On the Solubility of Aliphatic Hydrocarbons in 7 M Aqueous Urea

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Solubility measurements proved that, at 25 °C, methane and ethane are more soluble in water than in 7 M aqueous urea, whereas propane, *i*-butane, *n*-butane, and neopentane are more soluble in 7 M aqueous urea than in water. No convincing explanation of these experimental data has been provided up to now. An extension of an emerging theory of hydrophobic hydration is devised to account for the solubility of aliphatic hydrocarbons in 7 M aqueous urea. The conclusions reached are: (a) the work of cavity creation is always greater in 7 M aqueous urea than in water, contrasting the transfer; (b) the solute−solvent van der Waals interaction energy is always greater in magnitude in 7 M aqueous urea than in water, favoring the transfer. The latter contribution increases in magnitude with hydrocarbon size more rapidly than the difference in the work of cavity creation, explaining the existence of a threshold size for the solubility enhancement. The reorganization of H-bonds in both the solvent systems is a compensating process that does not affect the Gibbs energy change, but determines the positive sign of the transfer enthalpy and entropy changes for all hydrocarbons.

Introduction

The ability of urea to denature the native structure of globular proteins is well-known, but the mechanism of its action has not been definitely assessed.[1] To clarify the matter, several workers[2,3] investigated the transfer process of model compounds from water to aqueous solutions of high urea concentration. In particular, Wetlaufer and colleagues,[4] in the middle sixties, measured the solubilities, expressed on a molar concentration scale, of six aliphatic hydrocarbons in water and in 7 M aqueous urea to calculate the transfer Gibbs energy changes. Solubility measurements were performed in the temperature range 2−50 °C, and the transfer enthalpy and entropy changes were obtained by means of a van't Hoff analysis. The values of the thermodynamic functions at 25 °C, adopting the Ben-Naim standard state,[5] are reported in Table 1. The Ben-Naim standard quantities refer to the transfer from a fixed position in water to a fixed position in 7 M urea, using the molar concentration scale, and are denoted by a superscript filled circle. The Ben-Naim standard eliminates the volume effects present when a solute molecule is transferred between solvents having different densities and accounts solely for the solute−solvent coupling work. (At 25 °C the density is 0.99705 g cm^{-3} for water and 1.1044 g cm^{-3} for 7 M aqueous urea.)

The molar solubility at 25 °C of methane and ethane is lower in 7 M urea than in water, whereas that of propane, *i*-butane, *n*-butane, and neopentane is greater in 7 M urea than in water.[4] Therefore, the $\Delta G^\bullet$ values are positive for methane and ethane, but negative for the remaining four hydrocarbons. All the numbers, positive or negative, however, are small because the solubilities are similar in the two solvent systems: $\Delta G^\bullet = 0.8$ kJ mol^{-1} for methane and −0.7 kJ mol^{-1} for neopentane. Clearly, the data emphasize that the effects of urea on the solubility of alkanes in water are subtle and depend on the

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TABLE 1: Ben-Naim Standard Thermodynamic Quantities Associated with the Transfer of Six Aliphatic Hydrocarbons from H$_2$O to 7 M Aqueous Urea at 25 °C; They Come from Ref 4^a

	σ (Å)	$\Delta H^\bullet$ (kJ mol^{-1})	$\Delta S^\bullet$ (J K^{-1} mol^{-1})	$\Delta G^\bullet$ (kJ mol^{-1})
CH$_4$	3.70	5.4	15.3	0.8
C$_2$H$_6$	4.38	8.2	26.4	0.4
C$_3$H$_8$	5.06	7.2	24.3	−0.1
i-C$_4$H$_{10}$	5.55	6.5	23.3	−0.5
n-C$_4$H$_{10}$	5.65	7.8	27.8	−0.5
C(CH$_3$)$_4$	5.89	7.2	26.5	−0.7

^{a} The hard-sphere diameters of the six solutes are listed in the second column; they come from ref 14. *Note.* Wetlaufer and colleagues[4] estimated an overall precision of ±2% for their molar solubility determinations; this should give rise to an uncertainty in the $\Delta G^\bullet$ values of about ±0.1 kJ mol^{-1} at 25 °C.

hydrocarbon size. (The customary hard-sphere diameters of the alkanes considered are listed in the second column of Table 1.) In this respect, it is worth noting that the plot of the alkane solubility at 25 °C versus the solute size has a characteristic V-shape both in water and 7 M urea,[4,6] indicating that the two solvent systems should not be qualitatively different. Furthermore, both the enthalpy and entropy of transfer from water to 7 M urea are positive for all the six aliphatic hydrocarbons. It appears that entropy contributions favor the transfer, whereas enthalpy contributions contrast it. The rationalization of all such data should be a stringent test for any theoretical approach to the hydrophobicity puzzle,[7] but, at the best of our knowledge, an unambiguous interpretation has not been provided hitherto.

