The application of the thermodynamic perturbation theory to study the hydrophobic hydration

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The thermodynamic perturbation theory was tested against newly obtained Monte Carlo computer simulations to describe the major features of the hydrophobic effect in a simple 3D-Mercedes-Benz water model: the temperature and hydrophobe size dependence on entropy, enthalpy, and free energy of transfer of a simple hydrophobic solute into water. An excellent agreement was obtained between the theoretical and simulation results. Further, the thermodynamic perturbation theory qualitatively correctly (with respect to the experimental data) describes the solvation thermodynamics under conditions where the simulation results are difficult to obtain with good enough accuracy, e.g., at high pressures. © 2013 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4812744>]

I. INTRODUCTION

There are many important biological and technological processes taking place in aqueous solutions. Often such processes include solutes that are (at least partially) non-polar. Hydration of non-polar particles (hydrophobic hydration) is an unusual process compared to other solvation processes.^{1–3} Although the solvation is usually determined by the enthalpy change of the process, in spite of the favourable enthalpy of transfer ($\Delta H_{TR} < 0$) for non-polar solutes (i.e., enthalpy for the process of transferring non-polar particle from vacuum to bulk water) at low temperatures, non-polar particles do not dissolve in water. The process is endergonic ($\Delta G_{TR} > 0$) due to the negative entropy of transfer $\Delta S_{TR} < 0$.^{1,2} Both, enthalpy and entropy changes, strongly increase with temperature. This fact is summarized by stating that the heat capacity of transfer is high and positive ($\Delta C_{p,TR} \gg 0$), since

$$\Delta C_{p,TR} = \frac{d\Delta H_{TR}}{dT} = T \frac{d\Delta S_{TR}}{dT}, \quad (1)$$

where T is temperature. These features are known as hydrophobic effect.^{1–5}

Since the hydrophobic effect plays an important role in many common processes in nature (e.g., protein folding, ligand binding) and technology (e.g., micelle formation), it has been extensively studied experimentally,^{6–10} as well as by computer simulations using explicit and implicit water models. While the explicit models (such as Transferable intermolecular potential (TIP) or Simple point charge (SPC)) present a big computational difficulty and are often too expensive to explore full temperature or pressure dependencies, the implicit models are faster but often inaccurate. Further, the computer simulation results are, in general, subject to a relative large statistical error that makes the quantities, such

as the heat capacity, difficult to determine with high enough accuracy.^{11,12}

Another approach to study the thermodynamics of solvation comes from the theory of liquids. One of the appealing features of such calculations is that they are computationally much more efficient and, as a result, provide the thermodynamic quantities in an analytical form, so that they can be calculated very accurately. In the last decades, the development of the associative Ornstein-Zernike (OZ) equation made it possible to include the strongly orientational dependent potential between water molecules into such calculations.^{13–16} The theories are known to treat hot water (near boiling point) more accurately than cold water (near room temperature).¹⁷

Theories based on thermodynamic perturbation method and associative OZ integral equation have been used to describe the thermodynamics of hydration of a simple two-dimensional solvent in Ben-Naim water model, known also as the Mercedes-Benz (MB) water model,^{17,18} and good agreement with the computer simulations was obtained. Similar theories have been, for few cases, tested also on three-dimensional model of pure water.¹⁹

In order to explore the performance of the thermodynamic perturbation theory (TPT) in describing the hydrophobic hydration, we used the simplified water model, a three-dimensional version of the Ben-Naim water model (3D MB).¹² The model has previously been shown to capture the essential physics of water, namely, van der Waals interaction and hydrogen-bonding which are essential for hydrophobic hydration.^{5,11,20–24} The hydrophobic effect dependence on temperature, pressure, and solute size was explored.

The paper is organized as follows: After above-given Introduction, we describe the 3D MB water model in Sec. II. Details about Monte Carlo simulations are given in Sec. III, while in Sec. IV we present the TPT approach. In Sec. V, the results from computer simulations and TPT are compared and discussed. The main conclusions of this work are summarized in Sec. VI.

