COMMENTS

Comment on "The Mechanism of Hydrophobic Solvation Depends on Solute Radius" *J. Phys. Chem. B* **2000**, *104*, **1326**

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In a recent paper (W),[1] Southall and Dill (S&D) presented a molecular model of hydrophobic solvation grounded on the so-called Mercedes-Benz model of water,[2] originally devised by Ben-Naim.[3] S&D used both the Widom[4] test particle insertion method and a thermodynamic integration procedure to calculate the hydration thermodynamics of nonpolar solutes with very different sizes, performing NPT Monte Carlo simulations. They claimed that their model results account for the different mechanism of hydrophobic solvation for large nonpolar solutes (much larger than a water molecule) and small nonpolar solutes. Such claim, however, does not seem entirely justified, as shown below. In writing the present Comment we recognize that the Mercedes-Benz model is limited by construction, being two-dimensional (2D) and that it is not strictly pertinent to compare 2D and 3D. However, to attach a clear physical meaning to the results obtained by S&D, a qualitative comparison is necessary because real molecules are 3D objects.

S&D adopted the Ben-Naim standard state,[5] and denoted the hydration thermodynamic functions by the subscript tr (i.e., transfer from gas phase to water). We adopt the same standard state, so that the experimental data used in this Comment correspond, in principle, to those computed by S&D. We also remark that the present Comment is not concerned with the hydration of large planar nonpolar surfaces, a topic correctly accounted for by the theory developed by Lum, Chandler and Weeks;[6] but it is concerned with the hydration of real nonpolar solutes, such as noble gases and aliphatic hydrocarbons.

It should be recognized that the trend of ΔG_{tr} as a function of the solute diameter calculated by S&D, and shown in Figure 1 of W, does not correspond to the experimental one. The experimental values of the thermodynamic functions associated with the hydration of the six noble gases and 10 aliphatic hydrocarbons at 25 °C are collected in Table 1, together with their customary hard-sphere diameters, σ.[7,8] The size of the solutes considered ranges from $\sigma = 2.63$ Å for helium to $\sigma = 7.22$ Å for *n*-octane and has to be compared with the size of a water molecule, $\sigma = 2.75$ Å (such σ values serve only to make clear, in an approximate way, how large are the solutes considered with respect to a water molecule, and their use does not imply that *n*-octane is a sphere in water). Since helium is the smallest solute available on the Earth, there are no real
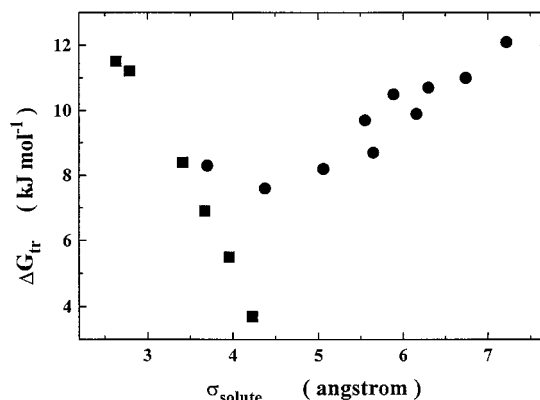
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Figure 1. Experimental values of the hydration Gibbs energy changes, ΔG_{tr}, at 25 °C, for noble gases (filled squares) and aliphatic hydrocarbons (filled circles) versus the solute's hard-sphere diameter, σ_{solute}.

TABLE 1: Thermodynamic Data for the Hydration Process of Noble Gases and Aliphatic Hydrocarbons at 25 °C, Corrected for the Ben-Naim Standard State[a]

	σ, Å	$\Delta C_{p,tr}$, J K^{-1} mol^{-1}	ΔH_{tr}, kJ mol^{-1}	ΔS_{tr}, J K^{-1} mol^{-1}	ΔG_{tr}, kJ mol^{-1}
He	2.63	122	1.8	−32.5	11.5
Ne	2.79	143	−1.3	−41.9	11.2
Ar	3.41	195	−9.6	−60.4	8.4
Kr	3.67	218	−13.0	−66.8	6.9
Xe	3.96	250	−16.8	−74.8	5.5
Rn	4.23	−	−19.1	−76.2	3.7
CH$_4$	3.70	218	−10.9	−64.4	8.3
C$_2$H$_6$	4.38	284	−17.2	−83.2	7.6
C$_3$H$_8$	5.06	332	−21.0	−97.9	8.2
i-C$_4$H$_{10}$	5.55	377	−21.9	−106.0	9.7
n-C$_4$H$_{10}$	5.65	390	−23.6	−108.3	8.7
C(CH$_3$)$_4$	5.89	486	−22.8	−111.7	10.5
n-C$_5$H$_{12}$	6.16	−	−26.0	−120.4	9.9
n-C$_6$H$_{14}$	6.30	−	−29.1	−135.5	10.7
n-C$_7$H$_{16}$	6.74	−	−31.6	−142.9	11.0
n-C$_8$H$_{18}$	7.22	−	−37.4	−166.0	12.1

[a] All the values are from ref 8, except those for the last three aliphatics that are from ref 7. A similar collection of experimental data, not corrected for the Ben-Naim standard state, is reported in Table 2 of ref 19.

solutes significantly smaller than a water molecule. This means that the first linear regression shown in Figure 1 of W has not a clear physical meaning, because it covers a size range devoid of real solutes.