Actually, during the past 35 years, only two approaches[8,9] have been devised to account for the solubility data of Wetlaufer and colleagues in a convincing way. This paucity can be interpreted using the reasoning of Muller,[9] who wrote: "This may be due largely to a reluctance of interested workers to expose themselves to the risk of devastating criticism similar to that in a paper of Holzer and Emerson,[10] who pointed out

that applications of the concept of water structure promotion often involved qualitative arguments *sufficiently indeterminate so as to be capable of producing several contradictory conclusions.* Any model that is now to be considered viable must be cast in a form that allows specific numerical values to be calculated for at least a few observable properties so that it can be checked against reality."

The approach devised in this article fulfills this requirement, and is also free of problems related to the concept of water structure enhancement or destruction. It is grounded on a general theory of solvation,[11–14] and leads to a reliable explanation of the solubility data of Wetlaufer and colleagues.

Theory Section

From a theoretical point of view,[11–14] the transfer of a solute molecule from a fixed position in water to a fixed position in 7 M urea has to be dissected in the following subprocesses: (i) breaking solute−solvent interactions in H_2O; (ii) closing the cavity therein; (iii) creating a cavity in 7 M urea to accommodate the solute molecule; (iv) turning on the solute−solvent interactions in 7 M urea. Accordingly, the standard Gibbs energy change is given by the following relation:

$$\Delta G^{\bullet} = [\Delta G_c(7 \text{ M urea}) - \Delta G_c(H_2O)] + [E_a(7 \text{ M urea}) - E_a(H_2O)] = \Delta\Delta G_c + \Delta E_a \quad (1)$$

where ΔG_c, the work of cavity creation, and E_a, the average solute−solvent van der Waals interaction energy, represent the direct perturbation of each solvent system.[13,15] In response to direct perturbation, solvent molecules reorganize with associated enthalpy and entropy contributions.[15] For the latter we use the notation ΔH^h and ΔS^h because the reorganization involves a rearrangement of H-bonds in both H_2O and 7 M aqueous urea. Therefore, the standard transfer enthalpy and entropy changes are:

$$\Delta H^{\bullet} = [E_a(7 \text{ M urea}) - E_a(H_2O)] + [\Delta H^h(7 \text{ M urea}) - \Delta H^h(H_2O)] = \Delta E_a + \Delta\Delta H^h \quad (2)$$

$$\Delta S^{\bullet} = [\Delta S_x(7 \text{ M urea}) - \Delta S_x(H_2O)] + [\Delta S^h(7 \text{ M urea}) - \Delta S^h(H_2O)] = \Delta\Delta S_x + \Delta\Delta S^h \quad (3)$$

In eq 3, ΔS_x is the entropy contribution due to the excluded volume effect associated with cavity creation in the solvent; it is exactly related to the work of cavity creation:

$$\Delta S_x = -\Delta G_c/T \quad (4)$$

because ΔG_c is a measure of the probability that a certain region of space is devoid of solvent molecules.[16]

It is important to recognize that eqs 1−3 imply that the reorganization of H-bonds does not affect the standard Gibbs energy change because it is a compensating process in both solvent systems:

$$\Delta H^h = T\Delta S^h \quad (5)$$

as demonstrated by several scientists using different routes.[17] In particular, Lee[18] showed that compensation holds when the solute−solvent interactions are weak in comparison with the solvent−solvent interactions. This condition is fulfilled by aliphatic hydrocarbons in both H_2O and 7 M urea, because van der Waals interactions are weak with respect to H-bonds.

