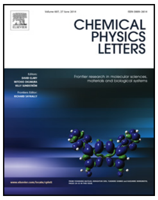
Chemical Physics Letters 616–617 (2014) 44–48

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett



Pairwise association of neopentane as a function of hydrostatic pressure

Giuseppe Graziano

Dipartimento di Scienze e Tecnologie, Università del Sannio, Via Port'Arsa 11, 82100 Benevento, Italy

ARTICLE INFO

Article history:
Received 10 September 2014
In final form 1 October 2014
Available online 16 October 2014

ABSTRACT

It is shown that the contact-minimum configuration of two neopentane molecules is favoured on increasing hydrostatic pressure over the range 1–4000 atm, at room temperature, in line with the methane results (Graziano, 2014). This is due to the decrease in water accessible surface area accompanying the association, that leads to a gain in configurational/translational entropy of water molecules, whose magnitude increases with hydrostatic pressure. Of course, the strengthening of pairwise hydrophobic interaction cannot shed light on the pressure-induced denaturation of globular proteins.

1. Introduction

There is increasing interest to investigate and understand the effect of hydrostatic pressure on the conformational stability of globular proteins [1,2]. Since hydrophobic interaction, HI, is considered to be the main stabilizing contribution of the folded state [3], several computational investigations have been devoted to shed light on the effect of hydrostatic pressure on the pairwise HI of methane [4–6]. It was shown that, on increasing pressure, the potential of mean force of methane does not change qualitatively, but the solvent-separated configuration of two methane molecules should become favoured with respect to the contact-minimum, *cm*, configuration. By assuming that the solvent-separated configuration corresponds to an unfolded conformation and the *cm* configuration corresponds to the folded state of globular proteins, this computational finding was used to suggest that the pressure-induced denaturation should be due to a penetration of water molecules in the hydrophobic interior of the folded state [5–7].

Actually, these computer simulation results have recently been questioned (and so also the water penetration model for the pressure-induced denaturation). I have performed a theoretical analysis of the effect of hydrostatic pressure on the pairwise HI of methane [8], from which it emerged that the *cm* configuration is favoured on increasing pressure (i.e., there is a strengthening of pairwise HI, not a weakening). This result has nicely been confirmed by the detailed Monte Carlo simulations of Dias and Chan [9]. Therefore, it would be interesting to perform a similar analysis of the effect of hydrostatic pressure on the pairwise HI of a larger nonpolar solute like neopentane. The Gibbs energy difference between the *cm* configuration of two neopentane molecules and the dissociated configuration becomes more negative on increasing hydrostatic pressure, in line with the methane results. The strengthening of pairwise HI is because the corresponding decrease in water accessible surface area [10], WASA, reducing the solvent-excluded volume effect, leads to a gain in the configurational/translational entropy of water molecules, whose magnitude increases with the rise of the volume packing density of water caused by hydrostatic pressure [8].

The *cm* configuration of two nonpolar molecules cannot be considered akin to the folded state of a globular protein and pairwise HI is not a good model for intra-molecular HI [8,9]. The latter is dominated by the polymeric nature of proteins that leads to the formation of permanent voids on chain folding [2]. The presence of voids in the folded state is the unavoidable consequence of the impossibility to perfectly fill the space with a rigid covalently-linked chain that has a lot of different side chains. This reasoning implies that the results obtained for pairwise HI cannot be used to rationalize the pressure-induced denaturation of globular proteins.

2. Theory

2.1. Hydrophobic hydration

The process of inserting a solute molecule at a fixed position in water is dissected into two sub-processes: (a) creation of a cavity suitable to host the solute molecule; (b) insertion of the solute molecule into the cavity and turning on the solute–solvent attractive potential [11,12]. When the latter is weak in comparison to the solvent–solvent attractive potential, the fluctuations in the average