The plot of the experimental ΔG_{tr} values versus σ_{solute} is reported in Figure 1: such a plot has a characteristic V-shape, as first pointed out by Abraham,[9] and completely contrasts with that calculated by S&D. It is worth noting that such shape does not qualitatively change by plotting the experimental ΔG_{tr} values versus the accessible surface area of the solutes (plot not shown). Experimental data indicate that, on increasing the size, the solubility of noble gases increases, whereas that of aliphatic hydrocarbons decreases. In a recent work,[8] we demonstrated that the V-shape plot can be interpreted and rationalized by means of the general equation:[10]

$$\Delta G_{tr} = \Delta G_c + E_a \qquad (1)$$

where ΔG_c represents the work of creating a cavity of suitable size to accommodate the solute molecule in the solvent and is always a positive quantity, while E_a is the work of turning on the solute−solvent attractive potential (i.e., van der Waals interactions) and is always a negative quantity. The solubility is determined by the balance of these two contrasting terms. We showed that[8] for noble gases, on increasing the size, the E_a term increases, in absolute value, more rapidly than the ΔG_c term, enhancing the solubility; while, for aliphatic hydrocarbons, on increasing the size, the ΔG_c term increases more rapidly than the E_a term, lowering the solubility.

The trend of ΔG_{tr} versus the solute diameter shown by S&D in Figure 1 of W corresponds, practically, to that of ΔG_c versus the solute diameter. In fact, the plot of ΔG_c versus $\sigma_{solute}/\sigma_{water}$, calculated by means of scaled particle theory,[11] and reported in Figure 2, qualitatively resembles Figure 1 of W. This is due to the fact that S&D, by using both the Widom test particle insertion method and a thermodynamic integration procedure, implicitly took into account the work of cavity creation related to the excluded volume effect upon solute insertion into water. The change in the slope of the ΔG_{tr} function calculated by S&D on increasing the solute diameter is similar to that of the work of cavity creation shown in Figure 2. In this regard it should be recognized that the trend of ΔG_c versus the solute diameter does not depend on the choice of scaled particle theory to calculate it, as demonstrated by detailed computer simulations.[12] Therefore, the change in the plot slope cannot be considered as a firm indication of a change in the solvation mechanism.

Actually, the problem is that S&D did not take correctly into account the contribution to ΔG_{tr} coming from E_a, the solute−water van der Waals interaction energy. They assumed that the well-depth in the Lennard-Jones potential ϵ_{LJ} is constant for all the nonpolar solutes considered, even though the solute diameter increases, and is equal to that of water.[1] This assumption is not physically correct. First, the value of ϵ_{LJ} is proportional to the molecular polarizability and increases with the molecular size.[13] Second, the customary value of ϵ_{LJ} for water is smaller than those for noble gases and aliphatic hydrocarbons, except helium and neon.[10,13] Several workers have stressed the fundamental role played by the solute−water van der Waals interactions in determining the solubility of noble gases and aliphatic hydrocarbons.[14] In particular, Jorgensen and co-workers[15] calculated that, at room temperature, E_a(kJ mol^{-1}) = −12.1 for CH_4, −20.1 for C_2H_6, −27.6 for C_3H_8, −32.7 for i-C_4H_{10}, −34.7 for n-C_4H_{10}, −36.0 for $C(CH_3)_4$, and −41.8 for n-C_5H_{12}. To gain perspective, such estimates have to be compared with the experimental values of ΔG_{tr} at 25 °C for the same solutes: ΔG_{tr}(kJ mol^{-1}) = 8.3 for CH_4, 7.6 for C_2H_6, 8.2 for C_3H_8, 9.7 for i-C_4H_{10}, 8.7 for n-C_4H_{10}, 10.5 for $C(CH_3)_4$, and 9.9 for n-C_5H_{12}.

Thus, S&D significantly underestimated the contribution to ΔG_{tr} coming from E_a. Such an underestimate is the cause of the fact that the trend of the calculated ΔG_{tr} function versus the solute diameter, shown in Figure 1 of W, does not qualitatively resemble the experimental one shown in Figure 1 of the present Comment. In addition, it has other strong consequences.