Calculation Procedure

The work of cavity creation is calculated by means of the following equation from scaled particle theory (SPT):[19,20]

$$\Delta G_c = RT[K_0 + K_1(\sigma_2/\sigma_1) + K_2(\sigma_2/\sigma_1)^2 + K_3(\sigma_2/\sigma_1)^3] \quad (6)$$

where: $K_0 = -\ln(1 - \xi)$; $K_1 = u = 3\xi/(1 - \xi)$; $K_2 = u (u + 2)/2$; $K_3 = \xi P v_1/RT$. In these relations R is the gas constant; ξ is the volume packing density of pure 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., $\xi = \pi\sigma_1^3 N_{Av}/6v_1$); P is the hydrostatic pressure over the liquid; σ_1 and σ_2 are the hard-sphere diameters of the solvent and solute molecules, respectively. For water we use $\sigma_{H_2O} = 2.75$ Å,[21] close to the location of the first peak in the oxygen−oxygen pair correlation function of liquid water,[22] $v_{H_2O} = 18.07$ cm³ mol⁻¹ at 25 °C, so that $\xi = 0.363$.

The fundamental point is that eq 6 is also applied to calculate ΔG_c in 7 M aqueous urea. We assume that 7 M aqueous urea, even though it is a binary solvent system, can be treated as a "uniform" solvent characterized by a single mean hard-sphere diameter and a single mean molar volume.[23] Specifically, we use the relation:

$$\sigma(7 \text{ M urea}) = x_{H_2O}\sigma_{H_2O} + x_{urea}\sigma_{urea} \quad (7)$$

where the molar fraction of water in 7 M urea $x_{H_2O} = 0.844$, and that of urea $x_{urea} = 0.156$; $\sigma_{H_2O} = 2.75$ Å, and σ_{urea} has to be properly selected.

Cabani and colleagues[24] reported that: (a) The van der Waals volume of urea is equal to 32.6 cm³ mol⁻¹, corresponding to 54.1 Å³ per molecule; this is the volume of a sphere of 4.7 Å diameter. (b) The partial molar volume of urea in water at 25 °C is equal to 44.2 cm³ mol⁻¹, corresponding to 73.4 Å³ per molecule; this is the volume of a sphere of 5.2 Å diameter. Therefore, we have lower and upper bounds for the hard-sphere diameter of urea. We deliberately fix $\sigma_{urea} = 5.0$ Å, in the middle of the allowed range. Inserting this value in eq 7, $\sigma(7 \text{ M urea}) = 3.10$ Å. In the same manner:

$$v(7 \text{ M urea}) = x_{H_2O}v_{H_2O} + x_{urea}v_{urea} \quad (8)$$

where $v_{H_2O} = 18.07$ cm³ mol⁻¹ and, in keeping with Muller,[9] the molar volume of crystalline urea $v_{urea} = 45.4$ cm³ mol⁻¹ at 25 °C. Therefore, $v(7 \text{ M urea}) = 22.3$ cm³ mol⁻¹. The obtained estimates of $\sigma(7 \text{ M urea})$ and $v(7 \text{ M urea})$ allow the calculation of the mean volume packing density of 7 M urea, $\xi(7 \text{ M urea}) = 0.421$. These simple computations show that the solvent system 7 M aqueous urea has both a mean hard-sphere diameter and a mean volume packing density greater than those of water.

The physical validity of our approach and the reliability of eqs 7 and 8 are supported by the following data: (a) There is, practically, no volume change associated with the mixing of urea and water.[25] (b) Neutron-scattering measurements[26] unequivocally show that urea does not affect both the oxygen−oxygen and hydrogen−hydrogen pair correlation functions of water, confirming the indications of previous IR and NMR investigations,[27] and of molecular dynamics simulations.[28,29] Specifically, Finney[30] wrote: "neutron data show that the urea molecules seem to fit quite comfortably into the water structure, without significantly ordering or disordering it. Concepts of

TABLE 2: Gibbs Energy Cost of Cavity Creation[a]

	$\Delta G_c(H_2O)$	$E_a(H_2O)$	$E_a^*(H_2O)$	ΔG_c(7 M urea)	E_a(7 M urea)	E_a^*(7 M urea)
CH_4	21.1	−12.7	−12.1	23.9	−14.7	−14.0
C_2H_6	27.8	−20.2	−20.1	31.6	−23.6	−23.3
C_3H_8	35.5	−27.2	−27.6	40.3	−32.1	−32.0
i-C_4H_{10}	41.7	−32.3	−32.7	47.3	−38.4	−37.9
n-C_4H_{10}	43.0	−34.2	−34.7	48.8	−40.5	−40.2
$C(CH_3)_4$	46.3	−36.0	−36.0	52.4	−42.8	−41.8

