ELSEVIER

Biophysical Chemistry 101–102 (2002) 173–185

Biophysical Chemistry

www.elsevier.com/locate/bpc

Hydration entropy change from the hard sphere model

Giuseppe Graziano[a], Byungkook Lee[b,*]

[a]*Faculty of Science, University of Sannio, Via Port'Arsa, 11-82100 Benevento, Italy*
[b]*Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bldg. 37, Room 5120, 37 Convent Drive, MSC 4262, Bethesda, MD 20892-4262, USA*

Received 23 January 2002; received in revised form 30 April 2002; accepted 30 April 2002

Abstract

The gas to liquid transfer entropy change for a pure non-polar liquid can be calculated quite accurately using a hard sphere model that obeys the Carnahan–Starling equation of state. The same procedure fails to produce a reasonable value for hydrogen bonding liquids such as water, methanol and ethanol. However, the size of the molecules increases when the hydrogen bonds are turned off to produce the hard sphere system and the volume packing density rises. We show here that the hard sphere system that has this increased packing density reproduces the experimental transfer entropy values rather well. The gas to water transfer entropy values for small non-polar hydrocarbons is also not reproduced by a hard sphere model, whether one uses the normal (2.8 Å diameter) or the increased (3.2 Å) size for water. At least part of the reason that the hard sphere model with 2.8 Å size water produces too small entropy change is that the size of water is too small for a system without hydrogen bonds. The reason that the 3.2 Å model also produces too small entropy values is that this is an overly crowded system and that the free volume introduced in the system by the addition of a solute molecule produces too much of a relief to this crowding. A hard sphere model, in which the free volume increase is limited by requiring that the average surface-to-surface distance between the solute and water molecules is the same as that between the increased-size water molecules, does approximately reproduce the experimental hydration entropy values.
© 2002 Elsevier Science B.V. All rights reserved.

Keywords: Entropy; Hydration; Hard sphere mixture; Hydrophobicity

1. Introduction

When a non-polar molecule is transferred from a fixed position in the gas phase to a fixed position in water, there is a large reduction in entropy. This decrease in entropy is the reason for hydrophobicity, i.e. the low solubility of non-polar molecules in water compared to other solvents, at least at room temperature. But there is still much debate in the literature on the origin of hydrophobicity and of this entropy change [1–5].

If one is interested in understanding which properties of water molecule and of the water

*Corresponding author. Tel.: +1-301-496-6580; fax: +1-301-402-1344.
E-mail address: bk@nih.gov (B. Lee), graziano@unisannio.it (G. Graziano).

0301-4622/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0301-4622(02)00199-0

liquid are responsible for the phenomenon of hydrophobicity, it is clear that an appropriate model system, whether real or theoretically constructed, would be useful. The hard sphere fluid is a useful system for this purpose because it is the simplest system other than the ideal gas. From the known accurate equation of state, most thermodynamic quantities can be calculated for this system. The similarities and differences between this system and the aqueous system tend to give insight as to which properties are common to all liquids and which are special to the aqueous system, which has extensive hydrogen bonds. It is well known that some properties, for example the free energy of cavity formation, can be calculated with surprising accuracy from an appropriately chosen hard sphere system [6,7], although some suggest that this agreement may be more fortuitous than fundamental [3,4]. Sharp et al. [8] used the hard sphere system to study the volume-dependent term in the entropy expression. The hard sphere system has served as the reference liquid in perturbation-type theories [9] and it and its close cousin, the Lennard–Jones liquid, have been used as a reference liquid for comparison with more realistic water models in simulation studies [10–13]. More recently, combination of simulation and information theory approach showed that density fluctuations within spherical volumes in liquids were Gaussian in water [2,14], but deviate from Gaussian in some systems with spherically symmetric molecules without hydrogen bonds [15–17]. Such observations illustrate the value of simpler model systems in illuminating special characters of water.

A hard sphere system is defined by: the size of the one or more hard sphere species in the system; the number density of these species; and the temperature. The pressure and other thermodynamic quantities are determined once these three (sets of) parameters are given. Therefore, one has to choose appropriate values of these parameters when one constructs a hard sphere system to be used as the reference system for a real system. The temperature is invariably set equal to that of the real system to which the hard sphere system will be compared. The number density is also usually chosen to be the same between the real and the hard sphere systems. But we suggest in this article that this may not always be the best choice and that a case can be made for deliberately choosing a system with different number densities.

The choice of the proper hard sphere size is a difficult issue. For example, it has been pointed out that water molecules have two sizes, one for the hydrogen bonded case and the other when they make only a van der Waals contact [13]. There probably is no completely satisfactory way of choosing the hard sphere size since no real molecule is a hard sphere. Because many properties of a hard sphere system depend sensitively on the hard sphere size, the uncertainty associated with the proper choice of the hard sphere sizes reduces the value of the hard sphere system as the reference system [18]. Nevertheless, a hard sphere system will continue to be a valuable system for the study of hydrophobicity because there will always be a need for a simple reference system to which the aqueous system may be compared.

In this paper, we explore the entropy change upon inserting a hard sphere solute molecule into a hard sphere system and relate it to the corresponding entropy change for the real system. Since the entropy change depends on the hard sphere size, we consider two systems, one with the small, and the other with the larger, size for the solvent molecules. We find that, in the case of the neat system wherein the solute is the same species as the solvent, the hard sphere system that uses the larger solvent size nearly reproduces the entropy change of the real system. For the cases when the solute is not the same as the solvent species, change of the solvent size alone does not make the hard sphere system to produce entropy values that are comparable to that of the real system. In such cases, however, a reference system may have to be considered in which the number density is different from that of the real system. We find that a hard sphere system that uses the larger solvent size and the altered number density produces solvation entropy changes that are remarkably similar to the corresponding hydration entropy changes of the real system. The physical meaning and possible implications of these observations on the phenomenon of hydrophobicity are discussed.

