# Entropy Convergence in the Hydration Thermodynamics of *n*-Alcohols

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Using experimental data from the literature, entropy convergence in the hydration thermodynamics of *n*-alcohols is shown to occur at about 125 °C. The phenomenon is reproduced in a more-than-qualitative manner by means of a theoretical approach that accounts for the entropy contributions associated with (a) creation of a cavity in water, (b) turning on solute−water van der Waals interactions, and (c) turning on the solute−water H-bonding potential. The density of water and the effective size of water molecules with their temperature dependence play the pivotal role for the occurrence of entropy convergence, together with the property of the alcohol hydroxyl group to form the same number of H-bonds with water molecules regardless of the length of the alkyl chain.

## Introduction

The phenomenon of entropy convergence was put forward by Privalov[1] in the realm of protein unfolding thermodynamics in his review of 1979. Entropy convergence refers to the finding that entropy change curves versus temperature for a series of homologous compounds undergoing the same physicochemical process (i.e., transfer from the pure liquid phase to water, transfer from the gas phase to water, and transfer from the hydrophobic core of a globular protein to the water contact) cross each other and reach the same solute-independent value at a single temperature, $T_S^*$, called the entropy convergence temperature. The first tentative explanation was provided by Baldwin[2] in 1986, on the basis of the entropy convergence characterizing the transfer of hydrocarbons from the pure liquid phase to water. The transfer entropies converged at $T_S^* \cong 386$ K, where their value is close to zero. It was then shown that entropy convergence at $T_S^* \cong 386$ K was a general feature of several processes whose common property is the transfer of nonpolar moieties to water.[3] This finding raised much interest on entropy convergence because there was the hope that a rationalization of this phenomenon could provide a key to unravel the subtleties of protein folding/unfolding thermodynamics.[4−7] Actually, the availability of larger data sets has pointed out that entropy convergence does not occur in the unfolding thermodynamics of globular proteins.[8] On the other hand, it has been shown unequivocally that entropy convergence is a real phenomenon in the hydration (gas-to-water transfer) of noble gases and hydrocarbons.[9] It should be interesting to verify if entropy convergence occurs in the hydration thermodynamics of polar solutes such as *n*-alcohols, whose hydroxyl group interacts strongly with water molecules.

Such an attempt was first performed by Murphy[10] in 1994 by constructing an MPG (after Murphy, Privalov, and Gill[3]) entropy plot, a plot of the total hydration entropy change, $\Delta S^\bullet$, versus the total hydration heat capacity change, $\Delta C_p^\bullet$, at a single temperature, 25 °C, for the hydration of the first eight *n*-alcohols (the superscript filled circle indicates a Ben-Naim standard

quantity[11]). When there is entropy convergence, this plot is a straight line whose slope provides the value of convergence temperature.[3,4] The MPG entropy plot for the first eight *n*-alcohols does not give a straight line with the statistical robustness necessary to conclude that entropy convergence occurs (i.e., the linear correlation coefficient $r = -0.9898$ for eight points). In this respect, one has to consider that the best way to assess the existence of entropy convergence is to construct a plot of $\Delta S^\bullet$ versus temperature for several solutes and to observe the crossing of all functions at a single temperature. This is the procedure adopted in the present work.

Values of $\Delta C_p^\bullet$ for ethanol, *n*-propanol, *n*-butanol, and *n*-pentanol over the temperature range 5−125 °C were determined by Makhatadze and Privalov.[12] The group additivity contributions computed by these authors allow the calculation of $\Delta C_p^\bullet$ also for methanol, *n*-hexanol, *n*-heptanol, and *n*-octanol. By using these hydration heat capacity data in conjunction with the experimental values of $\Delta H^\bullet$, $\Delta S^\bullet$, and $\Delta G^\bullet$ at 25 °C for all eight *n*-alcohols,[13,14] the latter thermodynamic functions can be calculated over the temperature range 5−125 °C. These values, listed in Table 1 of the Supporting Information, show some general features valid for all eight *n*-alcohols: (a) the values of $\Delta G^\bullet$ are large and negative and increase with increasing temperature; (b) the values of $\Delta H^\bullet$ and $\Delta S^\bullet$ are large and negative and increase substantially with temperature; (c) the values of $\Delta C_p^\bullet$ are large and positive and decrease monotonically as the temperature is raised, except for methanol and ethanol above 75 °C. It is worthwhile to note that large and negative $\Delta S^\bullet$ values and large and positive $\Delta C_p^\bullet$ values are a feature shared also by the hydration of nonpolar molecules.[15,16]

