Research paper

Energetics of the *contact minimum* configuration of two hard spheres in water

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ABSTRACT

Changes in thermodynamic functions for the formation of the *contact minimum*, *cm*, configuration of two hard spheres (i.e., two cavities) are calculated by means of a physically-based geometric approach over a large temperature range. The decrease in water accessible surface area due to *cm* formation causes a gain in translational entropy of water molecules, driving the process. This produces a negative Gibbs energy change, whose magnitude slightly increases with temperature. The process is exothermic due to the decrease in hydration shell size, but this enthalpy change is entirely compensated by a corresponding entropy contribution.

1. Introduction

The association of nonpolar molecules in water, called hydrophobic interaction, HI, is considered to be the main driving force of protein folding, micelle and double-layer membranes formation, and molecular recognition events [1,2]. The simplest HI, involving only two molecules, is called pairwise HI and has carefully been investigated by means of computer simulation techniques and theoretical approaches [1–14]. It emerged that the potential of mean force of pairwise HI [i.e., the trend of $\Delta G(HI)$ as a function of the distance between the two interacting molecules] shows a first deep minimum, corresponding to the *contact minimum*, *cm*, configuration, a maximum corresponding to the desolvation barrier, and a second shallow minimum, corresponding to the solvent-separated configuration. Nevertheless, the molecular-level origin of pairwise HI is still not entirely clarified.

In a recent review, Pratt and colleagues [15] wrote: 'The molecular theory of hydrophobic effects, and particularly of hydrophobic interactions, has been a distinct intellectual challenge for many decades. The intellectual challenge originates with the entropy-driven character of hydrophobic interactions. Explanation of those entropies requires molecular statistical mechanics.' Pratt and colleagues have shown [16], by means of MD simulations using the SPC/E water model [17] over a large temperature range, that the formation of the *cm* configuration of two hard spheres (i.e., two cavities) is thermodynamically favoured, but they have not clari-

fied which is the driving force of the process at a molecular level. They referred to a 'proper involvement of the actual equation of state of liquid water' in the calculations (but the SPC/E water model does not reproduce several basic properties of liquid water [10]), and claimed that the formation of the *cm* configuration is endothermic and so entropy-driven [16]. However, since there are no icebergs surrounding small nonpolar molecules in water [18,19], the entropy gain cannot be due to a reduction in the iceberg size upon formation of the *cm* configuration. Pratt and colleagues wrote nothing on this point. Moreover, they did not explain why the association of two hard spheres should be endothermic, considering that the only enthalpic contribution has to come from the reorganization of water-water H-bonds. Since Ashbaugh and Pratt obtained that the enthalpy change for the creation of a methane-sized cavity in water is a positive quantity [20] (i.e., the process is endothermic: the H-bonds among the water molecules in the hydration shell of the cavity are more broken than those in bulk water), and there is a reduction in hydration shell size upon the formation of the *cm* configuration of the two cavities, the latter process is expected to be exothermic. These unsettled points highlight why I think that a further investigation on this subject would be important.

I have developed a simple geometric approach to rationalize pairwise HI, grounded on the basic role played by the solvent-excluded volume effect in solvation phenomena [21–23]. The geometric approach is re-derived, extended and used to study the thermodynamics of *cm* formation of two cavities, whose radius corresponds to that of a methane molecule. In addition, the same

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approach reproduces the lengthscale dependence of *cm* energetics recently obtained by means of Monte Carlo simulations [24].

2. Geometric approach

There is no direct energetic attraction between two hard spheres and the formation of the *cm* configuration is ruled solely by the contribution provided by water molecules. Adopting the formalism originally proposed by Ben-Naim [1], the corresponding Gibbs energy change is given by:

$$\Delta G(HI) = \delta G(HI) \qquad (1)$$

where $\delta G(HI)$ represents the indirect part of the reversible work necessary to produce the *cm* configuration. Since there are no direct energetic attractions among hard spheres and water molecules, $\delta G(HI)$ is simply given by the term that takes into account the change in the reversible work of cavity creation (i.e., a hard sphere can be treated as a cavity at a fixed position):

$$\delta G(HI) = \delta G_c = \Delta G_c(\text{two spheres}) - 2 \cdot \Delta G_c(\text{single sphere}) \qquad (2)$$

where $\Delta G_c(\text{single sphere})$ is the Gibbs energy cost to create a spherical cavity of σ_c diameter, and $\Delta G_c(\text{two spheres})$ is the Gibbs energy cost to create a couple of spherical cavities, each of σ_c diameter, at contact distance [i.e., a dumbbell in which the distance between the two cavity centres has to be equal to the diameter of the single spherical cavity, d(centre-to-centre) = σ_c]. To the best of my knowledge, there are no analytical relationships to calculate the Gibbs energy change for the creation of a dumbbell cavity in a liquid [25]. Therefore a different procedure has been devised.