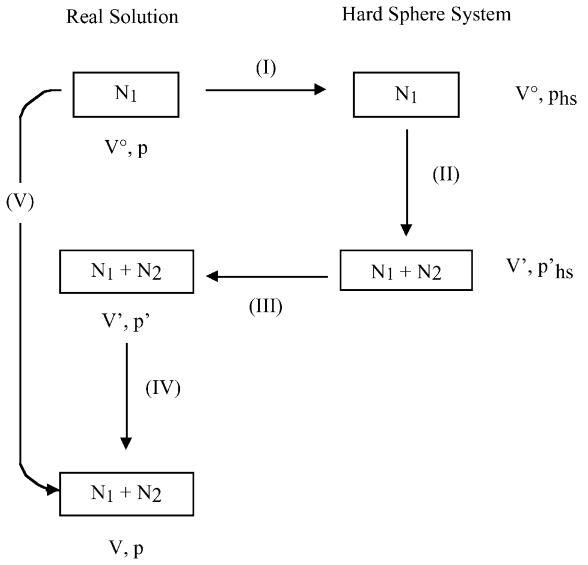

Fig. 1. Decomposition of the constant pressure solvation process. The process considered is the insertion of N_2 molecules of a solute species into a pure liquid containing N_1 solvent molecules under constant temperature and pressure (step V). This solute insertion process is considered in four steps as follows: Initially the pure liquid has volume V^o under pressure p. In step I, the attractive interaction between solvent molecules is turned off under constant volume to obtain a hard sphere fluid of the same volume. The pressure rises to p_{hs}. In step II, N_2 hard spheres are inserted, which will turn into the real solute molecules when the attractive interaction is turned on later. This insertion process is carried out in such a manner that the volume of the system changes to V' and the pressure to p'_{hs}. The attractive interaction is then turned back on in step III, again under the constant volume condition, to obtain a real solution with volume V' and a different pressure p'. Finally, if the pressure p' is not the same as the pressure of the original system, the volume of the solution is allowed to change in step IV until the pressure reaches the starting pressure.

2. Theory

2.1. Absolute entropy change upon insertion of a solute molecule in a liquid

The main process of interest in this paper is that of adding a small amount of a solute species into a pure liquid under constant temperature and pressure (step V in Fig. 1). We imagine carrying out this process in four consecutive steps as follows. In step I, the soft attractive interaction between molecules is turned off under the constant volume condition. We shall refer to the molecules obtained after this step 'hard spheres' since they interact with other molecules through the hard part of the potential. However, they still have the internal and rotational degrees of freedom. We assume that these degrees of freedom are completely separable from the translational degrees of freedom and that the molecules behave like hard spheres when they interact with other molecules. The pressure of the system rises to p_{hs} upon this step. In step II, 'hard spheres' corresponding to the solute molecules are added. The volume of the system is allowed to change during this process by an amount to be designated as $\bar{v}_{hs}$ per molecule. $\bar{v}_{hs}$ is normally set equal to $\bar{v}_2$, the partial molecular volume of the solute species in the final (non-hard sphere) solution, but we consider a more general model in this work in which $\bar{v}_{hs}$ is allowed to be different from $\bar{v}_2$. The pressure of the system generally changes upon this insertion. Step III is the reverse of step I in which the soft attractive interaction between molecules is turned back on under the constant volume condition. Finally, when $\bar{v}_{hs}$ is not equal to $\bar{v}_2$, an additional step, step IV, is needed in order to bring the volume of the system to that of the final solution after step V. Step IV is carried out for the real (non-hard sphere) solution. The pressure of the system returns to the original pressure in this step.

The partial molecular entropy of the solute, s_2, is given by:

$$s_2 = s_V = \frac{\partial(\Delta S_I + \Delta S_{II} + \Delta S_{III} + \Delta S_{IV})}{\partial N_2} = s_{II} + s_{III} + s_{IV} \quad (1)$$

in which ΔS_I through ΔS_{IV} are the entropy changes in steps I through IV, respectively, N_2 is the number of solute molecules added, and s_I through s_V are the entropy changes per solute molecule in steps I–V, respectively. s_I is missing in the expression since ΔS_I does not depend on N_2. s_{II} and s_{IV} are the entropy changes per solute molecule that occur entirely within the hard sphere and the real systems, respectively, whereas s_{III} is the entropy change per solute molecule upon conversion of the hard sphere system to the real system. s_{III}

represents the entropy difference between the hard sphere model and the real system.

The entropy change for step IV is given by:

$$s_{IV}=\left(\frac{\partial S}{\partial V}\right)_T\left(\frac{\partial V}{\partial N_2}\right)_{IV}=\frac{\alpha}{\beta}(\bar{v}_2-\bar{v}_{hs}) \quad (2)$$

where α and β are the thermal expansion coefficient and the compressibility, respectively, of the solution. We have assumed that the volume change during step IV is sufficiently small that α/β remains constant and recognized that when the solution is dilute, the volume change upon step V is equal to $N_2\bar{v}_2$. Obviously, when $\bar{v}_{hs}$ is chosen to equal $\bar{v}_2$, step IV is not needed and the entropy change associated with this step is zero.

The entropy change upon step II has been computed by many, including Sharp et al. [8] who used the Percus–Yevick equation of state for the hard sphere mixtures. We follow a similar procedure but use the Carnahan–Starling equation of state [19], which is considered to be more accurate, and specialize to the infinitely dilute solution. The procedure is to obtain the expression for the total entropy of the hard sphere mixture and then obtain the entropy change upon solute addition by differentiating the total entropy with respect to the number of solute molecules.

The entropy of a 'hard sphere' mixture is given by:

$$S=S^{ir}+S^{id}+S^{e} \quad (3)$$

where S^{ir} is the entropy due to the internal and rotational degrees of freedom; S^{id} is the entropy of the ideal gas mixture of the same composition, volume and temperature; and S^{e} is the excess entropy. We assume that the internal and rotational degrees of freedom of each molecule are independent, in which case S^{ir} is given by:

$$S^{ir}=\Sigma\ N_i\ s_i^{ir} \quad (4)$$

where N_i is the number molecules of species i and s_i^{ir} is the entropy of a 'hard sphere' of species i from the internal and rotational degrees of freedom. S^{id} is given by:

$$S^{id}=-k\sum N_i\left[\ln(\rho_i\Lambda_i^3)-\frac{5}{2}\right] \quad (5)$$

where k is the Boltzmann's constant, ρ_i is the number density of species i, and $\Lambda_i=h/\sqrt{2\pi m_i kT}$ is the momentum partition function of species i, where h is the Planck constant, m_i is the molecular mass of species i, and T is the absolute temperature. For a system that obeys the Carnahan–Starling equation of state, S^{e} is given by [19]:

$$S^{e}=-Nk\left[-\frac{3}{2}(1-y_1+y_2+y_3)+\frac{3y_2+2y_3}{(1-\xi)}+\left(\frac{3}{2}\right)\frac{1-y_1-y_2-y_3/3}{(1-\xi)^2}+(y_3-1)\ln(1-\xi)\right] \quad (6)$$