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II. 3D MB WATER MODEL

In the 3D MB water model each water molecule is represented as a Lennard-Jones (LJ) particle with an additional orientationally dependent potential that tries to mimic the hydrogen-bonding of true water.¹² Therefore, the interaction potential between two water molecules is

$$U(\mathbf{X}_i, \mathbf{X}_j) = U_{LJ}^{11}(r_{ij}) + U_{HB}(\mathbf{X}_i, \mathbf{X}_j), \quad (2)$$

where r_{ij} is the distance between centres of particles i and j , and $\mathbf{X}_i$ is vector denoting position and orientation of particle i . U_{LJ}^{mn} is modified Lennard-Jones potential

$$U_{LJ}^{mn}(r_{ij}) = \begin{cases} 4\epsilon_{LJ}^{mn} \left[\left(\frac{\sigma_{LJ}^{mn}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{LJ}^{mn}}{r_{ij}} \right)^6 \right], & \text{if } \sigma_{LJ}^{mn} < 0.85r_{HB} \\ 4\epsilon_{LJ}^{mn} \left[\left(\frac{\sigma_{LJ}^{mn'}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{LJ}^{mn'}}{r_{ij}} \right)^6 \right], & \text{if } \sigma_{LJ}^{mn} \geq 0.85r_{HB} \end{cases}, \quad (3)$$

where ϵ_{LJ}^{mn} denotes the well-depth, σ_{LJ}^{mn} is the contact parameter, m is 1 if i th particle is water or 2 if it is solute and the same is for n . For particles with $\sigma_{LJ}^{mn} < 0.85r_{HB}$, the interaction is usual Lennard-Jones. For bigger particles the potential has the same form, but now with $\sigma_{LJ}^{mn'} = 0.85r_{HB}$ and $r'_{ij} = r_{ij} - \sigma_{LJ}^{mn} + 0.85r_{HB}$. Using this potential, we got rid of artificially exaggerated potential well around big solutes. The hydrogen-bonding (HB) term is the sum of interactions over all possible pairs of HB arms,

$$U_{HB}(\mathbf{X}_i, \mathbf{X}_j) = \sum_{k,l}^4 U_{HB}^{kl}(r_{ij}, \boldsymbol{\Omega}_i, \boldsymbol{\Omega}_j), \quad (4)$$

where $U_{HB}^{k,l}$ is the interaction between HB arms k and l on two particles and vector $\boldsymbol{\Omega}_i$ denotes the orientation of particle i . The interaction between two HB arms of different particles is

$$U_{HB}^{kl}(r_{ij}, \boldsymbol{\Omega}_i, \boldsymbol{\Omega}_j) = \epsilon_{HB} G(r_{ij} - r_{HB}) G(\mathbf{i}_k \mathbf{u}_{ij} - 1) G(\mathbf{j}_l \mathbf{u}_{ij} + 1). \quad (5)$$

Here, $\mathbf{u}_{ij}$ is the unit vector pointing from particle i to particle j , $\mathbf{i}_k$ is the unit vector representing arm k on particle i , and $G(x)$ is unnormalized Gaussian function,

$$G(x) = e^{-x^2/2\sigma^2}. \quad (6)$$

The model does not make a distinction between hydrogen-bond donors and acceptors. The strongest hydrogen-bond is formed when two arms are pointing towards each other particles' centres while centres being separated by r_{HB} . We used the following values for parameters: $\epsilon_{LJ}^{ww} = 0.05|\epsilon_{HB}|$ and $\sigma_{LJ}^{ww} = 0.7r_{HB}$, where $\epsilon_{HB} = -1$ and $r_{HB} = 1$. All thermodynamic quantities were expressed in reduced units normalized to $|\epsilon_{HB}|$ and r_{HB} : $T^* = k_B T / |\epsilon_{HB}|$, $U^{EX*} = U^{EX} / |\epsilon_{HB}|$, $V^* = V / r_{HB}^3$, and $P^* = P r_{HB}^3 / |\epsilon_{HB}|$. All distances were expressed in r_{HB} . The value of parameter σ in Eq. (6) was chosen to be 0.085 as in other studies of this model.^{12,25,26}

The nonpolar solute is modeled as Lennard-Jones particle without hydrogen-bonding arms. Our solution in the simulation was infinitely diluted, therefore we had to specify only the water-solute potential. The parameters were obtained using the standard Lorentz-Berthelot rules. The well-depth was taken to be $\epsilon_{LJ}^{12} = 0.05$ in all cases, while contact parameter, σ_{LJ}^{12} , was varying.