[a] Calculated by means of SPT, in water and 7 M urea; solute−solvent van der Waals interaction energy in water and 7 M urea, obtained using the relation $E_a = \Delta G^\bullet - \Delta G_c$, where $\Delta G^\bullet$ is the solvation Gibbs energy in water or 7 M urea. $E_a^*(H_2O)$ and E_a^*(7 M urea) are the values calculated by Jorgensen and co-workers,[34] and by means of eq 9, respectively. All the entries are in kJ mol^{-1} units.

structure breaking and structure making ... are not supported by the neutron scattering results, which are direct measurements of structure." In this respect one should bear well in mind the ability of water molecules to form H-bonds in very different geometrical configurations, as a consequence of their 2−2 tetrahedral H-bonding functionalities. Furthermore, Linse, Wallqvist, and colleagues,[29] on the basis of a sophisticated theoretical investigation, concluded: "The large attractive energy makes urea resemble, both structurally and energetically, a water-like particle behaving similarly to a solvated water dimer and presenting roughly six H-bonds to the surrounding liquid water."

Results

The values of ΔG_c at 25 °C, calculated using eq 6, in water and 7 M urea are reported in the second and fifth columns, respectively, of Table 2. The estimates are larger in 7 M urea than in water: for methane, $\Delta G_c = 21.1$ kJ mol^{-1} in H_2O against 23.9 kJ mol^{-1} in 7 M urea; for neopentane, $\Delta G_c = 46.3$ kJ mol^{-1} in H_2O against 52.4 kJ mol^{-1} in 7 M urea. According to SPT,[13,14,19,20] the magnitude of ΔG_c is determined by two geometrical factors of the solvent: the hard-sphere diameter of its molecules, σ; and its volume packing density, ξ. ΔG_c increases on decreasing the value of σ, and on increasing the value of ξ. The addition of urea to water to make a 7 M solution increases both the mean hard-sphere diameter of the solvent (3.10 Å for 7 M urea vs 2.75 Å for H_2O), and the mean volume packing density (0.421 for 7 M urea vs 0.363 for H_2O). The two things affect ΔG_c in an opposite way, but the second one prevails, rendering ΔG_c in 7 M urea larger than in water. This finding is qualitatively correct from a physicochemical point of view, because the addition of urea to water determines an increase of the surface tension,[31] and the direct proportionality between the work of cavity creation in a solvent and its surface tension is well established.[32] Also, computer simulations indicate that the work of cavity creation is greater in 7 M urea than in water.[33]

The values of E_a in water and 7 M urea are determined in a "hybrid manner" using the relation $E_a = \Delta G^\bullet - \Delta G_c$, where $\Delta G^\bullet$ are the experimental data for the two solvation processes: gas → H_2O and gas → 7 M urea. The values of $\Delta G^\bullet$ (gas → H_2O) and those of $\Delta G^\bullet$ (gas → 7 M urea) come from the work of Wetlaufer and colleagues[4]; according to Ben-Naim,[5] $\Delta G^\bullet = RT \cdot \ln(C_g/C_l)$, where C_g and C_l are the molar concentrations of the hydrocarbon in the gas phase and in the liquid, respectively. (Note that, on the basis of the conditions adopted by Wetlaufer and colleagues,[4] $C_g = 0.0409$ mol L^{-1} at 25 °C for all hydrocarbons.) The E_a values, determined in the "hybrid manner", are reported in the third and sixth columns, respectively, of Table 2. It proves that E_a is larger, in absolute value, in 7 M urea than in water: for methane, $E_a = -12.7$ kJ mol^{-1} in H_2O against −14.7 kJ mol^{-1} in 7 M urea; for neopentane, $E_a = -36.0$ kJ mol^{-1} in H_2O against −42.8 kJ mol^{-1} in 7 M

TABLE 3: Values of $\Delta\Delta G_c$, ΔE_a, $\Delta\Delta H^h$, $\Delta\Delta S_x$, and $\Delta\Delta S^h$ Associated with the Transfer of the Six Aliphatic Hydrocarbons from Water to 7 M Urea at 25 °C[a]

