

# Comment on “Water’s Structure around Hydrophobic Solutes and the Iceberg Model”

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The molecular origin of the poor solubility of nonpolar species in water is still a debated argument,<sup>1</sup> especially for the desire to find a clear connection between the features of water structural reorganization and the peculiar thermodynamic signatures. In a recent article,<sup>2</sup> Galamba has tried to provide support for the classical and pictorial iceberg model proposed by Frank and Evans<sup>3</sup> in 1945, because he considers such a model appealing for the straightforward explanation of the thermodynamic features of hydrophobic hydration at room temperature. Indeed, iceberg formation should readily account for the large entropy loss associated with the hydration of nonpolar solutes at room temperature. Galamba has performed NPT molecular dynamics (MD) trajectories, each 1 ns long, of xenon, methane, ethane, and benzene using the polarizable AMOEBA<sup>4</sup> water model. He has found no significant increase or decrease in the structural organization of water molecules in the first hydration shell of such solutes.<sup>2</sup> This fundamental result contrasts with the iceberg model. However, Galamba insisted and selected only a subset of the water molecules constituting the first hydration shell (i.e., excluding those in direct contact with the solute and keeping those having four water molecules as nearest neighbors). He calculated that, for these subsets of water molecules, the average value of the tetrahedral order parameter<sup>5</sup>  $\langle q \rangle$  is larger than that of bulk water, suggesting a local increase in structural order. According to Galamba,<sup>2</sup> this finding lends support for a moderate interpretation in terms of the iceberg model. In fact, he wrote: “The present results indicate that water ordering around small hydrophobic solutes does contribute to the negative entropy and the large heat capacity that characterize the transfer of a nonpolar molecule to water, opposite to the current view on hydrophobic hydration.” This sentence is not strictly correct and misleading. I would like to put Galamba’s results in the general scenario of hydrophobic hydration in order to provide a right perspective to interested but not expert readers.

The first point to underscore is the fact that the increase of  $\langle q \rangle$  found by Galamba is very small and holds only for a subset of the water molecules in the first hydration shell (i.e.,  $\langle q \rangle$  amounts to 0.673 for the subset of methane, 0.676 for the subset of ethane, and 0.652 for bulk water at 25 °C; see Figure 3 in ref 2; note that  $\langle q \rangle$  should be equal to 1 for a perfect tetrahedral network, and is equal to 0.9 for the two tetrahedra shown in Figure 4b of ref 2). In fact, both the oxygen–oxygen radial distribution function of water molecules in the first hydration shell of methane and the oxygen–oxygen radial distribution function of the subset of water molecules in the

same hydration shell are indistinguishable from that of bulk water at the same temperature (see Figure 6 in ref 2). This important result is in line with experimental data obtained from neutron diffraction measurements,<sup>6</sup> and demonstrates that there is no increase of structural order in the hydration shell of nonpolar solutes. Actually, experimental data suggest that such hydration shells are slightly more disordered than bulk water,<sup>6,7</sup> in line with the application of Muller’s model,<sup>8,9</sup> and a correct analysis of thermodynamic data. It should be recognized that the Ben-Naim standard hydration enthalpy change is given by<sup>10</sup>

$$\Delta H^\bullet = E_a + \Delta H_r \quad (1)$$

where  $E_a$  is the direct solute–water interaction energy and  $\Delta H_r$  is the enthalpy change due to the reorganization of water–water H-bonds upon solute insertion. The  $E_a$  quantity can reliably be calculated by means of computer simulations. By comparing the experimental  $\Delta H^\bullet$  values with the calculated  $E_a$  estimates, it emerges that  $\Delta H_r$  for nonpolar solutes, is a small and positive quantity, at room temperature. At 25 °C,  $\Delta H^\bullet = -10.9$  kJ mol<sup>−1</sup> for methane and  $-17.2$  kJ mol<sup>−1</sup> for ethane,<sup>10</sup> whereas  $E_a = -13.5$  kJ mol<sup>−1</sup> for methane and  $-21.7$  kJ mol<sup>−1</sup> for ethane<sup>11</sup> (other  $E_a$  estimates<sup>12</sup> prove to be always larger, in magnitude, than the experimental  $\Delta H^\bullet$  numbers). Since  $\Delta H_r = \Delta H^\bullet - E_a = 2.6$  kJ mol<sup>−1</sup> for methane and 4.5 kJ mol<sup>−1</sup> for ethane, there is no increase in structural order for the water molecules in the first hydration shell of such solutes. Upon the insertion of a nonpolar solute, water molecules reorganize and, due to their smallness and 2–2 tetrahedral functionalities, are able to avoid the loss of H-bonds, regardless of the presence of the solute<sup>9,10</sup> (i.e., the  $\Delta H_r$  numbers are small in comparison to the energy of a single H-bond, around 20 kJ mol<sup>−1</sup>, and there are a lot of water–water H-bonds in such hydration shells).