The model captures the main features of the hydrophobic effect: the transfer free energy, ΔG^* , is positive and decreases with temperature. The transfer enthalpy, ΔH^* , and transfer entropy, $T^* \Delta S^*$, of a hydrophobic particle as a function of temperature first increase and then start to decrease with temperature,²⁷ as observed experimentally.² As a function of the solute size, the thermodynamics of two different mechanisms of hydrophobic hydration are properly described by the model. In cold water, the insertion of a small hydrophobic solute is opposed by the entropy change, while for a large hydrophobic solute, the insertion is opposed by the enthalpy change and favoured by the entropy change. The two mechanisms are reflected in the free energy of transfer per unit solute surface area that, when plotted as a function of a solute size, scales differently for small and large solutes.²⁷

It is worth mentioning that recently Dias *et al.*^{25,26,28} came up with the modified version of a 3D MB model, which includes the additional parameters and where the interaction potential depends on its local environment. With these modifications they reproduced the solid phase (ice) and pair distribution functions of real water. Since our goal was to test the TPT on 3D model with orientationally dependent potential, we applied it to the computationally more efficient original 3D MB model.

III. MONTE CARLO SIMULATION

We performed isothermal-isobaric (NPT) Monte Carlo simulations of 5000 3D MB particles. We adopted periodic boundary conditions and minimum image convention to mimic the infinite system.²⁹ To obtain the thermodynamic quantities of insertion of a hydrophobe, we used the Widom's particle insertion method.²⁹

First, the system of 5000 3D MB particles was equilibrated in 10 equilibration runs of 10^8 steps. Here one step means an attempt to change the volume of the simulation box or position/orientation of 3D MB particle. Probability of making an attempt to change the volume was chosen such that on average it occurred once per pass (1 pass = N particles). Attempts to change the position or orientation of a 3D MB particle had the same probability. After equilibration, the results of insertion thermodynamics were collected in 10 production runs, each of length of 10^8 steps. Averages were computed and the statistical errors were estimated as the standard deviations of the production runs.

For systems between $T^* = 0.2$ and $T^* = 0.3$, the initial configuration was chosen randomly. To equilibrate systems at lower temperatures, we started from the equilibrated configuration at $T^* = 0.2$ and slowly cooled the systems in steps of $\Delta T^* = 0.01$. After each cooling step, we performed a few equilibration runs at new temperature before going to lower temperature.

During production runs we performed Widom's particle insertion method.^{11,29} Every 1000 steps we made 1000 attempts to insert a hydrophobe. Using test-particle equations, we computed the transfer free energy, enthalpy, entropy, and volume:¹¹

$$\beta \Delta G_{TR} = -\ln \langle e^{-\beta \epsilon} \rangle_N, \quad (7)$$

$$\Delta H_{TR} = \frac{\langle H_{N+1} e^{-\beta\epsilon} \rangle_N}{\langle e^{-\beta\epsilon} \rangle_N} - \langle H_N \rangle_N, \quad (8)$$

$$T \Delta S_{TR} = \Delta H_{TR} - \Delta G_{TR}, \quad (9)$$

$$\Delta V_{TR} = \frac{\langle V e^{-\beta\epsilon} \rangle_N}{\langle e^{-\beta\epsilon} \rangle_N} - \langle V \rangle_N, \quad (10)$$

where ϵ is the interaction energy of the test particle with the surrounding solvent, $\beta = 1/k_B T$, where k_B is Boltzmann's constant and T is the temperature. H_N is the enthalpy of the pure solvent and $H_{N+1} = H_N + \epsilon$. Averages are performed over the pure reference fluid.