	$\Delta\Delta G_c$ (kJ mol^{-1})	ΔE_a (kJ mol^{-1})	$\Delta\Delta H^h$ (kJ mol^{-1})	$\Delta\Delta S_x$ (J K^{-1} mol^{-1})	$\Delta\Delta S^h$ (J K^{-1} mol^{-1})
CH_4	2.8	−2.0	7.4	−9.4	24.7
C_2H_6	3.8	−3.4	11.6	−12.8	39.2
C_3H_8	4.8	−4.9	12.1	−16.1	40.4
i-C_4H_{10}	5.6	−6.1	12.6	−18.7	42.0
n-C_4H_{10}	5.8	−6.3	14.1	−19.5	47.3
$C(CH_3)_4$	6.1	−6.8	14.0	−20.5	47.0

[a] The $\Delta\Delta H^h$ estimates are obtained performing the difference $\Delta H^\bullet - \Delta E_a$; those of $\Delta\Delta S^h$ performing the difference $\Delta S^\bullet - \Delta\Delta S_x$, where the $\Delta\Delta S_x$ values are calculated using eq 4.

urea. To confirm this finding, the values of E_a calculated for aliphatic hydrocarbons in TIP4P water by Jorgensen and co-workers,[34] using Monte Carlo simulations, are listed in the fourth column of Table 2; the latter are very close to those obtained in the "hybrid manner" (compare the third and fourth columns of Table 2). In addition, Jorgensen's values of E_a in H_2O can be used to estimate E_a in 7 M urea according to the following relation:

$$E_a(\text{7 M urea}) = E_a(H_2O) \cdot \xi(\text{7 M urea})/\xi(H_2O) \qquad (9)$$

whose physical reliability is grounded in the general expression of the solute−solvent van der Waals interaction energy,[12,20] which indicates that E_a is directly proportional to the solvent packing density ξ. The values calculated by means of eq 9 are listed in the seventh column of Table 2, and are close to those obtained in the "hybrid manner" and reported in the sixth column of Table 2. Therefore, we can conclude that alkane−solvent van der Waals interactions are stronger in 7 M urea than in water. This finding is qualitatively correct considering the large polarizability of the urea molecule, due to the six π electrons, practically delocalized over the entire molecule, and its very large dipole moment (i.e., the addition of urea to water causes a significant increase of the dielectric constant[35]).

The solubility of aliphatic hydrocarbons in 7 M urea with respect to water is governed by the balance between $\Delta\Delta G_c$ and ΔE_a. The first quantity is positive, whereas the second one is negative; however, both are not large and increase, in absolute value, with the size of alkanes, remaining close in magnitude (see the second and third columns of Table 3). In fact, the solubilities are similar in the two solvents for all the alkanes considered; the differences are small and due to subtle effects. For methane, $\Delta\Delta G_c = 2.8$ kJ mol^{-1} and $\Delta E_a = -2.0$ kJ mol^{-1}, so that it is less soluble in 7 M urea than in water; for neopentane, $\Delta\Delta G_c = 6.1$ kJ mol^{-1} and $\Delta E_a = -6.8$ kJ mol^{-1}, so that it is more soluble in 7 M urea than in water. The analysis shows that ΔE_a increases in magnitude with hydrocarbon size more rapidly than $\Delta\Delta G_c$, leading to the existence of a threshold size for the solubility enhancement of aliphatic hydrocarbons due to urea.

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J. Phys. Chem. B, Vol. 105, No. 13, 2001 **2635**

Therefore, the question is: Why is the increase in the magnitude of ΔE_a, passing from methane to neopentane, greater than that of $\Delta\Delta G_c$? We suggest the following explanation. In going from H_2O to 7 M urea, the increase of ΔG_c is a simple consequence of the change in the packing properties of the solvent system. In E_a, the increase in magnitude is not only determined by the change in the packing properties of the solvent system, but it is also caused by direct contact interactions between the solute and urea molecules in the hydration shell. The number of urea molecules located, by chance, in the hydration shell of an aliphatic hydrocarbon increases with the size of the latter, determining the behavior of ΔE_a. In this respect, eq 9 cannot be considered fully satisfactory because it assumes $E_a \propto \xi$. In fact, even though it gives estimates for E_a in 7 M urea that are larger than those in water, the corresponding ΔE_a values are, for all hydrocarbons, smaller in magnitude than those of $\Delta\Delta G_c$ [i.e., calculate $E_a*(7\ M\ urea) - E_a*(H_2O)$ in Table 2, and compare such values with those of $\Delta\Delta G_c$ in the second column of Table 3].