When a cavity is created at constant temperature and pressure, the volume of the liquid increases by the partial molar volume of the cavity. However, the existence of the cavity imposes a strict geometric constraint on solvent molecules [23,26]: their centres can arrive at most to touch the so-called solvent-accessible surface area of the cavity (the water accessible surface area [27], WASA, of the cavity, if the solvent is water). This is the solvent-excluded volume effect associated with cavity creation and is the molecular origin of the ΔG_c quantity: a loss in translational entropy of solvent molecules due to the decrease in the configurational space accessible to solvent molecules [21–23,26]. Therefore, the ΔG_c quantity is purely entropic in all liquids [28], and has to be proportional to cavity WASA [26]. This has been verified on keeping fixed the cavity van der Waals volume and modifying the cavity shape by means of both classic SPT calculations [26,29], and computer simulations using detailed water models [30,31].

Pairwise HI can be treated on the same theoretical grounds by recognizing that, in the *cm* configuration of two spherical cavities, a significant decrease in the overall WASA happens (i.e., a decrease in the solvent-excluded volume with respect to the situation in which the two spherical cavities are far apart). The WASA fraction of a single spherical cavity that becomes buried in the *cm* configuration, f_{WASA}, is exactly given by [21]:

$$f_{WASA} = 2\pi \cdot (1 - \cos\alpha)/4\pi \qquad (3)$$

where $\cos\alpha = d(\text{centre-to-centre})/(\sigma_c + \sigma_w)$, σ_w is the diameter of water molecules, fixed to 2.8 Å and considered to be temperature-independent [23], and d(centre-to-centre) = σ_c at *cm*. The WASA decrease leads to a gain in translational entropy for water molecules that, in turn, produces a negative δG_c quantity. The latter can be calculated by means of the following analytical relationship [21,22]:

$$\delta G_c = -2 \cdot f_{WASA} \cdot \Delta G_c(\text{single sphere}) \qquad (4)$$

The reliability of this geometric relationship is supported by the fact that: (a) its use has allowed the calculation of $\Delta G(HI)$ numbers close to those obtained by means of computer simulation approaches for several nonpolar solutes [21,23]; (b) it leads readily to the so-called zero-separation theorem [22,32], in the case of complete interpenetration of the two spherical cavities [i.e., d (centre-to-centre) = 0]; (c) a robust linear relationship has been obtained between the $\Delta G(HI)$ values for the *cm* configuration of 13 alkane pairs and the WASA buried upon association [13].

On the other hand, the *cm* configuration of two hard spheres can be modelled by means of a prolate spherocylindrical cavity, whose van der Waals volume is two times that of a single sphere, $V_{vdw} = 2 \cdot V_{vdW}(\text{single sphere})$. This requirement corresponds to physical reality. This geometric approximation can be fully understood on looking at Fig. 1, that shows a side view of the *cm* configuration of two spheres and a corresponding prolate spherocylinder. On this basis, the δG_c quantity can be calculated by performing the difference between the Gibbs energy cost to create such a prolate spherocylindrical cavity and two times the Gibbs energy cost to create a single spherical cavity in water:

$$\delta G_c = \Delta G_c(\text{spherocylinder}) - 2 \cdot \Delta G_c(\text{single sphere}) \qquad (5)$$

Extending this line of reasoning, the enthalpy change associated with the formation of *cm* configuration can be calculated by means of the two relationships:

$$\delta H_c = -2 \cdot f_{WASA} \cdot \Delta H_c(\text{single sphere}) \qquad (6)$$

$$\delta H_c = \Delta H_c(\text{spherocylinder}) - 2 \cdot \Delta H_c(\text{single sphere}) \qquad (7)$$

where $\Delta H_c(\text{single sphere})$ and $\Delta H_c(\text{spherocylinder})$ are the enthalpy change associated with the creation of a single spherical cavity and a prolate spherocylindrical cavity in water, whose van der Waals volume $V_{vdW} = 2 \cdot V_{vdW}(\text{single sphere})$, respectively. Agreement between the results produced by Eqs. (4) and (5) for the δG_c quantity, and by Eqs. (6) and (7) for the δH_c quantity should be considered an indication of reliability and consistency of the geometric approach.

It has been shown that the classic scaled particle theory, SPT, formulas can be obtained by the application of both the fundamental measure theory of Rosenfeld [33], and the morphometric approach grounded on the Hadwiger theorem [34]. This confirms the general validity of SPT and its deep geometric ground. In addition, it should be recognized that, even though the second virial coefficient of dumbbells is different from that of prolate spherocylinders [35], the present situation is completely different. I am describing the formation of the *cm* configuration of two hard
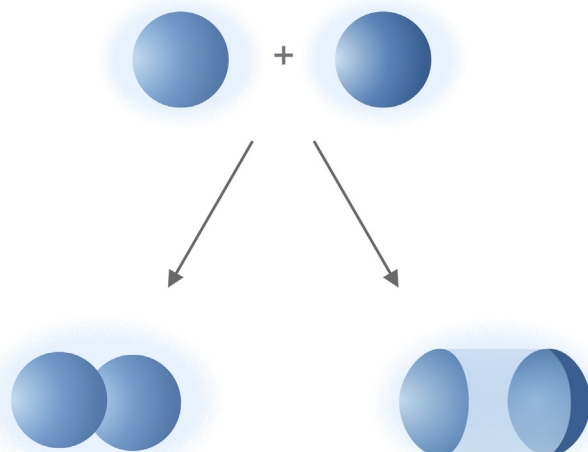

Fig. 1. A comparison between the dumbbell exactly representing the *contact minimum* configuration of two hard sphere, and the prolate spherocylinder approximating it.