In this equation, N is the total number of molecules in the system and ξ is the volume packing density defined as $\sum N_i v_i/V$, where $v_i=\pi d_i^3/6$ is the physical volume of a molecule of species i, d_i being the diameter of the molecule, and V is the volume of the system. For a binary system, y_1, y_2 and y_3 are defined as follows:

$$y_1=\Delta_{12}\frac{(d_1+d_2)}{\sqrt{d_1d_2}},$$

$$y_2=\Delta_{12}\sum_i^2\left(\frac{\xi_i}{\xi}\right)\frac{\sqrt{d_1d_2}}{d_i},$$

$$y_3=\left[\sum_i^2\left(\frac{\xi_i}{\xi}\right)^{2/3}x_i^{1/3}\right]^3,$$

and

$$\Delta_{12}=\frac{\sqrt{\xi_1\xi_2}}{\xi}\frac{(d_1-d_2)^2}{d_1d_2}\sqrt{x_1x_2},$$

where $\xi_i=N_iv_i/V$ and $x_i=N_i/N$. For a sufficiently dilute binary system, Eq. (6) can be written as:

$$S^{e}=k(NA+N_2B) \quad (7)$$

with

$$A=-\frac{\xi(4-3\xi)}{(1-\xi)^2} \quad (7a)$$

and

$$B=(r-1)^2\left[\ln(1-\xi)-A+\left\{2\ln(1-\xi)-\frac{5-3\xi}{4-3\xi}A\right\}r\right] \quad (7b)$$

where $r=d_2/d_1$.

The entropy change upon step II solute insertion per molecule is given by:

$$s_{II}=\partial S/\partial N_2=s_2^{ir}+s_2^{id}+s_2^{e} \quad (8)$$

in which

$$s_2^{id}=-k\left[\ln(\rho_2\Lambda_2^3)-\frac{3}{2}-\frac{\bar{v}_{hs}}{\bar{v}_1}\right], \quad (8a)$$

where $\bar{v}_1$ is the partial molar volume of the solvent species and

$$s_2^{e}=k(A+B+C) \quad (8b)$$

with

$$C=N\frac{\partial A}{\partial N_2}=N\frac{\partial A}{\partial \xi}\frac{\partial \xi}{\partial N_2}=\frac{2\xi(2-\xi)}{(1-\xi)^3}\left(\frac{\bar{v}_{hs}}{\bar{v}_1}-r^3\right). \quad (8c)$$

We have assumed that the solution is so dilute that the partial molar volume and the packing density of the solution is the same as those of the pure solvent and that the $N_2\partial B/\partial N_2$ term can be ignored.

2.2. Connection to the experimentally measurable transfer entropy changes

The entropy change, s_2, computed above is the total entropy change that includes the contribution from the translational degrees of freedom of the solute molecule. The entropy change upon insertion of a solute molecule at a fixed position in the liquid is given by the Ben-Naim standard entropy, s_2^*, which is related to the total change by [20,21]

$$s_2=s_2^*-k\ln(\rho_2\Lambda_2^3)+k(\alpha T+3/2). \quad (9)$$

Combining Eqs. (1) and (8) and Eq. (9), we obtain

$$s_2^*=s_2^{ir}+k\left(\frac{\bar{v}_{hs}}{\bar{v}_1}-\alpha T\right)+s_2^{e}+s_{III}+s_{IV}. \quad (10)$$

Since the only degrees of freedom that contribute to the entropy of a molecule fixed at a position in the ideal gas phase is internal and rotational degrees of freedom,

$$s_2^*(\text{gas})=s_2^{ir}(\text{gas}). \quad (11)$$

If we now assume that the entropy from the internal and rotational degrees of freedom in the 'hard sphere' phase is the same as that in the ideal gas phase, i.e.

$$s_2^{ir}(\text{h.s. liquid})=s_2^{ir}(\text{gas}), \quad (12)$$

the Ben-Naim standard entropy change upon gas to liquid transfer process is given by:

$$\Delta s_2^*=s_2^*(\text{liq})-s_2^*(\text{gas})=k\left(\frac{\bar{v}_{hs}}{\bar{v}_1}-\alpha T\right)+s_2^{e}+s_{III}+s_{IV}. \quad (13)$$

This expression can be used to compute s_{III} for a given hard sphere model using the experimental solvation entropy values and the properties of the solvent. Equivalently, we will define calculated entropy change for the hard sphere model, $\Delta s_2^*(\text{hs})$, as

$$\Delta s_2^*(\text{hs})=k\left(\frac{\bar{v}_{hs}}{\bar{v}_1}-\alpha T\right)+s_2^{e}+s_{IV} \quad (14)$$

and compare it to the experimentally measured Δs_2^*. The difference between these two quantities is s_{III}.

3. Methods and results

3.1. Entropy of pure liquids

We first consider the case wherein a molecule is transferred from the gas phase to its own neat liquid phase. The liquids and their physical properties used are listed in Table 1. The hard sphere sizes chosen are the conventional ones that have been used in the literature. The experimental and the hard sphere model (hs1) Δs_2^* values are given in Table 2. The experimental values are those reported by Ben-Naim and Marcus [22]. These

Table 1
Some physical properties of the selected liquids at 25 °C

	d (Å)	$\bar{v}_1$ (cm^3 mol^{-1})	$\alpha\times10^3$ (K^{-1})	ξ
n-C_5H_{12}	5.78	116.12	1.591	0.524
$C(CH_3)_4$	5.80	123.31	1.200	0.499
n-C_6H_{14}	6.02	131.62	1.407	0.523
c-C_6H_{12}	5.63	108.75	1.214	0.517
Benzene	5.26	89.41	1.240	0.513
Toluene	5.64	106.86	1.086	0.530
CCl_4	5.37	97.09	1.226	0.503
H_2O	2.75	18.07	0.257	0.363
CH_3OH	3.69	40.73	1.189	0.389
C_2H_5OH	4.34	58.68	1.089	0.439

d: Hard sphere diameters from [48] for n-pentane and n-hexane, from [7] for neopentane, from [6] for water, and from [49] for all other liquids. $\bar{v}_1$: Molar volumes from the same references as for the hard sphere diameters. α: Thermal expansion coefficients from [50] for n-pentane, n-hexane, methanol and ethanol, and from [51,52] for all others. ξ: Volume packing density.

were obtained as the temperature derivative of the corresponding Gibbs energy difference, ΔG^*, along the liquid–vapor equilibrium line rather than along the constant pressure condition, but the difference should be negligible [23]. The model Δs_2^* values are those obtained using Eq. (14) with the $\bar{v}_{hs}$ set to equal $\bar{v}_2$, which in this case is equal to $\bar{v}_1$, the molar volume of the liquid.