We turn now to the analysis of the transfer enthalpy and entropy changes. The $\Delta\Delta S_x$ values are calculated using eq 4, whereas those of $\Delta\Delta H^h$ and $\Delta\Delta S^h$ are obtained performing the differences $\Delta H^\bullet - \Delta E_a$ and $\Delta S^\bullet - \Delta\Delta S_x$, respectively. Such estimates of $\Delta\Delta H^h$, $\Delta\Delta S_x$, and $\Delta\Delta S^h$ are listed in the fourth, fifth, and sixth columns, respectively, of Table 3. Looking at such numbers, it is evident that $\Delta H^\bullet$ and $\Delta S^\bullet$ are dominated by the contributions arising from the reorganization of H-bonds which are positive for all the solutes considered: $\Delta\Delta H^h > |\Delta E_a|$ and $\Delta\Delta S^h > |\Delta\Delta S_x|$. Because the reorganization of H-bonds gives rise to small positive values of ΔH^h and ΔS^h for the solvation of aliphatic hydrocarbons in water,[13-15] the finding above implies that such quantities are positive and significantly larger in 7 M urea. H-bond reorganization in the hydration shell is an endothermic process and leads to an entropy increase in both water and 7 M urea. However, the rupture of H-bonds (or better, their distortion from linearity) is greater in 7 M aqueous urea than in H_2O. This is surely related to the geometrical constraints imposed by the presence of the solute molecule on the solvent molecules forming the hydration shell. When the latter are exclusively water molecules, the so-called straddling mechanism is the optimum way to avoid the loss of H-bonds.[7] However, when there are also urea molecules, the straddling mechanism cannot function as well as in pure water because the planarity of urea molecules does not allow the formation of all the possible H-bonds. This conclusion agrees with the claim by Muller,[9] and with the results of molecular dynamics simulations performed by Laidig and Daggett.[36] Clearly, the emerging picture of H-bond reorganization does not resemble the iceberg or clathrate formation proposed by various authors,[37,38] but is the correct one, because it is in line with the results from neutron-scattering and X-ray absorption spectroscopy measurements.[39,40]

Discussion

The analysis performed indicates that, even though the alkane−solvent van der Waals interactions are stronger in 7 M urea than in water, the transfer enthalpy change is positive because the contribution from H-bond reorganization proves to be large, positive, and dominant. Similarly, even though the entropy decrease due to the excluded volume effect for cavity creation is larger in 7 M urea than in water, the transfer entropy change is positive because the contribution from H-bond reorganization is large, positive, and dominant. However, the solubility is not affected by the reorganization of H-bonds

because the latter is a compensating process that does not modify the Gibbs energy balance. This is influenced by alkane-solvent van der Waals interactions which favor the transfer from water to 7 M urea, and by the excluded volume entropy contributions which contrast the transfer from water to 7 M urea. The subtle balance of these two terms governs the transfer process. The explanation of the solubility data of Wetlaufer and colleagues emerging from our approach appears sound.

In general, the application of SPT to solvents such as water and 7 M aqueous urea may seem questionable. However, Reiss[19] suggested the following model for a liquid. The attractive part of the intermolecular potential determines the density of the liquid. Once the density is fixed, the liquid can be regarded as an assembly of hard spheres confined within a defined volume and proves to be amenable to SPT treatment. This is done using the experimental values for the density and molecular size of the liquid solvent in SPT equations. Such a model corresponds to the physical principles underlying the famous and successful Weeks, Chandler, Andersen theory of liquids.[41] Its validity implies that packing and excluded volume effects play a pivotal role in most liquid properties. Solvation is one of them, as pointed out unequivocally by both theoretical approaches[12,13] and computer simulations.[42] As a consequence, the work of cavity creation in a solvent is a fundamental quantity and has to be properly taken into account.