---

E-mail address: graziano@unisannio.it

http://dx.doi.org/10.1016/j.cplett.2014.10.018
0009-2614/

value of the solute–solvent attractive potential energy are small [11–13], and the Ben-Naim standard [14] hydration Gibbs energy change, $\Delta G^{\bullet}$, is given by:

$$\Delta G^{\bullet} = \Delta G_c + E_a \tag{1}$$

where ΔG_c is the reversible work of cavity creation, and E_a is the solute–solvent attractive potential energy. The two terms, ΔG_c and E_a, represent, respectively, the direct entropic and energetic perturbations of water caused by solute insertion [11–13]. In response to such direct perturbation, water molecules reorganize leading to a rearrangement of H-bonds. The latter reorganization is characterized by an almost complete enthalpy-entropy compensation when the solute–solvent attractive interactions are weak in comparison to solvent–solvent interactions [15]. The latter condition is satisfied by nonpolar solutes in water over a large range of temperatures and pressures, on the basis of available structural data [6,16]. Thus, the $\Delta G^{\bullet}$ magnitude is solely determined by the direct perturbation of the solvent.

The classic SPT formula [17], that has also been derived by means of geometric arguments [18], is used to calculate reliable estimates of ΔG_c to create a spherical cavity in water:

$$\Delta G_c = RT \cdot \left\{ -\ln(1-\xi) + \left[\frac{3\xi}{1-\xi}\right] \cdot x + \left[\frac{3\xi}{1-\xi}\right] \cdot x^2 + \left[\frac{9\xi^2}{2(1-\xi)^2}\right] \cdot x^2 \right\} + P \cdot V_2 \tag{2}$$

where R is the gas constant, ξ is the volume packing density of the solvent, which is defined as the ratio of the physical volume of a mole of solvent molecules over the molar volume of the solvent, v_1 (i.e., $\xi = \pi\sigma_1^3 \cdot N_{Av}/6v_1$); P is the hydrostatic pressure over the liquid; V_2 is the van der Waals volume of the solute, in line with SPT derivation [17]; $x = \sigma_2/\sigma_1$, and σ_1 is the hard sphere diameter of the solvent molecules; σ_2 is the hard sphere diameter of the solute molecule and corresponds to the cavity diameter, defined as the diameter of the spherical region from which any part of the solvent molecules is excluded.

It is worth noting that: (a) the $P \cdot V_2$ term in Eq. (2) originates from the expansion of the system volume due to cavity creation, operating at constant pressure; (b) the $P \cdot V_2$ magnitude is negligible for molecular-sized cavities when $P = 1$ atm, but is significant when P is very high [8]. Differentiating ΔG_c with respect to pressure, one obtains the following expression for the partial molar volume of the cavity [19]:

$$\begin{aligned} \mathrm{PMV}_c = {} & (N_{Av} \cdot \pi \cdot \sigma_2^3/6) + [RT \cdot \xi \cdot \beta_T/(1-\xi)^3] \cdot [(1-\xi)^2 \\ & + 3(1-\xi) \cdot x + 3(1+2\xi) \cdot x^2] \end{aligned} \tag{3}$$

where β_T is the isothermal compressibility of the solvent at the different pressures; note that, by adopting the Ben-Naim standard [14], the contribution $\beta_T \cdot RT$ to PMV, is excluded from the outset. The first term in Eq. (3) corresponds to the van der Waals volume of the solute molecule to be hosted in the cavity; the second term is the contribution coming from the non-perfect packing of solvent molecules around the cavity due to basic geometric constraints.

The experimental density of water at 25 °C, over the 1–4000 atm pressure range, listed in the second column of Table 1, has been used to perform calculations [20,21]. The following effective hard sphere diameters have been selected and considered to be pressure independent: (a) $\sigma(H_2O) = 2.8$ Å [22], which is close to the first peak location in the O—O radial distribution function of water, a location that shows little dependence on pressure at room temperature [6,16]; (b) $\sigma(\text{neop}) = 5.8$ Å [23], and $V_{vdW}(\text{neop}) = N_{Av} \cdot \pi \cdot \sigma(\text{neop})^3/6 = 61.5$ cm^3 mol^{-1}, is also a pressure independent quantity.