Table 2 shows that both the experimental and the model entropy values are negative for all liquids. This is an expected result since the solute and solvent are the same species in this case and the reported entropy values represent the entropy per molecule of the pure liquid. Liquids have a structure and, as was pointed out earlier [21], the entropy values given represent the increase in the amount of structure due to the increase in the size of the system by one molecule. Table 2 also shows that the experimental and the model entropy values agree well for all non-polar liquids. In contrast, the agreement is poor for water, methanol and ethanol, which form hydrogen bonds.

An obvious possible reason for the large difference between the model and the experimental entropy values in the case of water is that the difference represents additional structure in real water that is due to the hydrogen bonding, which

Table 2
The experimental (exp) and hard sphere model (hs1) Δs_2^* values for the transfer from gas to the neat liquid phase in J K^{-1} mol^{-1} units at 25 °C

	Δs_2^*(exp)	Δs_2^*(hs1)
n-C_5H_{12}	−39.8	−42.3
$C(CH_3)_4$	−36.2	−36.0
n-C_6H_{14}	−45.9	−41.6
c-C_6H_{12}	−44.4	−39.8
Benzene	−45.2	−39.0
Toluene	−50.3	−42.5
CCl_4	−42.5	−36.9
H_2O	−51.3	−14.0
CH_3OH	−56.7	−19.2
C_2H_5OH	−65.5	−25.5

is not present in the hard sphere system. However, there is also the less well recognized issue of the proper solvent size to use. As mentioned in the Section 1, two sizes can be assigned to water molecules, one for the case when they hydrogen bond and another, a significantly larger one, for the case when they do not. The result of Table 2 was obtained using the size that is appropriate for the former case. However, since a hard sphere system does not have hydrogen bonds, one could argue that a more proper hard sphere model would be the one with the larger size.

The possible sizes of water, methanol and ethanol molecules after their hydrogen bonds have been turned off are given in Table 3. The 3.17 Å diameter for water is the Lennard–Jones σ parameter in the SPCE model of water [24] and is between 3.15 Å for the same parameter in the TIP4P model [25] and 3.2 Å that one of us used in an earlier work [26]. The 4.10 and 4.66 Å, respectively, for methanol and ethanol are the diameters of the spheres that have the same volume

Table 3
Alternate diameter, packing density and the experimental (exp) and hard sphere model (hs2) neat phase transfer Δs_2^* values for hydrogen bonding liquids at 25 °C

	d (Å)	ξ	Δs_2^*(exp) (J K^{-1} mol^{-1})	Δs_2^*(hs) (J K^{-1} mol^{-1})
H_2O	3.17	0.556	−51.3	−47.0
CH_3OH	4.10	0.534	−56.7	−43.7
C_2H_5OH	4.66	0.544	−65.5	−45.9

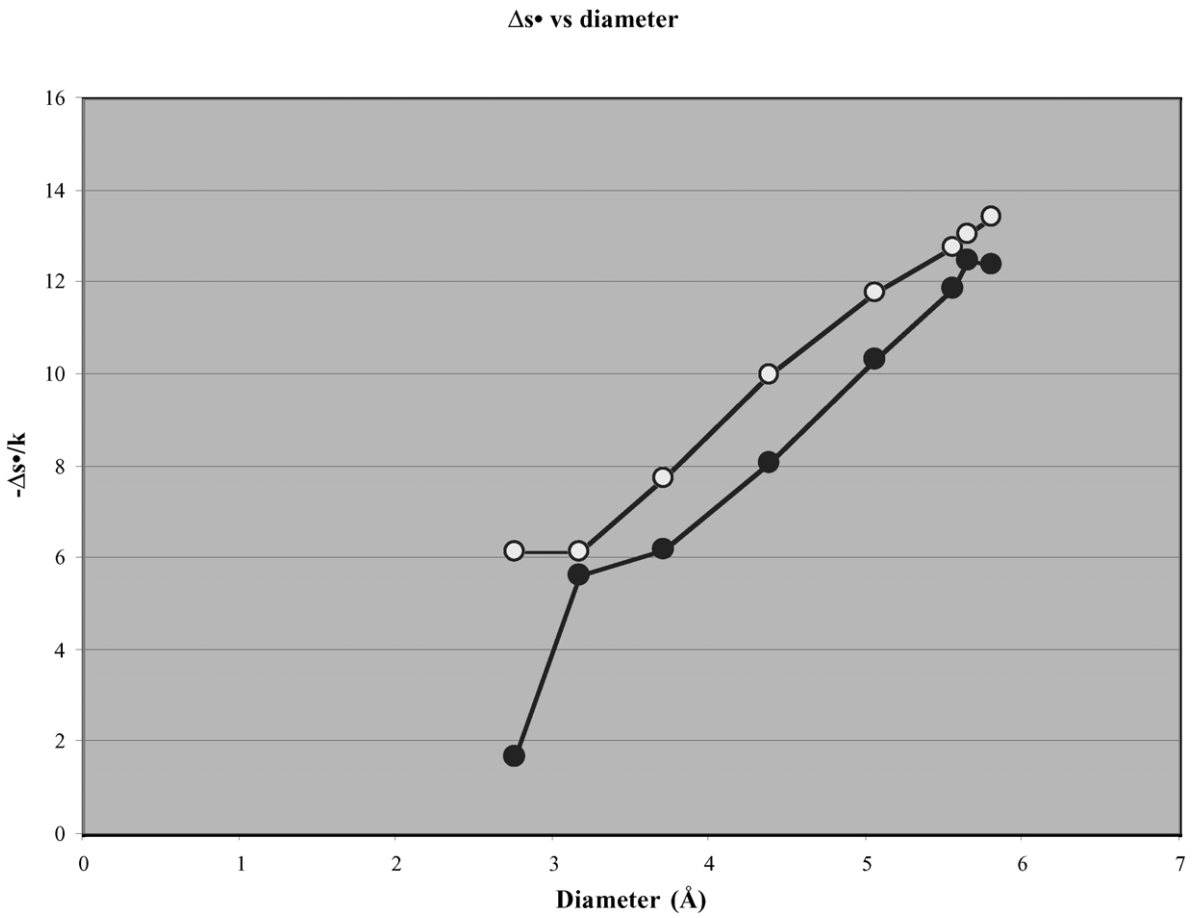

Fig. 2. Negative of the experimental (open circles) and model (closed circles) hydration $\Delta s_2^{\bullet}$ values, in units of k the Boltzmann's constant, as a function of the diameter of the solute molecules. The first two points are for water as solute species, with 2.75 and 3.17 Å diameters. The other points are for methane, ethane, propane, isobutane, normal butane and neopentane. The calculations for these latter solutes were made using the hs3 model. (See the text.)

as that obtained from the van der Waals volume-increments for each molecule [18,27]. Although the entropy values calculated from this model (hs2) are still smaller than the experimental values, they become remarkably similar to the experimental values. The change in the entropy values for water can also be seen by the first two pairs of points in Fig. 2, which show the experimental and model entropy values for water with 2.75 and 3.17 Å diameter, respectively.