The fundamental point is that the plot of $\Delta S^\bullet$ versus temperature for the eight *n*-alcohols shows the occurrence of entropy convergence at about 125 °C, excluding methanol (see Figure 1). At the convergence temperature $T_S^* \cong 125$ °C, $\Delta S^\bullet$ is large and negative, amounting to about $-45$ J K$^{-1}$ mol$^{-1}$. This is an important finding because it emphasizes that entropy convergence in aqueous solution occurs not only for the hydration of nonpolar compounds, such as noble gases and hydrocarbons, but also for the hydration of polar compounds such as *n*-alcohols, which are engaged in H-bonds with water

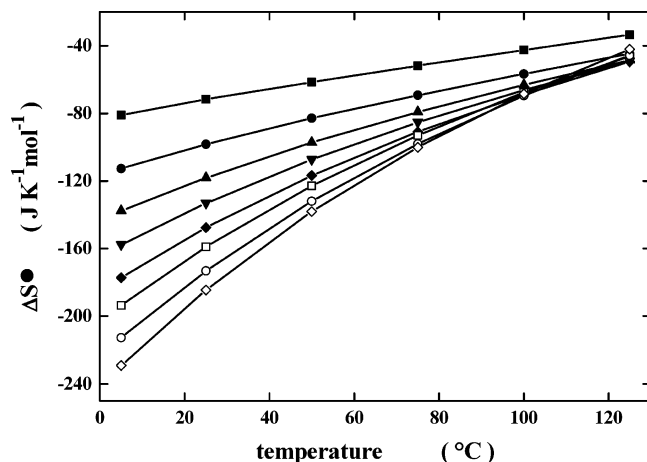* Phone: +39/0824/305133. Fax: +39/0824/23013. E-mail: graziano@unisannio.it.

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**Figure 1.** Plot of $\Delta S^{\bullet}$ versus temperature for the first eight *n*-alcohols: methanol (filled squares); ethanol (filled circles); *n*-propanol (filled up-triangles); *n*-butanol (filled down-triangles); *n*-pentanol (filled diamonds); *n*-hexanol (open squares); *n*-heptanol (open circles); *n*-octanol (open diamonds).

molecules. The rationalizations so far provided for the occurrence of entropy convergence in water account solely for the entropy contribution due to cavity creation (i.e., insertion into water of a hard sphere solute), in the assumption that turning on nonpolar compound—water attractive interactions is a purely energetic process that does not afford any entropy contribution.[9,17−19] The latter assumption cannot be considered valid for the hydration of polar compounds such as *n*-alcohols and should be rejected.

In the present work, it is shown that the occurrence of entropy convergence in the hydration thermodynamics of *n*-alcohols can be more-than-qualitatively reproduced by considering $\Delta S^{\bullet}$ as the sum of three terms: (a) the entropy contribution associated with cavity creation in water, (b) the entropy contribution associated with the structural reorganization of water molecules upon turning on the alcohol—water van der Waals attractions, and (c) the entropy contribution associated with the orientational restriction of the water molecules around the hydroxyl group as a consequence of H-bond formation.

**Theory Section**

According to Ben-Naim,[11] hydration refers to the transfer of a solute molecule from a fixed position in the ideal gas phase to a fixed position in water at constant temperature and pressure. It corresponds to inserting an external perturbing potential, $\Psi(\mathbf{X})$, where $\mathbf{X}$ is a vector representing a single configuration of the $N$ molecules of water.[20] On the basis of Widom's potential distribution theorem,[21] the Ben-Naim standard Gibbs energy change is

$$\Delta G^{\bullet} = -RT \ln\langle\exp[-\Psi(\mathbf{X})/RT]\rangle_{\mathrm{p}} \qquad (1)$$

where the subscript p means that the ensemble average is performed over the pure solvent configurations, assuming an NPT ensemble. In other words, in performing the ensemble average in eq 1, one has to consider the configurations of the system before the insertion of the perturbing potential, so that the Boltzmann weights in the average do not include $\Psi(\mathbf{X})$, that acts as a ghost.

