¹ Surface tension of water decreases as the water gets warmer. We

show in the right panel of Figure 7 the excess potential of a Lennard-Jones particle in the CSW fluid, when the solute diameter is five times larger than the solvent.

C. Pressure dependence

Solvation thermodynamics was investigated in a broad pressure range from $p^* = 0.01$ to $p^* = 0.30$ ($T^* = 1.0$) and the results are shown in Figure 8. The free energy of solvation increases monotonically with pressure. With an increase of pressure, solvent density also increases and it becomes more difficult to insert a solute molecule into a denser solvent phase. This should not be interpreted as decreased

FIG. 7. (Left) Cross-over temperature where the entropy of solvation is zero changes with the solute size. (Right) Free energy of solvation for a large apolar solute ($\sigma_{LJ} = 5.0$) as a function of temperature.

FIG. 8. Calculated pressure trends of transfer thermodynamics for modified LJ solutes of various sizes, as indicated in the figure.

solubility at higher pressures, which would clearly contradict Henry's law. Calculated free energies of solvation correspond to the transfer of the solute from vacuum in the solution, while Henry's law is concerned with the transfer of the solute from gaseous phase at a particular pressure to the solution at the same pressure.

Much more interesting are the pressure dependence of the enthalpy and entropy. In the low-pressure regime, the enthalpy and the entropy of solvation, and the solute partial volume decrease as the pressure grows up to $p^* = 0.15$. This is due to disordered solvent with many degrees of freedom and attainable configurations at low pressure and density. Introducing solute particles in the system increases this disorder. At larger pressures, the packing is denser and well defined cavities begin to form. At intermediate pressures, they are of comparable size to that of solute, resulting in a decrease of entropy upon solvation. The entropic and enthalpic contribution mostly cancel out, resulting in a monotonic increase of free energy of solvation. Above the inflection point, the trend is reversed.

At extreme pressures, the packing density gets so dense that a solute particle cannot fit into cavities and the entropy of transfer again increases. Heat capacity, however, decreases monotonically with pressure in the whole investigated range. Experimental data on pressure dependence of non-polar solvation in water are extremely scarce. Turning to simulation results from point charge water models, we found that our results correctly predict observed trends. As calculated for methane hydration in the TIP4P model,⁶² upon increasing pressure there is a monotonic increase in free energy of solvation, decrease of solute partial volume and heat capacity, and a non-monotonic ("U-shaped") dependence of enthalpy and entropy of the solvation.

V. CONCLUSION

We have carried out extensive Monte Carlo simulations to investigate solvation of apolar solutes of various size in the CSW water-like liquid. The temperature, pressure, and solute size dependence of various thermodynamic quantities

were studied. Our simulations covered the whole liquid range of the CSW model, from low to high temperatures and extremely low to high pressures just below the solidification. Solute diameter varied from one-half to five times of the solvent diameter.

We have shown that the CSW model captures the anomalous properties of hydrophobic solvation that are typical of water. Those arise from the competition between the entropic and enthalpic contribution to the free energy of solvation. At low temperatures, the entropy of solvation is unfavorable because the solute molecules force additional ordering of solvent molecules. At high temperatures, a large positive enthalpy of solvation is the main reason for the positive sign of free energy. As with apolar solutes in water, the CSW model predicts a temperature of minimum solubility that depends upon the solute size.

The mechanism of solvation is different for small and large particles. For small particles, the free energy of solvation scales with volume. For larger particles, it scales with surface area. For small particles, the free energy of solvation at higher temperatures is larger while for large particle the opposite is true. Pressure dependence shows a distinct minimum in entropy and enthalpy of solvation irrespective of the solute size. The effects, however, cancel out and the total free energy of solvation increases monotonically with pressure.

We can conclude that the CSW model predicts the size and pressure dependence that have been experimentally observed in water. This makes CSW a promising model for studying general trends and influences of water in processes with the hydrophobic effect as the main driving force. Due to its computational inexpensiveness, it can be employed to simulate very large systems where simulations with more complex models take too long.

ACKNOWLEDGMENTS

We appreciate the support of the Slovenian Research Agency (P1 0103-0201 and J1 4148) and National Institutes of Health (NIH) Grant No. GM063592. M.H. is supported by the “Young Researcher” programme of Slovenia.

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