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The formation of a cavity in water: Changes of water distribution and prediction of the excess chemical potential of a hard-sphere solute under increasing pressure

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ABSTRACT

This work deals with the formation of a spherical cavity in water along the isotherm at 298 K. A striking effect of increasing pressure was found on the radial distribution functions obtained by Monte Carlo simulations, with significantly different behaviors observed when increasing the cavity radius at 8000 atm and 1 atm. At a fixed cavity radius, a pressure increase up to 10,000 atm leads to increased hydration structure. At a constant high pressure, structure is maintained even increasing the cavity radius, while it is lost at atmospheric pressure. Particular focus is on the value at contact, G(r), the central quantity in Scaled Particle Theory that is related to the derivative with respect to the radius of the work required to form the cavity. Within the limit of very small radii, exact conditions were applied to these two quantities. This allowed us to readily determine, at any pressure along the isotherm, the parameters of a simple model used to compute the excess chemical potential associated with the hydration of a hard sphere. This was made possible thanks to heuristic models used to describe how the number density of water changes along the isotherm and how the second moment of water distribution depends on the first moment. Use was also made of additional information on a cavity of molecular size. Apart from the dependence on pressure of hydrophobic solvation, this work also concerns calculation of the so-called cavitation contribution to the free energy of solvation when this is computed within implicit solvent models.

1. Introduction

According to thermodynamics [6,5], excess chemical potential or pseudochemical potential [6] expresses how the free energy of the system changes as a solute molecule is added to the solvent at a fixed position. For a hard-sphere solute–solvent potential, at constant T, this quantity is equal to the reversible work necessary to form a cavity in the solvent [25,30,8,3]. The translation kinetic energy of the solute is added to obtain the chemical potential, from which other important thermodynamic quantities can be computed from derivatives with respect to state variables, such as pressure and temperature [6,5]. Dependence on these variables of hydrophobic hydration and hydrophobic interactions has received particular interest in biochemistry, because of their relevance in the folding of proteins [6,3]. Due to the complexity of these systems, the mechanism of this process is still under discussion [27,7]. However, important insight has been provided into this field by the study of the excess chemical potential computed for simple modeled hydrophobic solutes [11,15,21]. Using information theory, Hummer et al. [15] studied small aggregates of methane in water over a wide range of pressure observing that these are destabilized by increasing pressure. From this observation, which is consistent with simulation and experimental results, they concluded that pressure denaturation of a protein involves incorporation of water into the protein.

This work studies the pressure dependence of the excess chemical potential associated with the insertion of hard-sphere solutes at infinite dilution in water along the isotherm of 298 K. A purely repulsive potential can be used to model interactions between a hydrophobic solute and water. However, it is also important for the computation of the so-called "cavitation contribution" to the free energy of solvation within polarizable continuum models [31,8] as the solute is enclosed in a molecular cavity defined by the union of spheres. When using these methods the focus is on the quantum treatment of the solute, and most of the computational time is spent for the electrostatic contribution [1], and, depending on the method used, for the dispersion contribution [2]. It is in this context that it is useful to develop simple heuristic expressions in order to compute thermodynamic quantities related to the solvation process of these simple modeled solutes [8,10].

At infinite dilution conditions, interactions between solute molecules can be neglected and only solute–solvent interactions give a contribution to the excess chemical potential. This can be computed using a coupling parameter method [13], which requires information on how the solvent distribution function changes from the initial state of pure solvent to the final state in which the solute–solvent interaction is completely coupled.

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This method implies the study of "intermediate states" which are generally unrealistic. When applied to a hard-sphere solute–solvent interaction, the solute insertion process is equivalent to scaling the radius of a cavity from zero up to a final contact radius, r, as shown in the original paper of Scaled Particle Theory (SPT) [25]. Thus, our interest in the formation of a cavity in a solvent is extended to such small cavities that they cannot host any real solute.

Within SPT [25,30,3], the excess chemical potential associated with cavity formation is related to the probability that no centers of the solvent molecules will be found in the spherical region defined by the contact radius. On the basis of statistical mechanics, this probability is expressed in terms of pure solvent quantities that can be computed from the number density and integrals involving many-particle correlation functions. These integrals define the second and higher moments of the pure solvent distribution functions and can be written in terms of probabilities that exactly n centers of the solvent molecules can be found in the cavity volume [25]. As specified in the literature [25,14], the excess chemical potential written in terms of moments is of general validity and can be applied to cavities of an arbitrary shape and using a realistic model potential for interactions between solvent molecules. However, as only the first two moments are easily available, its application is limited to very small cavities so that $n \leq 2$ or requires the computation of modeled probabilities. These can be computed within an information theory based on the first two moments, as demonstrated by Hummer et al. [14]. Here, we work within SPT and apply the general relation based on probabilities (Eq. 3.11 of Ref. [25]) only to such a small sized-cavity that the excess chemical potential is directly computed from the first two moments. SPT conditions are then applied at an appropriate radius close to the extreme of the range where the contribution of higher moments vanishes. These conditions involve derivatives of the excess chemical potential with respect to the cavity radius.