In general, the insertion of a solute molecule in a solvent requires the exclusion of the solvent molecules from the region of space that will be occupied by the solute because a liquid is a condensed state of the matter.[22] In addition, for the insertion

of alcohols in water, it may be useful to consider that the alcohol—water interaction potential consists of two contributions: the van der Waals attractions and the H-bonding potential. On this basis, simple physical considerations suggest that the perturbing potential has to be factorized in the following manner:[20]

$$\exp[-\Psi(\mathbf{X})/RT] = \zeta(\mathbf{X}) \exp[-\psi_{\mathrm{a,vdW}}(\mathbf{X})/RT] \times$$
$$\exp[-\psi_{\mathrm{a,H\text{-}bond}}(\mathbf{X})/RT] \quad (2)$$

where $\zeta(\mathbf{X})$ can assume only values of 1 or zero depending on whether there is a suitable cavity to host the solute molecule in the given solvent configuration; $\psi_{\mathrm{a,vdW}}(\mathbf{X})$ represents the van der Waals attractions, and $\psi_{\mathrm{a,H-bond}}(\mathbf{X})$ represents the H-bonding potential between the inserted alcohol molecule and the surrounding water molecules. By means of eq 2, the $\Delta G^{\bullet}$ expression becomes

$$\Delta G^{\bullet} = -RT \ln\langle\zeta(\mathbf{X})\rangle_{\mathrm{p}} - RT \ln\langle\exp[-\psi_{\mathrm{a,vdW}}(\mathbf{X})/RT]\rangle_{\mathrm{c}} -$$
$$RT \ln\langle\exp[-\psi_{\mathrm{a,H\text{-}bond}}(\mathbf{X})/RT]\rangle_{\mathrm{s}} \quad (3)$$

where the subscript c means that the ensemble average is performed over the solvent configurations possessing a suitable cavity to host the solute and the subscript s means that the ensemble average is performed over the solvent configurations possessing the suitable cavity occupied by the solute molecule which interacts by means of van der Waals attractions with surrounding water molecules. Equation 3 indicates that $\Delta G^{\bullet}$ is the sum of three terms:

$$\Delta G^{\bullet} = \Delta G_{\mathrm{c}} + \Delta G_{\mathrm{a}}(\mathrm{vdW}) + \Delta G_{\mathrm{a}}(\mathrm{H\text{-}bond}) \qquad (4)$$

where $\Delta G_{\mathrm{c}}$ is the reversible work of cavity creation, $\Delta G_{\mathrm{a}}(\mathrm{vdW})$ is the reversible work of switching on van der Waals attractions, and $\Delta G_{\mathrm{a}}(\mathrm{H\text{-}bond})$ is the reversible work of switching on the H-bonding potential. Clearly, eqs 3 and 4 do not imply additivity of independent contributions: the alcohol—water van der Waals attractions are turned on given that the cavity has already been created, and the alcohol—water H-bonding potential is turned on given that both the cavity has already been created and the van der Waals attractions have already been switched on.[23,24]

On the basis of eq 4, the Ben-Naim standard entropy change associated with the hydration of *n*-alcohols is given by

$$\Delta S^{\bullet} = -(\partial\Delta G^{\bullet}/\partial T)_{\mathrm{P}} = \Delta S_{\mathrm{c}} + \Delta S_{\mathrm{a}}(\mathrm{vdW}) + \Delta S_{\mathrm{a}}(\mathrm{H\text{-}bond})$$
$$(5)$$

where the physical meaning of the three terms on the right-hand side has to be clarified. Adopting the Ben-Naim standard, the solute molecule is at a fixed position in the liquid and only changes in the accessibility of its internal degrees of freedom upon the gas-to-water transfer can provide an entropy contribution.[25,26] The latter contribution, however, is usually neglected because it is small in comparison to the entropy contributions arising from the reorganization of water molecules upon solute insertion. Thus, one assumes that all of $\Delta S^{\bullet}$ is caused by the reorganization of water molecules, even though this may be a defective assumption in the case of *n*-alcohols for the presence of the hydroxyl group.[26]

Moreover, it is important to make a further deepening. According to a fundamental theorem of statistical mechanics,[27] the reversible work to create a cavity of a given diameter, $\sigma_{\mathrm{c}}$,

in a liquid is exactly related to the probability of finding zero molecules in such a volume:

$$\Delta G_c = -RT \ln p_0(\sigma_c) = -RT \ln \langle \zeta(\sigma_c) \rangle_P \qquad (6)$$

where $p_0(\sigma_c)$ is the probability that a spherical region of diameter at least equal to $\sigma_c$, centered at an arbitrary position, does not contain solvent molecules (the position of the cavity has to be fixed but arbitrarily in the liquid volume because the liquid density is uniform under equilibrium conditions). Clearly, the probability $p_0(\sigma_c)$ corresponds exactly to the ensemble average value of the function $\zeta$ defined above. Direct application of equilibrium thermodynamics to eq 6 leads to[28]

$$\Delta S_c = -(\partial \Delta G_c / \partial T)_P = R \ln \langle \zeta(\sigma_c) \rangle_P +$$
$$RT[\partial \ln \langle \zeta(\sigma_c) \rangle_P / \partial T] = \Delta S_{c,xv} + \Delta S_{c,sr} \quad (7)$$