3.2. Solvation of hydrocarbons in benzene

In order to provide a contrast to the hydration data to be presented in the next sub-section, the entropy values were also calculated for transfer of methane and ethane from the gas phase to benzene. The solvent properties used were as given in Table 1 and $\bar{v}_{hs}$ was set equal to $\bar{v}_2$ for both of the solute species. The experimental and the model $\Delta s_2^{\bullet}$ values are given in Table 4. The model values are sensitively dependent on the value of the partial molar volume of the solute species used and the use of slightly larger $\bar{v}_2$ yields model $\Delta s_2^{\bullet}$ values that are nearly identical to the experimental values. The required change in the value of $\bar{v}_2$ is not large in view of the uncertainties associated with the experimental values. We note, for example, that

Table 4
The diameter, partial molar volume in benzene and the experimental (exp) and hard sphere model (hs) Δs_2^* values for the transfer of methane and ethane from the gas phase to liquid benzene at 25 °C

	d (Å)	$\bar{v}_2$ ($cm^3\ mol^{-1}$)	Δs_2^*(exp) ($J\ K^{-1}\ mol^{-1}$)	Δs_2^*(hs) ($J\ K^{-1}\ mol^{-1}$)
CH_4	3.70	52 (57)	−3.7	−10.4 (−3.8)
C_2H_6	4.38	73 (76)	−8.4	−12.0 (−8.1)

d: Hard sphere diameters from [32]. $\bar{v}_2$: Partial molar volumes from Ben-Naim [28], p. 320. The values in parentheses are those that produce nearly experimental (Δs_2^* values. Δs_2^*: Ben-Naim standard gas to benzene transfer entropy. The experimental (exp) values are from [53], after correction to the Ben-Naim standard. The model values in parentheses are those obtained using the $\bar{v}_2$ values in parentheses.

the experimental partial molar volume of methane in benzene is quoted as 52 $cm^3\ mol^{-1}$ by Ben-Naim [28] and Smith and Walkley [29], but as 57 $cm^3\ mol^{-1}$ by Miller and Hildebrand [30]. Thus, in the case of dissolution of these solute species in benzene, the hard sphere model reproduces the experimental solvation entropy values rather accurately.

3.3. Hydration of hydrocarbons

The necessary data and the results of the calculations for the entropy change for the hydration of small hydrocarbon molecules are compiled in Table 5. The partial molar volumes for methane, ethane and propane are the experimental values from Cabani et al. [31]. The values for the other three solutes are estimates calculated using the group contributions provided by the same group. The compressibility of water used was 46×10^{-12} cm^2/dyne at 25 °C. The Δs^*(exp) values are from Graziano [32]. The Δs_2^*(hs1), Δs_2^*(hs2) and Δs_2^*(hs3) values given are the solvation entropy changes calculated for the three different hard sphere models described below.

In the first model (hs1), the normal size, 2.75 Å, was used for water and $\bar{v}_{hs}$ was set equal to $\bar{v}_2$. This model gives solvation entropy values that are much less negative than the corresponding experimental hydration entropy changes. When the size of the solvent hard spheres was increased to 3.17 Å (hs2, the second model), the entropy values became generally even less negative than those for the first model and changed sign for some solute species.

The hard sphere system hs2 is more crowded than hs1 since the size of the solvent molecules has been increased without increasing volume. The extent of crowding can be measured by means of the volume packing density, ξ, but this measure gives the amount of empty space relative to the physically occupied space. An absolute measure of the size of the empty space is given by the notion of the 'border' thickness [33,34]. The border thickness, δ_i, of species i in a solution is defined by

$$\bar{v}_i=(\pi/6)(d_i+2\delta_i)^3. \quad (15)$$

As examined in great detail by one of us some time ago [34], the border thickness defined this way gives the thickness of the shell around the solute molecule that is devoid of solvent if solvent

Table 5
Hydration entropy changes of small hydrocarbons at 25 °C

	d (Å)	$\bar{v}_2$ ($cm^3\ mol^{-1}$)	$\bar{v}_{hs}$ (hs3) ($cm^3\ mol^{-1}$)	Δs_2^* (exp) ($J\ K^{-1}\ mol^{-1}$)	Δs_2^* (hs1) ($J\ K^{-1}\ mol^{-1}$)	Δs_2^* (hs2) ($J\ K^{-1}\ mol^{-1}$)	Δs_2^* (hs3) ($J\ K^{-1}\ mol^{-1}$)
CH_4	3.70	37.3	26.6	−64.4	−13.7	37.6	−51.6
C_2H_6	4.38	51.2	41.0	−83.2	−26.5	18.1	−66.9
C_3H_8	5.06	67.0	59.8	−97.9	−47.2	−25.6	−85.6
i-C_4H_{10}	5.55	82.9	76.5	−106.0	−59.3	−45.2	−98.5
n-C_4H_{10}	5.65	83.1	80.2	−108.3	−70.5	−79.4	−103.6
$C(CH_3)_4$	5.80	98.2	86.0	−111.7	−50.0	−1.1	−102.8

d: Hard sphere diameters for neopentane from [7] and for all other alkanes from [32]. $\bar{v}_2$: Partial molar volumes of the solutes from [31]. $\bar{v}_{hs}$: Step II volume expansion per mole of solute added. From Eq. (16). Δs_2^*: Ben-Naim standard gas to water transfer entropy. The experimental (exp) values are from [32]. See the text for an explanation of the model (hs1, 2, 3) values.

Table 6
Values of different terms that contribute to Δs_2^* of methane hydration from different hard sphere models at 25 °C

	A	B	C	$\bar{v}_{hs}/\bar{v}_1 - \alpha T$	s_{IV}/k	Sum[a]	Δs_2^* (exp)/k
Hs1	−2.604	0.674	−1.708	1.988	0	−1.65	−7.75
Hs2	−6.577	0.415	8.697	1.988	0	4.52	−7.75
Hs3	−6.577	0.415	−2.166	1.395	0.719	−6.21	−7.75

[a] Sum of the terms across each row. Equals calculated Δs_2^*/k.