IV. THERMODYNAMIC PERTURBATION THEORY

In the thermodynamic perturbation theory,^{15,16} first thing we need to calculate is the Helmholtz free energy of a system. For our system this quantity is calculated as a sum of two terms, the Lennard-Jones and hydrogen-bond term:

$$\frac{A}{Nk_B T} = \frac{A_{LJ}}{Nk_B T} + \frac{A_{HB}}{Nk_B T}. \quad (11)$$

In Eq. (11), A_{LJ} is the Helmholtz free energy of a mixture of Lennard-Jones spheres, and A_{HB} is contribution of the hydrogen-bonds of water molecules to the free energy. N denotes the total number of particles, T is the absolute temperature, and k_B is Boltzmann's constant. A_{LJ} is calculated using the Barker-Henderson perturbation theory³⁰ with the hard-sphere (HS) mixture as a reference system:

$$\begin{aligned} \frac{A_{LJ}}{Nk_B T} = \frac{A_{HS}}{Nk_B T} - 4\pi \varrho x_1 x_2 d_{12}^2 g_{12}^0(d_{12})(d_{12} - D_{12}) \\ + 2\pi \varrho \beta \sum_{kl=1}^2 x_k x_l \int_{\sigma_{kl}}^{\infty} g_{kl}^0(r) U_{LJ}^{kl}(r) r^2 dr, \end{aligned} \quad (12)$$

where x_1 denotes a mole fraction of 3D MB water molecules and x_2 a mole fraction of solute molecules, $U_{LJ}^{kl}(r)$ is the Lennard-Jones potential and ϱ the total number density. Furthermore, $g_{kl}^0(r)$ is the pair distribution function for the reference hard-sphere mixture, which is obtained by solving the Percus-Yevick integral equation. The parameter d_{12} is calculated by

$$d_{12} = \frac{D_{11} + D_{22}}{2}, \quad (13)$$

where D_{ij} is defined as

$$D_{ij} = \int_0^{\sigma_{ij}^{LJ}} (1 - e^{-\beta U_{LJ}^{ij}(r)}) dr. \quad (14)$$

In Eq. (12), A_{HS} is the hard-sphere mixture contribution to the Helmholtz free energy. To calculate the HS term of the Helmholtz free energy, we use Eq. (11) (see Mansoori *et al.*³¹ and references therein):

$$\begin{aligned} \frac{A_{HS} - A_{ideal}}{Nk_B T} = -\frac{3}{2}(1 - y_1 + y_2 + y_3) + \frac{3y_2 + 2y_3}{1 - \xi} \\ + \frac{3}{2} \frac{1 - y_1 - y_2 - \frac{1}{3}y_3}{(1 - \xi)^2} + (y_3 - 1) \ln(1 - \xi), \end{aligned} \quad (15)$$

where ξ is the overall packing fraction calculated as sum of packing fractions for each particle:

$$\xi = \xi_1 + \xi_2. \quad (16)$$

Individual packing fractions are calculated by

$$\xi_i = \frac{\pi}{6} \varrho x_i D_{ii}^3, \quad (17)$$

and y_i are defined as

$$y_1 = \frac{\Delta_{12} (D_{11} + D_{22})}{\sqrt{D_{11} D_{22}}}, \quad (18)$$

$$y_2 = \Delta_{12} \left(\frac{\xi_1}{\xi} \sqrt{\frac{D_{22}}{D_{11}}} + \frac{\xi_2}{\xi} \sqrt{\frac{D_{11}}{D_{22}}} \right), \quad (19)$$

$$y_3 = \left(\left(\frac{\xi_1}{\xi} \right)^{2/3} x_1^{1/3} + \left(\frac{\xi_2}{\xi} \right)^{2/3} x_2^{1/3} \right)^3. \quad (20)$$

The parameter Δ_{12} is calculated by the following expression:

$$\Delta_{12} = \frac{\sqrt{\xi_1 \xi_2} (D_{11} - D_{22})^2}{\xi D_{11} D_{22}} \sqrt{x_1 x_2}. \quad (21)$$