The entropy change due to cavity creation consists of two contributions. The first one on the right-hand side of eq 7, $\Delta S_{c,xv} = -\Delta G_c/T$, accounts for the selection of the solvent configurations containing the desired cavity and represents the contribution due to the excluded volume effect (i.e., the subscript xv stands for excluded volume). The second one, $\Delta S_{c,sr} = \Delta H_c/T$, accounts for the structural reorganization of solvent molecules around the cavity (i.e., the subscript sr stands for structural reorganization), and it proves to be exactly given by the ratio of the enthalpy change upon cavity creation over the temperature (i.e., this entropy term is perfectly compensated for by a corresponding enthalpy term).[28] It is worth noting that, in every solvent, the first contribution is a large and negative quantity.

The entropy contributions associated with turning on both the alcohol−water van der Waals attractions and H-bonding potential are due to a structural reorganization of water molecules manifested in a rearrangement of H-bonds.[20,24] As a consequence, $\Delta S_a(\text{vdW}) = \Delta S_{a,sr}(\text{vdW})$ and $\Delta S_a(\text{H-bond}) = \Delta S_{a,sr}(\text{H-bond})$, so that the overall entropy change associated with the hydration of $n$-alcohols is given by

$$\Delta S^\bullet = \Delta S_{c,xv} + \Delta S_{c,sr} + \Delta S_{a,sr}(\text{vdW}) + \Delta S_{a,sr}(\text{H-bond}) \quad (8)$$

Now, a computational procedure has to be devised to calculate the four terms on the right-hand side of eq 8 with the aim to reproduce the occurrence of entropy convergence in the hydration thermodynamics of $n$-alcohols.

**Calculation Procedure**

Estimates of $\Delta G_c$ as a function of temperature are calculated by means of scaled particle theory,[29,30] SPT, because, even though SPT was constructed for hard sphere fluids, its application to water has provided reliable and consistent results.[20,31,32] By assuming that the cavity size, $\sigma_c$, is the diameter of the spherical region from which any part of any solvent molecule is excluded, the SPT relationship for $\Delta G_c$ is the following:[30]

$$\Delta G_c = RT[K_0 + K_1(\sigma_c/\sigma_1) + K_2(\sigma_c/\sigma_1)^2 + K_3(\sigma_c/\sigma_1)^3] \quad (9)$$

where $K_0 = -\ln(1 - \xi)$, $K_1 = u = 3\xi/(1 - \xi)$, $K_2 = u(u + 2)/2$, and $K_3 = \xi P v_1/RT$. In these relations, $R$ is the gas constant; $\xi$ 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., $\xi = \pi \sigma_1^3 N_A/6v_1$); $\sigma_1$ is the hard sphere diameter of the solvent molecules, and $P$ is the pressure. There is still debate on what is the correct pressure to use in eq 9, that of the real liquid or that of the corresponding hard sphere fluid. Since $\Delta G_c$ is the

**TABLE 1: Experimental Values of Molar Volume, Isothermal Compressibility, and Thermal Expansion Coefficient of Water over the Temperature Range 0−150 °C, at 1 atm (from ref 34)[a]**

| $T$, °C | $v$, cm³ mol⁻¹ | $\beta_T \cdot 10^{12}$, cm² dyn⁻¹ | $\alpha \cdot 10^6$, K⁻¹ | $\sigma$, Å | $\xi$ |
|---|---|---|---|---|---|
| 0 | 18.023 | 50.9 | −68.1 | 2.705 | 0.346 |
| 25 | 18.073 | 45.2 | 257.2 | 2.715 | 0.349 |
| 50 | 18.238 | 44.2 | 457.6 | 2.71 | 0.344 |
| 75 | 18.485 | 45.6 | 612.7 | 2.69 | 0.332 |
| 100 | 18.803 | 49.0 | 750.1 | 2.67 | 0.319 |
| 125 | 19.191 | 54.4 | 884.7 | 2.63 | 0.299 |
| 150 | 19.655 | 62.3 | 1027.8 | 2.59 | 0.279 |

[a] In the last two columns are reported the effective hard sphere diameters of water molecules determined by fitting the experimental $\beta_T$ values by means of SPT eq 10 and the corresponding volume packing density, $\xi$.

work to create the cavity in the real liquid, not in the corresponding hard sphere fluid, $P$ has to be the experimental one, 1 atm, the hydrostatic pressure over the liquid.[33] This value has been used in all of the SPT calculations.