Table 7
Values of different terms that contribute to the model Δs_2^* at 25 °C

	A	B	C	$\bar{v}_{hs}/\bar{v}_1 - \alpha T$	s_{IV}/k	Sum[a]
CH_4(b)[b]	−5.323	0.779	3.085	0.212	0	−1.25
C_2H_6(b)[b]	−5.323	0.270	3.158	0.447	0	−1.45
Water[c]	−6.577	0	0	0.923	0	−5.65
CH_4[d]	−6.577	0.415	−2.166	1.395	0.728	−6.21
C_2H_6[d]	−6.577	2.405	−6.767	2.192	0.694	−8.06
C_3H_8[d]	−6.577	6.460	−13.900	3.233	0.490	−10.30
i-C_4H_{10}[d]	−6.577	10.922	−20.787	4.157	0.436	−11.86
n-C_4H_{10}[d]	−6.577	12.009	−22.449	4.362	0.197	−12.46
$C(CH_3)_4$[d]	−6.577	13.759	−25.055	4.683	0.830	−12.37

[a] Sum of the terms across each row. Equals $\Delta s_2^*/k$.
[b] In benzene.
[c] Using 3.17 Å.
[d] In water of 3.17 Å diameter, using the hard sphere model hs3.

is considered as a continuum of constant packing density. The value of δ for water in water at 25 °C is 0.55 Å when $d = 2.75$ Å but decreases to 0.34 Å when $d = 3.17$ Å. On the other hand, the border thickness for methane in water is 0.61 Å. This means that, when a hard sphere of the size of a methane molecule is added in step II and the volume is allowed to increase by the partial molar volume of methane, the average distance between the surfaces of methane and water molecules is $0.61 + 0.34 = 0.95$ Å, nearly 50% larger than 2×0.34 Å, the average surface-to-surface distance between water molecules. This will create an extra entropy for the system as some of the water molecules 'spill out' into the border region between methane and water. In order to prevent this from happening, one can limit the volume increase in step II so that the surface-to-surface distance between methane and water molecules is the same as that between water molecules. This can be done by increasing the volume of the system by $\bar{v}_{hs}$ per molecule given generally by:

$$\bar{v}_{hs} = (\pi/6)(d_2 + 2\delta_1)^3. \quad (16)$$

Note that d_2 is the diameter of the solute molecule but δ_1 is 0.34 Å, the border thickness of the increased size water molecules.

The values of $\bar{v}_{hs}$ given in Table 5 were computed using Eq. (16). The hard sphere system obtained after this volume increase no longer has the same number density as the original real solution and the density has to be adjusted in step IV. The entropy values calculated for this hard sphere system, hs3, which uses these $\bar{v}_{hs}$ values and 3.17 Å as the diameter of water molecules, are given in the last column of Table 5 and compared to the experimental values in Fig. 2. It can be seen that this hard sphere model gives values that are remarkably similar to the hydration entropy values of the real system.

In order to see which features of the model produce the different entropy values, the values of the various terms that contribute to the entropy change were calculated. They are given for the

three hard sphere models for the hydration of methane in Table 6 and for several different solute and solvent species for selected hard sphere models in Table 7.

4. Discussion

4.1. Choosing the proper hard sphere model

As indicated in the Section 1, real molecules are not hard spheres and it is not always easy to determine the proper hard sphere model that would be most useful as a reference for the real aqueous system. There are three types of systems in terms of the ease with which a hard sphere model can be constructed: the non-polar liquid of small nearly spherical molecules, for which there is no substantial ambiguity in selecting the hard sphere size or the number density; the neat, polar liquid, for which the main issue is the choice of the proper hard sphere size; and the aqueous solution of non-polar solute, for which one has to choose both the hard sphere size and the number density.

For the straightforward case of the non-polar neat systems, hard sphere models produce entropy values that are similar to those of the real systems (Table 2). This means that s_{III} is nearly zero, and since the system is pure, that ΔS_{III} is nearly zero. Thus, the entropy of these liquids is determined mainly by the hard core packing effects and is not much altered by the soft interactions. This is a well-known observation [35]. The model values are generally somewhat less negative than the real values, suggesting either that the molecular sizes used are systematically a little too small or that the soft interactions do reduce the entropy slightly further. For the case of the methane and ethane dissolution in benzene, hard sphere models are again essentially straightforward to choose, although there is a minor problem stemming from the experimental uncertainty associated with the volume change of the system. The models give entropy values that are comparable to or slightly more negative than the real system (Table 4). This suggests that the non-spherical shape and/or interaction potential of benzene molecules make the packing slightly looser in these solutions than expected from those made of totally spherical molecules.

For pure liquids made of molecules that form hydrogen bonds, there are at least two possible sizes to consider for the hard spheres. In the case of water, the inter-molecular distance of closest approach is near 2.8 or 3.2 Å depending on whether the two molecules hydrogen bond or not, respectively. The entropy of the hard sphere model with the smaller size, hs1, is much larger than that of real water (Table 2). One obvious reason for this is that the molecules in hs1 are freely rotatable whereas the rotational degree of freedom in real water is highly restricted because of the hydrogen bonds. There is also a less obvious reason: In the hard sphere model, all interatomic distances in the range of 2.8 and 3.2 Å will occur with approximately equal probability whereas, in real water, interatomic distances will tend to occur at either 2.8 or 3.2 Å and much less frequently in-between, at least at room temperature. Thus, molecules in hs1 are expected to have more translational degree of freedom as well as an increased rotational degree of freedom. The actual difference between the hs1 and real water, as measured by $-s_{III}$, is 37 J K^{-1} mol^{-1} (Table 2). This is comparable to the rotational contribution to the gas phase entropy, which is 43.8 J K^{-1} mol^{-1} for water at 25 °C, calculated using the characteristic temperature value of 22.3 °C [36]. The fact that the former value is not larger, but somewhat less, than the latter suggests that not all rotational degree of freedom is frozen in real water. It should be noted that some 20–30% of all possible hydrogen bonds in water are thought to be broken at 25 °C [37,38].

The hard sphere model with the larger size, hs2, is in a way a more natural model system since this is the system that will be obtained if the hydrogen bonds were simply turned off from real water. This model will have the same rotational entropy as hs1 but less translational contribution since interatomic distances less than 3.2 Å do not occur in this system. It is remarkable that the value of s_{III} is nearly zero with this model (Table 3). Thus, hs2 is a model system wherein the increase in the rotational contribution to the neat phase entropy is nearly perfectly canceled by a reduction in the translational entropy.