A clear weakness of the present analysis is the assumption that 7 M urea, even though a binary solvent system, can be treated as a "uniform" solvent, characterized by a mean hard-sphere diameter and a mean molar volume. However, neutron-scattering measurements[26] and computer simulations[29] lend support to the reliability of our assumption because they show that urea does not alter the water structure and can be regarded as a water dimer. It is well established that SPT calculations are very sensitive to the choice of the hard-sphere diameters for both the solvent and solute molecules.[43] Even though it is a simplification to assign a single size to molecules that are not spherical, we use the customary values of hard-sphere diameter for both water and hydrocarbons, and a reasonable value for urea. In addition, the uncertainty in the values of σ_2 almost cancels out for a transfer process between two liquids; and the uncertainty in the hard-sphere diameter of water should affect the value of ΔG_c in water and 7 M aqueous urea in a similar way, because both the two solvent systems contain mainly water molecules.

It should be recognized that the approach devised by Frank and Franks[8] to explain the solubility data of Wetlaufer and colleagues leads to several contradictions and inconsistencies. It is grounded on the following assumptions: (a) Liquid water is a mixture of dense and bulky component microphases; (b) urea can dissolve only in the dense microphase, reducing the amount of bulky component and resulting a structure breaker; (c) the transfer enthalpy change is 6.7 kJ mol^{-1} for all the hydrocarbons. However, experiments and computer simulations do not support the existence in liquid water of dense and bulky microphases in equilibrium between each other.[44] Neutron-scattering measurements point out unequivocally that urea does not break the water structure;[26] the same result emerges from extensive molecular dynamics computer simulations.[29,45] The parameters selected to fit the solubility data led Frank and Franks to state that propane "does not make but breaks structure when it dissolves", in contrast with the original proposal by Frank and co-workers[37] that hydrocarbons are structure makers. However, it should not be forgotten that the approach by Frank

and Franks dates back to 1968, and in the meantime, the understanding of aqueous solutions has increased immensely.

Muller[46] proposed a simple and appealing mixture model to rationalize some puzzling features of hydrophobic hydration. He did not assume the existence of dense and bulky microphases, but he distinguished the hydration shell region surrounding the nonpolar solute molecules from the bulk of liquid water. The H-bonds, the fundamental actors of the Muller's model, populate two energy states that are different passing from the bulk to the hydration shell. To explain the solubility data of Wetlaufer and colleagues, Muller[9] further assumed that: (a) urea does not directly affect the H-bonding between water molecules, but its influence is simply due to space occupation, by chance, in the hydration shell; (b) the contribution of van der Waals interactions to the transfer of alkanes from water to 7 M urea is unfavourable. [See eq 11 of Muller's work, and note that, without the ad hoc introduction of such an equation, the model calculations of Muller were not able to reproduce the solubility data.] However, urea interacts favorably and strongly with water molecules as emphasized by its very good solubility in liquid water[47] and by the increase in surface tension[31] and dielectric constant[35] caused by its addition to liquid water. Simple but well-founded arguments lead to the conclusion that alkane−solvent van der Waals interactions are stronger in 7 M aqueous urea than in water, so that their contribution to the transfer has to be favorable.

The excluded volume effect caused by the creation of a cavity to accommodate the solute molecule in a solvent was completely neglected by Frank and Franks and by Muller. However, it is generally recognized that a liquid solvent is a condensed phase of the matter and a cavity has to be created to insert a solute molecule.[11−14] The excluded volume effect needs to be taken into account by any theoretical model claiming to rationalize hydrophobic hydration in molecular terms. Such concerns indicate that both Frank and Franks and Muller grounded their approaches on a series of assumptions that proved to be unreliable from a physicochemical point of view.

Clearly, it is not a simple task to assess the correctness of a theoretical approach; the ability to reproduce a limited set of experimental data cannot be considered a robust proof. However, the approach developed in this article is the logical extension of a general theory of solvation,[12,13] that has been successfully applied to rationalize the hydration thermodynamics of both nonpolar and polar solutes.[14,15,48] It makes use of simplifying assumptions, but it leads to a reliable physicochemical explanation of an unsettled question. The transfer from water to 7 M aqueous urea of aliphatic hydrocarbons is governed by the balance between the difference in the work of cavity creation in the two solvents, a term contrasting the process, and the difference in the solute−solvent van der Waals interaction energy, a term favoring the process. The reorganization of H-bonds between solvent molecules in the hydration shell is a compensating process that does not affect the transfer Gibbs energy change. The fundamental point is that such an explanation is in line with those emerging from the other applications of the theory, confirming its general validity and consistency.

References and Notes

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