The E_a value at 25 °C and 1 atm, −38.5 kJ mol^{-1}, has been fixed by using the experimental $\Delta G^{\bullet}$ number [11], and the classic SPT-ΔG_c estimate. This value is in the middle of estimates obtained by means of computer simulations in the TIP4P water model [24], −36.0 kJ mol^{-1}, and in the SPC water model [25], −39.9 kJ mol^{-1}. Moreover, since the E_a magnitude is proportional to ξ [13,19], and the latter increases with hydrostatic pressure (see the last column of Table 1), it should be reliable to assume that:

$$E_a(P) = E_a(1\,\text{atm}) \cdot \left[\frac{\xi(P)}{\xi(1\,\text{atm})}\right] \tag{4}$$

where $\xi(P)$ indicates the volume packing density of water at a given hydrostatic pressure.

2.2. Pairwise hydrophobic interaction

Bringing two nonpolar molecules, such as two neopentane molecules, from a fixed position at infinite separation to a fixed position at contact distance in water, keeping constant temperature and pressure, is called pairwise HI [26]. The associated Gibbs energy change is given by:

$$\Delta G(\text{HI}) = E(\text{contact}) + \delta G(\text{HI}) \tag{5}$$

where E(contact) is the neopentane–neopentane van der Waals interaction energy in the contact-minimum, *cm*, configuration, and should not depend on the presence of the solvent and its nature, and on hydrostatic pressure if the *cm* distance does not change; δG(HI) is the indirect part of the reversible work to do the process, and accounts for the specific features of the solvent in which pairwise HI occurs. A general relationship exists between δG(HI) and the Ben-Naim standard hydration Gibbs energy of the neopentane–neopentane *cm* configuration and of the neopentane molecule, respectively [26,27]:

$$\delta G(\text{HI}) = \Delta G^{\bullet}(\text{neop}\ldots\text{neop}) - 2 \cdot \Delta G^{\bullet}(\text{neop}) \tag{6}$$

Use of Eq. (1) in the definition of δG(HI) leads to:

$$\begin{aligned} \delta G(\text{HI}) = {} & [\Delta G_c[\text{neop}\ldots\text{neop}] - 2 \cdot \Delta G_c(\text{neop})] \\ & + [E_a(\text{neop}\ldots\text{neop}) - 2 \cdot E_a(\text{neop})] = \delta G_c(\text{HI}) + \delta E_a(\text{HI}) \end{aligned} \tag{7}$$

The δG(HI) value can be obtained by calculating: (a) ΔG_c to create in water a cavity suitable to host a couple of neopentane molecules in the *cm* configuration, and a cavity suitable to host a single neopentane molecule; (b) E_a to turn on the attractive interactions between a couple of neopentane molecules in the *cm* configuration or a single neopentane molecule and all the surrounding water molecules.

A decrease in solvent-excluded volume occurs upon association [27], and it can be accounted for by the WASA decrease upon association. The results of MD simulations have shown the occurrence of a robust linear relationship between the Gibbs energy of the *cm* configuration for 13 types of different alkane pairs and the average amount of WASA buried upon association [28]. In addition, it has been shown, by means of both classic SPT calculations [29], and computer simulations in detailed water models [30,31], that: (a) by

Table 1
Experimental values, at 25 °C, of the density, molar volume, isobaric thermal expansion coefficient and isothermal compressibility of water over the 1–4000 atm pressure range, extracted from the compilations of Kell [20], and of Wagner and Pruss [21]. The values of the volume packing density, calculated using $\sigma(H_2O) = 2.8$ Å, independent of pressure, are listed in the last column.

P (atm)	d (g cm^{-3})	v (cm^3 mol^{-1})	$\alpha_P \times 10^4$ (K^{-1})	$\beta_T \times 10^6$ (atm^{-1})	ξ
1	0.997	18.07	2.6	45.8	0.383
1000	1.038	17.36	3.6	36.5	0.399
2000	1.075	16.76	4.1	30.6	0.413
3000	1.102	16.35	4.3	24.7	0.423
4000	1.131	15.93	4.4	21.9	0.435