For the hydration of hydrocarbons, again two models can be considered: hs1, which uses the 2.75 Å size water, and hs2, which uses 3.17 Å. Both of these models produce hydration entropy values that are substantially larger than the experimental values, even becoming positive for small solute species (Table 5). The usual interpretation of this observation would be that a structure forms around the solute species in real water that is absent in the hard sphere model or that the water molecules around the solute molecule lose additional rotational degree of freedom. While this is possible, it is important that other possible reasons are carefully examined and eliminated before such conclusions are drawn. In the case of hs1, one obvious possibility is that the model contains hard spheres that are too small so that the newly introduced solute species has more room to move about than in real water. Approximate magnitude of this effect can be discerned by comparing the values of term A in the expression for s_2^e, Eq. (8b), for hs1 and hs2. Term A depends only on the solvent packing density (see Eq. (7a) and the next sub-section), which is low in hs1 and high in hs2. As can be seen in the example of methane hydration (Table 6), the effect is substantial, which indicates that the low solvent packing density is indeed a major reason for the relatively high hydration entropy of the hs1 model.

On the other hand, the reason that hs2 produces even higher hydration entropy than hs1 is that term C is large for hs2. This term arises from the change in packing density upon the introduction of the solute molecule (see Eq. (8c) and the next sub-section). Even though the solute molecule has the same physical size and causes the same volume increment in both models, there is a large negative change in packing density in the hs2 model because the starting solvent packing density is high. As described in Section 3.3, the solvent molecules 'spill over' into the free volume around the solute molecule in this model. Therefore, both the relatively high A term in the hs1 model and the large C term in the hs2 model arise from features of the models that are probably absent in real water.

Model hs3 is a modification of hs2, in which the 'spill over' is prevented by limiting the volume increase upon the solute insertion. This is done in such a manner that the average surface-to-surface distance between the solute and solvent molecule is the same as that between the solvent molecules. This causes the volume of the model solution unequal to that of the real solution, necessitating the additional step IV to complete the thermodynamic cycle. The fact that this model produces a larger negative entropy change is not surprising, but the degree to which this model reproduces the experimental values is remarkable. This indicates that the large reduction in entropy, which is a hallmark of the hydrophobic effect, can arise from causes other than the formation of hydrogen-bonded structure or loss of orientational degree of freedom.

4.2. The entropy formula for the hard sphere system

One of the virtues of the hard sphere system is that the entropy (and other thermodynamic quantities) can be calculated analytically so that it is possible to dissect the total into several components and examine each of them in detail. The values of each term that contributes to the entropy change are given in Tables 6 and 7.

Eq. (8b) shows that the excess entropy change upon addition of a hard sphere into a system of hard spheres is given by the sum of three terms. According to Eq. (7a), term A is always negative since the volume packing density of common liquids is always between 0 and 1. This term is present even when the solute added is the same species as the solvent. Therefore, this term represents the reduction in entropy due to the increase in the amount of structure upon increasing the size of the system by one molecule, regardless of whether the molecule added is the same as or different from the solvent species.

Calculations using Eq. (7b) show that the term B is positive for all values of r and ξ, except when $r=1$, in which case it is zero. Thus, this term raises solvation entropy when the solute is either larger or smaller than the solvent. The presence of this term presumably reflects the fact that there are more ways to pack a set of differently sized spheres than that of uniformly sized spheres. This

contribution can be substantial when the size difference is large (see Table 7).

Term C arises from the change in the volume packing density when a solute is added. This term is zero when the solute added is of the same species as the solvent, since the packing density does not change in this case. When the solute is of different size than the solvent, this term is usually non-zero. The $\partial A/\partial\xi$ term in Eq. (8c) is equal to $-(p_{hs}-p_{id})/p_{id\xi}$, where p_{hs} and p_{id} are the pressures of the hard sphere and ideal gas systems, respectively, that are obtained from the pure solvent system under the constant volume condition. Because this term is large, term C makes a large contribution to the solvation entropy, either positively when the volume is allowed to increase by more than $r^3\bar{v}_1$ or negatively when the volume is fixed or allowed to increase by less than $r^3\bar{v}_1$. This makes it important that the conditions for step II be chosen judiciously if the hard sphere model is to yield a useful result. Sharp et al. [8] considered a number of different conditions. The condition of the hs3 model is novel. It is designed to make the spacing between the solute and solvent molecules the same as that between the solvent molecules when they do not hydrogen bond.

4.3. Implications to the hydrophobicity

We note first that both the experimental and the calculated Δs_2^* values are negative for all cases considered, including pure polar and non-polar systems, solvating non-polar molecules in a non-polar solvent, and of course hydration of non-polar solutes. Therefore, the fact that hydration entropy change is negative, by itself, does not indicate that water forms an additional structure when a non-polar solute molecule is inserted. According to the hard sphere model, the negative entropy for the solvation of a methane and ethane in benzene (Table 7) arises from the presence of term A. This term is present in all cases and, as noted above, represents an increase in the amount of structure due to the increase in the size of the system upon addition of more molecules in the system.

On the other hand, although the entropy change is negative in all cases, it is much larger in magnitude for the hydration than for the solvation in benzene. Table 7 shows the hs3 model explanation of this phenomenon: the reason is that term C is negative for the hydration but is positive for the solvation in benzene. According to Eq. (8c), the sign of term C is determined by the factor $(\bar{v}_{hs}/\bar{v}_1-r^3)$. Using Eq. (15) for $\bar{v}_1$, and assuming that $\bar{v}_{hs}$ is given by Eq. (16) even for methane and ethane in benzene and that δ_1 is small, this factor is approximately given by:

$$(\bar{v}_{hs}/\bar{v}_1-r^3)\approx 6r^2(1-r)\delta_1/d_1 \qquad (17)$$

Thus the C term is positive for the solvation of methane and ethane in benzene simply because the solute molecules are smaller than the solvent molecule ($r<1$). For solute molecules larger than benzene, this term will become negative, as in the case of the hydration. However, this term will remain larger in magnitude for hydration than for solvation in benzene because d_1, to which both d_2 and δ_1 are compared, is smaller for water than for benzene. Therefore, this hard sphere model corroborates the suggestion made earlier by us [7,39,40] and by others [41–47] that it is the small size of water molecules that produces the hydrophobicity. The caveat is that it is difficult to establish if the hs3 model is indeed the appropriate model for water.