The second point to underscore is that, since there are no icebergs, it is necessary to provide a different explanation for the large entropy decrease associated with the hydration of nonpolar solutes at room temperature. In order to insert a molecule in a liquid, it is necessary to create a cavity suitable to host the solute.<sup>13</sup> This is a simple consequence of the fact that liquids are a condensed state of matter and, even though they possess a very large fraction of void volume, the latter is partitioned in very small pieces that are not useful for the insertion of a solute molecule (i.e., the most probable cavity diameter is about 0.5 Å in water at room temperature<sup>14</sup>). Therefore, cavity creation is an unavoidable step for a correct

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theoretical description of solvation processes and it has to be recognized that the reversible work of cavity creation is a purely entropic quantity. This has been demonstrated on statistical mechanical grounds,<sup>15</sup> but it is also possible to provide qualitative and convincing arguments. The existence of a spherical cavity causes a solvent-excluded volume because the centers of solvent molecules cannot enter the spherical shell between the van der Waals surface of the cavity and its solvent-accessible surface (note that, operating at constant temperature and pressure, the volume of the liquid increases, upon cavity creation, by a quantity corresponding to the partial molar volume of the cavity itself). This leads to a significant decrease in the configurational space accessible to solvent molecules, and thus to a large decrease in their configurational–translational entropy.<sup>16</sup> The described solvent-excluded volume effect is operative also in water and is the molecular origin of the entropy loss associated with the hydration of nonpolar solutes at room temperature. In fact, the Ben-Naim standard entropy decrease associated with the hydration of noncharged solutes, at 25 °C and 1 atm, can be well reproduced by the entropy change associated with the creation of a suitable cavity, calculated by means of classic scaled particle theory,<sup>17,18</sup> SPT (see Figure 1 in ref 17). For instance, at 25 °C and 1 atm,  $\Delta S^\circ = -64.4 \text{ J K}^{-1} \text{ mol}^{-1}$  for methane and  $-83.2 \text{ J K}^{-1} \text{ mol}^{-1}$  for ethane,<sup>10</sup> while  $\Delta S_c(\text{SPT}) = -64.4 \text{ J K}^{-1} \text{ mol}^{-1}$  for methane and  $-85.2 \text{ J K}^{-1} \text{ mol}^{-1}$  for ethane.<sup>19</sup> In addition, the reversible work of cavity creation has been calculated, by means of MD simulations, also in the polarizable AMOEBA water model, over a large temperature range, for different cavity diameters and the corresponding entropy changes proved to be large and negative around room temperature<sup>20</sup> (see Table 2 in ref 20).

The third and final point to underscore is related to the enthalpy–entropy compensation characterizing the process of water structure reorganization (i.e., water–water H-bond reorganization) upon solute insertion. Such enthalpy–entropy compensation has been demonstrated by several authors (Ben-Naim was the first one<sup>21</sup>), using different theoretical routes.<sup>22</sup> A more physically based demonstration is the one devised by Lee.<sup>23</sup> The occurrence of enthalpy–entropy compensation is a fundamental point and should not be forgotten in trying to rationalize hydrophobic hydration. In fact, if the water–water H-bond reorganization is characterized by a complete enthalpy–entropy compensation (i.e., the Gibbs energy change of the process is equal to zero), this process cannot be the cause of the poor solubility of nonpolar species in water.<sup>21–23</sup>

In conclusion, I have tried to underscore the following: (a) the results by Galamba, in line with experimental data and theoretical approaches, indicate that there is no structural order increase in the hydration shell of small nonpolar molecules; (b) the large entropy loss, characteristic of hydrophobic hydration at room temperature, is due to the solvent-excluded volume effect associated with the creation of a cavity suitable to host the solute molecule; (c) an almost complete enthalpy–entropy compensation holds for the water–water H-bond reorganization, so the latter process cannot be the cause of the poor solubility of nonpolar species in water. I think that Galamba's study is very interesting and useful exactly because it shows, by means of a careful and detailed determination of water structural reorganization in a realistic model of water, that there are no icebergs surrounding small hydrophobic solutes, at room temperature. Thus, one has to search elsewhere for the molecular origin of the entropy loss associated with hydrophobic hydration. Galamba himself wrote:<sup>2</sup> "If one considers

the average number of H-bonds in the first hydration shell, no significant enhancement or disruption was found relative to that in neat and bulk water." This should be the "take to home message" of Galamba's article.

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### Notes

The authors declare no competing financial interest.

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