The hydrogen-bonding part of the Helmholtz free energy is calculated by Refs. 32 and 33:

$$\frac{A_{HB}}{Nk_B T} = 4x_1 \left(\log y - \frac{y}{2} + \frac{1}{2} \right), \quad (22)$$

where y is the fraction of 3D MB molecules not bonded at one particular arm, obtained from the mass-action equation in the form:

$$y = \frac{1}{1 + 4\varrho_1 y \Delta}, \quad (23)$$

and ϱ_1 is the number density of water (MB) molecules and Δ is defined as

$$\Delta = 4\pi \int g_{11}^{LJ}(r) \bar{f}_{HB}(r^2) r^2 dr, \quad (24)$$

where $\bar{f}_{HB}(r)$ is an orientationally averaged Mayer function for the HB potential of one site. The pair distribution function $g_{11}^{LJ}(r)$ is obtained by solving the Percus-Yevick equation for the LJ sphere mixture. Once the Helmholtz free energy is obtained, other thermodynamic quantities may be calculated using standard thermodynamic relations.

V. RESULTS AND DISCUSSION

A. Temperature dependence

We first present the results for the transfer free energy, ΔG^* , as a function of temperature for different sizes of hydrophobic particles ($\sigma_S^* = \sigma_{LJ}^{22}/r_{HB}$). In Figure 1(a), results for $\sigma_S^* = 0.7$ (red), $\sigma_S^* = 1.5$ (green), and $\sigma_S^* = 2.0$ (blue) are shown. The symbols represent the results of the computer simulations and the lines are the results of the TPT theory. For the small solute size, an excellent agreement between the theory and simulation was observed in the whole temperature range studied. For larger hydrophobes, the theory follows the

FIG. 1. (a) Transfer free energy, ΔG^* , as a function of temperature. Different colours correspond to hydrophobes of different sizes: $\sigma_S^* = 0.7$ (red), $\sigma_S^* = 1.5$ (green), $\sigma_S^* = 2.0$ (blue). Lines show theoretical results and points show simulation results. (b) Transfer free energy, ΔG^* , as a function of temperature. Different colours correspond to different hydrophobe sizes: $\sigma_S^* = 0.3$ (light blue), $\sigma_S^* = 0.7$ (red). Lines show theoretical results and points show simulation results.

simulation data for relative high temperatures, but underestimates the ΔG^* at relative cold solutions. This is in agreement with previous observations.¹⁸

Figure 1(b) shows the qualitative difference in dependencies of ΔG^* as a function of temperature for a small and a large hydrophobe. One can see that for small hydrophobic sizes, the ΔG^* first slightly increases with temperature, and then decreases. This result is in agreement with the experimental observation for the thermodynamics of hydration of argon,² and is qualitatively different from the behavior of ΔG^* for larger hydrophobes. The TPT theory manages to correctly capture these subtle differences.

Figure 2 shows the transfer enthalpy, ΔH^* , and transfer entropy, $T^*\Delta S^*$, as a function of temperature, and for different solute sizes. Both functions first increase, and then start to decrease with temperature, as observed experimentally.² The agreement between the computer simulation results (symbols) and TPT (lines) is excellent in the whole temperature range studied, even for the large hydrophobic solutes. Since $\Delta G^* = \Delta H^* - T^*\Delta S^*$, this suggests that a possible reason for the above-described disagreement in ΔG^* could be an increasing numerical error in computer simulations with decreasing temperature. One can see large scattering of the computer simulation results for ΔH^* and $T^*\Delta S^*$ in cold solutions.

Another interesting quantity that is correlated with the changes in the microscopic structure of water upon hydration is a transfer volume, ΔV^* . It is known experimentally⁶ that for relative small solutes ΔV^* increases with the increasing temperature. Our results, again, for different solute sizes,

FIG. 2. (a) Transfer enthalpy, ΔH^* , and (b) transfer entropy, $T^*\Delta S^*$, as a function of temperature. Different colours correspond to hydrophobes of different sizes: $\sigma_S^* = 0.7$ (red), $\sigma_S^* = 1.5$ (green), $\sigma_S^* = 2.0$ (blue). Lines show theoretical results and points show simulation results.

are, as a function of temperature, presented in Figure 3. For small hydrophobic sizes, the ΔV^* is obtained by the computer simulations and TPT increases with temperature in the whole temperature range studied, while for larger solutes non-monotonous behavior is observed.