Finally we note that the experimental Δs_2^* values for hydration are linearly related to the size of the solute molecules (Fig. 2) and that the point for the gas to neat phase transfer of water falls in the same line when the larger size is used for water. The model values are always less negative than the experimental values, but follows the same general trend with respect to the solute size. Also the fact that the neat phase transfer of water falls on the same line is consistent with the hard sphere model in which water is treated like any other non-polar solute, except that its size happens to coincide with that of the solvent. The size dependence is, however, not linear in the hs3 model since the terms B, C and $(\bar{v}_{hs}/\bar{v}_1-\alpha T)$ all show cubic dependence on d_2.

References

[1] W. Blokzijl, J.B.F.N. Engberts, Angew. Chem. Int. Ed. Engl. 32 (1993) 1545.

[2] G. Hummer, S. Garde, A.E. Garcia, M.E. Paulaitis, L.R. Pratt, J. Phys. Chem. B 102 (1998) 10469.
[3] T. Lazaridis, Acc. Chem. Res. 34 (2001) 931.
[4] L.R. Pratt, Annu. Rev. Phys. Chem. 53 (2002) 409.
[5] N.T. Southall, K.A. Dill, A.D.J. Haymet, J. Phys. Chem. B 106 (2002) 521.
[6] R.A. Pierotti, J. Phys. Chem. 69 (1965) 281.
[7] B. Lee, Biopolymers 31 (1991) 993.
[8] K.A. Sharp, S. Kumar, P.J. Rossky, R.A. Friedman, B. Honig, J. Phys. Chem. 100 (1996) 14166.
[9] L.R. Pratt, D. Chandler, J. Chem. Phys. 67 (1977) 3683.
[10] H. Tanaka, J. Chem. Phys. 86 (1987) 1512.
[11] A. Pohorille, L.R. Pratt, J. Am. Chem. Soc. 112 (1990) 5066.
[12] L.R. Pratt, A. Pohorille, Proc. Natl. Acad. Sci. USA 89 (1992) 2995.
[13] B. Madan, B. Lee, Biophys. Chem. 51 (1994) 279.
[14] G. Hummer, S. Garde, A.E. Garcia, A. Pohorille, L.R. Pratt, Proc. Natl. Acad. Sci. USA 93 (1996) 8951.
[15] G.E. Crooks, D. Chandler, Phys. Rev. E 56 (1997) 4217.
[16] D.M. Huang, D. Chandler, Phys. Rev. E 61 (2000) 1501.
[17] S. Garde, H.S. Ashbaugh, J. Chem. Phys. 115 (2001) 977.
[18] K.E. Tang, V.A. Bloomfield, Biophys. J. 79 (2000) 2222.
[19] G.A. Mansoori, N.F. Carnahan, K.E. Starling, T.W. Leland, Jr., Chem. Phys. 54 (1971) 1523.
[20] A. Ben-Naim, J. Phys. Chem. 82 (1978) 792.
[21] B. Lee, Methods Enzymol. 259 (1995) 555.
[22] A. Ben-Naim, Y. Marcus, J. Chem. Phys. 81 (1984) 2016.
[23] A. Ben-Naim, Solvation Thermodynamics, Plenum Press, New York, NY, 1987, p. 100.
[24] H.J.C. Berendsen, J.R. Grigera, T.P. Straatsma, J. Phys. Chem. 91 (1987) 6269.
[25] W.L. Jorgensen, J. Chandrasekhar, J.D. Madura, R.W. Impey, M.L. Klein, J. Chem. Phys. 79 (1983) 926.
[26] J.P. Kocher, M. Prevost, S.J. Wodak, B. Lee, Structure 4 (1996) 1517.
[27] J.T. Edward, J. Chem. Educ. 47 (1970) 261.
[28] A. Ben-Naim, Water and Aqueous Solutions, Plenum, New York, 1974.
[29] E.B. Smith, J. Walkley, J. Phys. Chem. 66 (1962) 597.
[30] K.W. Miller, J.H. Hildebrand, J. Am. Chem. Soc. 90 (1968) 3001.
[31] S. Cabani, P. Gianni, V. Mollica, L. Lepori, J. Solut. Chem. 10 (1981) 563.
[32] G. Graziano, J. Chem. Soc. Faraday Trans. 94 (1998) 3345.
[33] J.T. Edward, P.G. Farrell, Can. J. Chem. 53 (1975) 2965.
[34] B. Lee, J. Phys. Chem. 87 (1983) 112.
[35] H. Reiss, Adv. Chem. Phys. 9 (1965) 1.
[36] E.A. Guggenheim, Thermodynamics, Fourth edition, North–Holland, Amsterdam, Netherlands, 1959, p. 131.
[37] B. Lee, G. Graziano, J. Am. Chem. Soc. 118 (1996) 5163.
[38] K.A.T. Silverstein, A.D.J. Haymet, K.A. Dill, J. Am. Chem. Soc. 122 (2000) 8037.
[39] B. Lee, Biopolymers 24 (1985) 813.
[40] G. Graziano, J. Phys. Chem. B 104 (2000) 9249.
[41] M. Lucas, J. Phys. Chem. 80 (1976) 359.
[42] K. Soda, J. Phys. Soc. Jpn. 62 (1993) 1782.
[43] L.E.S.d. Souza, D. Ben-Amotz, J. Chem. Phys. 101 (1994) 9858.
[44] A. Wallqvist, D.G. Covell, Biophys. J. 71 (1996) 600.
[45] M. Ikeguchi, S. Shimizu, S. Nakamura, K. Shimizu, J. Phys. Chem. B 102 (1998) 5891.
[46] G. Graziano, Biophys. Chem. 82 (1999) 69.
[47] E. Gallicchio, M.M. Kubo, R.M. Levy, J. Phys. Chem. B 104 (2000) 6271.
[48] M.H. Abraham, A. Nasehzadeh, J. Chem. Soc. Faraday Trans. 77 (1981) 321.
[49] E. Wilhelm, R. Battino, J. Chem. Phys. 55 (1971) 4012.
[50] J.F. Alary, M.A. Simard, J. Dumont, C. Jolicoeur, J. Solut. Chem. 11 (1982) 755.
[51] R.A. Pierotti, J. Phys. Chem. 67 (1963) 1840.
[52] R.A. Pierotti, Chem. Rev. 76 (1976) 717.
[53] M.H. Abraham, J. Am. Chem. Soc. 104 (1982) 2085.