In addition, I have used (a) the experimental values of liquid water density at 1 atm in the temperature range 0−150 °C compiled by Kell[34] and listed in the second column of Table 1 in terms of molar volume and (b) a temperature-dependent effective hard sphere diameter for water molecules. The temperature dependence of $\sigma_1$ has been obtained in the following manner (consider that $\sigma_c$ is assumed to be temperature-independent). As suggested by Pierotti,[35] the isothermal compressibility, $\beta_T$, should be the less questionable physical property for the determination of the effective hard sphere diameter of water molecules and its temperature dependence. In fact, in agreement with the physical picture of the liquid state advanced by Reiss[29,36] and Weeks, Chandler, and Andersen,[37] the density of the liquid is determined by the intermolecular attractions and any further isothermal compression should be assimilated to the process of repacking hard spheres. On these grounds, SPT provided the following relationship for $\beta_T$:[29]

$$\beta_T = \pi \sigma_1^3 [(1 - \xi)^4 / \xi(1 + 2\xi)^2]/6kT \qquad (10)$$

where $k$ is the Boltzmann constant. By using the experimental values of liquid water density and isothermal compressibility reported by Kell[34] over the temperature range 0−150 °C, eq 10 allows one to obtain estimates for the effective hard sphere diameter of water molecules at the different temperatures. Such $\sigma_1$ values are listed in the fifth column of Table 1 and correspond to those already reported by Reiss.[29] They slightly decrease with temperature (i.e., $\sigma_1 = 2.715$ Å at 25 °C, 2.67 Å at 100 °C, and 2.59 Å at 150 °C), because the molecules are more effectively able to penetrate one another's repulsive fields upon an increase in the random thermal energy.[29] Moreover, the $\sigma_1$ value at 25 °C is close to the location of the first peak in the oxygen−oxygen radial distribution function of liquid water determined by means of both X-ray and neutron scattering measurements.[38]

Even though an extended version of SPT able to treat arbitrary shaped cavities has been devised,[39] and the $n$-alcohol molecules are surely nonspherical, the classic version of SPT has been adopted because it does contain all the fundamental qualitative features of the reversible work of cavity creation.

Reliable estimates of $\Delta G_a(\text{vdW})$, the reversible work to turn on the alcohol−water van der Waals attractions, are calculated by means of Pierotti's relationship:[30]

$$\Delta G_a(\text{vdW}) = -(64/3)\xi \epsilon_{12}(\sigma_{12}/\sigma_1)^3 \qquad (11)$$

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where $\sigma_{12} = (\sigma_1 + \sigma_2)/2$ ($\sigma_1$ and $\sigma_2$ are the hard sphere diameters of the solvent and solute molecules, respectively) and $\epsilon_{12} = (\epsilon_1\epsilon_2)^{1/2}$ ($\epsilon_1$ and $\epsilon_2$ are the Lennard-Jones potential parameters for the solvent and solute, respectively), measuring the magnitude of the maximum attractive potential energy. Since in a recent work[40] I showed that such a formula works well by fixing $\epsilon_1/k = 100$ K for water and $\epsilon_2/k = 210$ K for a series of alkanes, the same parameter values are used here. The $\Delta G_a(\text{vdW})$ estimates have been calculated using the $\sigma_1$ and $\xi$ values listed in Table 1, and considering $\sigma_2 = \sigma_c$ and temperature-independent. Thus, the temperature dependence of $\Delta G_a(\text{vdW})$ is due to that of water density and effective hard sphere diameter.