In order to facilitate these calculations and apply SPT along the isotherm we describe the two first moments of water for spherical volumes as a function of radius and pressure. Such descriptions make use of a simple relation between the first moment and the water number density [14], which was modeled along the isotherm. This was also used in a heuristic expression proposed here to compute the second moment from the first moment using a modified Poisson distribution (see Appendix A).

Scaling the radius from small to larger sized-cavities so that a real solute can be hosted in, the approximate SPT expression [22,23] or the more flexible expressions based on the thermodynamics of surfaces [28] are generally used [24,8,10]. The effect of pressure on parameters entering such expressions has been little explored until now. At fixed conditions of P and T, such parameters are preferably determined by fitting procedures. However, a complete study of the effect of pressure on the thermodynamics of cavity formation would require a great number of very expensive simulations.

Here, we test these simple models at a very high pressure by comparison with simulation results. We show that a less expensive parametrization based on exact relations [25] gives results which are in agreement with those obtained by fitting.

This was made possible by the use of a relatively simple scheme formulated within the framework of SPT, with a limited number of conditions on the central function G(r), which is defined by the contact value of the cavity-solvent radial distribution function (rdf). As noticed above, these conditions were applied within the limit of a very small cavity, but some information on a molecular-sized cavity was employed in the parametrization. Differently from the approximate SPT expression, this is in fact necessary when using more flexible simple models.

2. Calculation

2.1. Excess chemical potential and $G(r)$

According to statistical mechanics [25], the excess chemical potential of a hard-sphere solute, here denoted by μ^*, can be computed from the probability that an empty region can be found in the solvent and it is written in terms of moments of the solvent distribution. Within the limit of a very small cavity, this relation involves only the first two moments,

$$\mu^* = -k_B \mathrm{T} \ln\left[1 - <n> + \frac{1}{2} \quad <n(n-1)>\right] \tag{1}$$

where n is the instantaneous number of molecular centers in the pure solvent contained in a sphere of radius r, whose average $<n>$ can be obtained from the number density ρ [14]. The third term in brackets gives the average number of pairs in the same volume and can be obtained from integrals involving the pair distribution function [25,14]. The expression above is valid for cavity volumes for which the contribution of higher moments vanishes ($n \leq 2$).

For larger cavities, the excess chemical potential is computed with a simple model formulated within the thermodynamics of surfaces [28]. We adopt the most common division [30,4] related to a cavity of radius r, which here defines the accessible surface and the exclusion volume to oxygen nuclei positions of water molecules. Namely,

$$\mu^*(r) = 4\pi\tilde{\gamma} f_c(r) r^2 + \mathrm{P}\left(\frac{4\pi}{3} r^3\right) \tag{2}$$

where $\tilde{\gamma}$ has the dimension of a surface tension and $f_c(r)$ is a function describing curvature corrections, which equals 1 for a cavity in the limit of an infinite radius. The average density of solvent centers on the cavity surface is given by ρ G(r), and G(r) is related to μ^* by the important relation derived from SPT [25,24],

$$\mathrm{G(r)} = \frac{1}{4\pi r^2 \rho k_B \mathrm{T}} \frac{d\mu^*}{dr}. \tag{3}$$

As remarked by Reiss et al. [25], μ^* equals the reversible work which is expended in the formation of the cavity. Given that this process is equivalent to the coupling of a hard-sphere interaction potential with contact distance r, the value of the rdf for the solvent centers excluded from the spherical region coincides at r with G(r).

Thus, as pair correlation functions are commonly calculated in simulations, this relation is very useful to validate simple models used to describe the radial dependence of f_c in Eq. (2). The general form of this model leads to the following simple expression for the derivative of μ^* with respect to r,

$$\frac{d\mu^*}{dr} = 4\pi\tilde{\gamma}\left(2r - 2\tilde{\delta} + \frac{\alpha}{r^2}\right) + \mathrm{P}\left(4\pi r^2\right) \tag{4}$$

where $\tilde{\delta}$ and α are parameters entering the curvature correction $f_c(r)$ [24,10].

2.2. Solvent compressibility

The coefficient of isothermal compressibility can be derived from density in accordance with the thermodynamic definition:

$$k_T^* = -\frac{1}{V}\left(\frac{\partial V}{\partial \mathrm{P}}\right)_\mathrm{T} = \frac{1}{\rho}\left(\frac{\partial \rho}{\partial \mathrm{P}}\right)_\mathrm{T} \tag{5}$$

or from volume fluctuations in the NPT ensemble, namely,

$$k_T^* = -\frac{< V^2 >_N - < V >_N^2}{k_B \mathrm{T} < V >_N}. \tag{6}$$