B. Solute size dependence

Another characteristic of the hydrophobic effect is its solute size dependence. The solvation free energy for large solutes increases linearly with area, while for small solutes it increases linearly with volume.^{23,34} The transition in the behavior is correlated to the thermodynamic nature of hydrophobic

FIG. 3. Transfer volume, ΔV^* , as a function of temperature. Different colours correspond to hydrophobes of different sizes: $\sigma_S^* = 0.7$ (red), $\sigma_S^* = 1.5$ (green), $\sigma_S^* = 2.0$ (blue). Lines show theoretical results and points show simulation results.

FIG. 4. (a) Transfer free energy, ΔG^* , (b) transfer enthalpy, ΔH^* , and (c) transfer entropy, $T^* \Delta S^*$, as a function of hydrophobe size (σ_s^*) at two different temperatures: $T^* = 0.2$ (red) and $T^* = 0.3$ (green). Points are simulation results and lines are theoretical results.

hydration: for small solutes, the entropy contribution to the change in free energy dominates ($T\Delta S > \Delta H$), but for larger solutes, $T\Delta S < \Delta H$.

Our results are for transfer free energy, ΔG^* , transfer enthalpy, ΔH^* , and transfer entropy, $T\Delta S^*$ at two different temperatures, $T^* = 0.2$ (red) and $T^* = 0.3$ (green), as a function of solute size shown in Figure 4. The symbols represent the results of the computer simulations and the lines are the results of the TPT theory.

For all three thermodynamic functions describing transfer of a hydrophobic particle, one can clearly distinct two areas of behavior, as observed experimentally.^{1,2,6–10,35,36} Further, the agreement between the theory and simulation is excellent for both temperatures, and in the whole range of solute sizes studied here.

FIG. 5. Transfer free energy, ΔG^* (solid), transfer enthalpy, ΔH^* (long dashed), and transfer entropy, $T^* \Delta S^*$ (short dashed), as a function of pressure for a hydrophobe $\sigma_s^* = 0.7$. Results of the TPT.

Results of the TPT, for a similar hydrophobe model, but for a smaller range of parameters, were previously presented by Bizjak.³⁷ His results are also consistent with our findings.

C. Pressure dependence

Last, we studied the pressure dependence of the hydrophobic effect. It has been established experimentally^{38–40} and theoretically⁴¹ that the free energy of solvation for small solutes increases with pressure almost linearly, while the enthalpy and entropy of solvation exhibit very little pressure dependence.

Due to a large statistical error, we did not succeed to obtain reliable computer simulation results and we are therefore presenting just the TPT results. Figure 5 is showing transfer free energy, ΔG^* (solid line), transfer enthalpy, ΔH^* (long dashed line), and transfer entropy, $T^* \Delta S^*$ (short dashed line), as a function of pressure for a hydrophobe $\sigma_s^* = 0.7$.

The transfer free energy increases almost linearly with pressure in agreement with previous observations.^{38–41} Further, the transfer enthalpy is a small negative value for low pressures, and slightly increases with pressure, which, again, is consistent with the previous results. The same is true for the entropy which is negative in the whole pressure range studied, and first shows a small increase, and then decreases upon further increase of pressure. In other words, the theory predicts that at higher pressures the solvation becomes increasingly dominated by the entropic contribution, relative to the enthalpic term, which is consistent with the observations of Rajamani *et al.*⁴²

VI. CONCLUSION

The thermodynamic perturbation theory was used to study the hydration thermodynamics of a simple model hydrophobe in a 3D MB water. The major features of the hydrophobic effect, its hydrophobe size, temperature dependence, and pressure dependence, were systematically studied in a large range of temperatures and hydrophobe sizes.

The results for transfer free energy, transfer enthalpy, transfer entropy, and transfer volume obtained by the TPT theory show excellent agreement with the computer simulation results for the same model for all the parameters studied. The

only exception is the low temperature behavior of the transfer free energy for large solutes where the results of the theory lie below the results of the computer simulation. We suspect this to be a consequence of the poor statistics of the computer simulations in this region.

Further, the TPT enabled us to study the thermodynamics of solvation under the conditions where the computer simulation results were unreliable due to the too large statistical uncertainty, namely, at high pressures. The results of the TPT under these conditions are consistent with the existing experimental and theoretical results.

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