Also the trend of ΔH_{tr} and $T\Delta S_{tr}$ versus the solute diameter, shown in Figure 2 of W, does not correspond to the experimental one; the change of sign in ΔH_{tr} and ΔS_{tr}, from negative to positive, for solutes with a diameter not significantly larger than that of water does not exist. This can be verified by looking at the values listed in Table 1. For all the nonpolar solutes
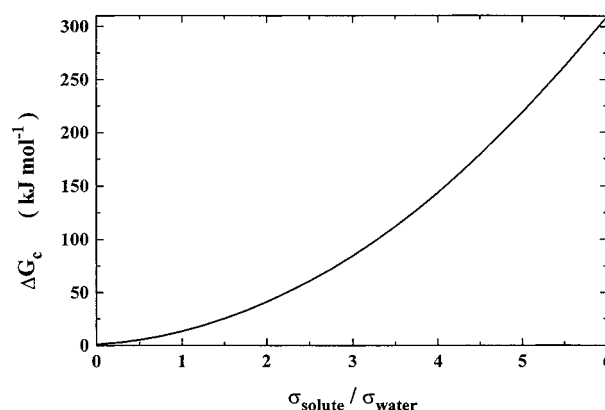

Figure 2. Trend of ΔG_c versus $\sigma_{solute}/\sigma_{water}$ at 25 °C for water, calculated by means of scaled particle theory. Data used for water: hard-sphere diameter, 2.75 Å; molar volume, 18.07 cm^3 mol^{-1}; volume packing density, 0.363.

considered, the values of ΔH_{tr} and ΔS_{tr} are negative and increase in magnitude with the size of the solute (the only exception is ΔH_{tr} = 1.8 kJ mol^{-1} for helium).

In general, the hydration enthalpy change is given by the sum of two contributions:[16] the solute−water van der Waals interactions, E_a, and the reorganization of H-bonds among water molecules in the hydration shell, ΔH_{reorg}. Figure 4 of W shows that the fraction of broken H-bonds in the hydration shell increases with the solute diameter, rendering ΔH_{reorg} an increasingly positive quantity. Therefore, S&D, having significantly underestimated the solute−water van der Waals interactions, found that ΔH_{tr} passes through zero at a solute diameter for which the ΔH_{reorg} contribution exactly balances their small E_a term. The problem is that the change of sign in ΔH_{tr} occurs for a solute whose size is less than twice that of water; such a solute cannot be considered significantly larger than a water molecule, even in 2D. We point out that, if the solute−water van der Waals interaction energy were correctly accounted for, being a negative and substantial quantity that increases in magnitude with solute size, the calculated ΔH_{tr} function should pass through zero at a far larger solute diameter. Clearly, since S&D obtained the ΔS_{tr} values by means of the relation $\Delta S_{tr} = (\Delta H_{tr} - \Delta G_{tr})/T$, the errors done in calculating ΔG_{tr} and ΔH_{tr} determined the wrong trend of ΔS_{tr} too.

Finally, the experimental $\Delta C_{p,tr}$ values are large positive, and increase with the solute diameter for all the nonpolar molecules for which reliable determinations exist (see Table 1).[8,17] Therefore, there is strong doubt on the validity of the S&D result that $\Delta C_{p,tr}$ should be zero as soon as the solute size is twice that of water (see Figure 3 of W). Again, such a size cannot be considered very large with respect to that of water molecules, even in 2D. In all probability the error in calculating ΔH_{tr} affected the results for $\Delta C_{p,tr}$.

To summarize the experimental data, we look at the hydration of neopentane, which is a nearly spherical molecule and has a molecular volume about 10 times larger than that of a water molecule. The neopentane molecule is large compared to that of water, but its hydration at 25 °C has $\Delta C_{p,tr}$ = 486 J K^{-1}mol^{-1}, ΔH_{tr} = −22.8 kJ mol^{-1}, ΔS_{tr} = −111.7 J K^{-1} mol^{-1}, and ΔG_{tr} = 10.5 kJ mol^{-1} (see Table 1). Thus, one wonders how large a spherical particle has to be in order to show positive values of ΔH_{tr} and ΔS_{tr} and a $\Delta C_{p,tr}$ of practically zero. Everyone knows that water molecules close to an extended planar nonpolar surface lose H-bonds; this geometrical fact was also confirmed using computer simulations.[18] Therefore, the question is: what

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is the size range for which the hydrophobic solvation mechanism changes? In other words: how large does a spherical particle have to be to be felt as flat by close by water molecules, rendering impossible the straddling mechanism? In our opinion the work of S&D did not address correctly this important topic; their result that the mechanism in 2D changes for solutes with a diameter less than twice that of water, is, at least, suspect.

All the above remarks are based exclusively on real experimental data. Clearly, a theoretical model of a phenomenon should not, in principle, fit the data, but should contain all the physics necessary to capture and explain the qualitative features and signatures of the phenomenon itself. The Mercedes-Benz model, even though 2D, is qualitatively correct for water. It should give qualitatively correct results also for hydrophobic solvation if all the relevant physical aspects are properly taken into account in the computer simulations. S&D, however, failed to do so because they did not give the correct weight to the van der Waals energetic interactions between water and nonpolar solutes.

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