The $\Delta G_a(\text{H-bond})$ term is the most difficult to calculate in a theoretical manner, and it is roughly estimated by making use of experimental data. In a previous analysis of the hydration thermodynamics of the first five *n*-alcohols,[24] it resulted that, by subtracting $\Delta G_c + \Delta G_a(\text{vdW})$ from the experimental $\Delta G^\bullet$ values, one obtains a practically constant, large, and negative quantity whose magnitude decreases slightly with temperature. On this basis, $\Delta G_a(\text{H-bond})$, the reversible work to turn on the alcohol–water H-bonding potential given that both the cavity has already been created and the van der Waals attractions have already been switched on, is calculated (in units of kilojoules per mole) by means of the following heuristic relationship:

$$\Delta G_a(\text{H-bond}) = -35 + 0.035T(°C) \qquad (12)$$

It means that $\Delta G_a(\text{H-bond})$ has the same magnitude for all of the *n*-alcohols considered because the hydroxyl group forms three H-bonds with water molecules, one as donor and two as acceptor, independent of the length of the alkyl chain. This is confirmed by neutron scattering measurements[41] and computer simulations.[42] Moreover, eq 12 implies that $\Delta H_a(\text{H-bond}) \cong E_a(\text{H-bond}) = -34.1$ kJ mol$^{-1}$ at 25 °C, and the physical significance of this number can be tested. Jorgensen and Madura[42b] calculated the interaction energy of methanol in TIP4P water at 25 °C and 1 atm, $E_a = -75.3$ kJ mol$^{-1}$. This value contains the contributions of both H-bonds and van der Waals interactions. The latter term for a methyl group[24] should amount to $-10$ kJ mol$^{-1}$, and thus, the H-bond term would be $-65$ kJ mol$^{-1}$ in the additivity assumption. Actually, the H-bond term has to be divided by 2 in order to assign half of the methanol–water H-bond energy to the solute and the other half to the water solvent. Thus, one obtains $E_a(\text{H-bond}) = -32.5$ kJ mol$^{-1}$ at 25 °C, close to the number coming from eq 12. A rough estimate of $E_a(\text{H-bond})$ can be obtained in another way. The number of H-bonds actually gained by the system upon the insertion of a *n*-alcohol molecule in water is $^3/_2$ because the three waters H-bonded to the alcohol hydroxyl group were, before insertion, H-bonded to other waters. According to Pauling,[43] the average energy of a H-bond in water is about $-21$ kJ mol$^{-1}$ at room temperature, and therefore, $E_a(\text{H-bond}) = -31.5$ kJ mol$^{-1}$, again close to the number coming from eq 12.

Finally, estimates of the various entropy contributions have been calculated by differentiating with respect to temperature the corresponding Gibbs energy terms.

## Results

Having established the existence of entropy convergence at $T_S^* \cong 125$ °C in the hydration thermodynamics of *n*-alcohols, it is important to try to reproduce this feature by means of a theoretical approach. Estimates of $\Delta G_c$, $\Delta G_a(\text{vdW})$, and $\Delta G^\bullet = \Delta G_c + \Delta G_a(\text{vdW}) + \Delta G_a(\text{H-bond})$ have been calculated for

**TABLE 2: For Spherical Solutes Whose Diameter Is Reported at the Top, Estimates of $\Delta G_c$ Are Listed in Part A, Estimates of $\Delta G_a(\text{vdW})$ Are Listed in Part B, and Estimates of $\Delta G_c + \Delta G_a(\text{vdW}) + \Delta G_a(\text{H-bond})$ Are Listed in Part C[a]**

| | T, °C | 3 Å | 5 Å | 7 Å | 10 Å | 15 Å |
|---|---|---|---|---|---|---|
| A | 0 | 12.9 | 29.7 | 53.5 | 102.6 | 219.6 |
| | 25 | 14.3 | 32.9 | 59.3 | 113.6 | 243.3 |
| | 50 | 15.1 | 34.6 | 62.4 | 119.5 | 255.9 |
| | 75 | 15.4 | 35.3 | 63.6 | 121.8 | 260.6 |
| | 100 | 15.4 | 35.3 | 63.4 | 121.2 | 259.0 |
| | 125 | 15.1 | 34.5 | 61.9 | 118.2 | 252.3 |
| | 150 | 14.5 | 33.1 | 59.3 | 113.1 | 241.2 |
| B | 0 | -10.4 | -25.7 | -51.3 | -115.2 | -311.9 |
| | 25 | -10.5 | -25.8 | -51.4 | -115.2 | -311.7 |
| | 50 | -10.3 | -25.4 | -50.8 | -114.0 | -308.5 |
| | 75 | -10.1 | -24.9 | -49.9 | -112.0 | -303.5 |
| | 100 | -9.8 | -24.3 | -48.7 | -109.5 | -297.1 |
| | 125 | -9.4 | -23.5 | -47.2 | -106.4 | -289.4 |
| | 150 | -9.0 | -22.5 | -45.5 | -102.9 | -280.6 |
| C | 0 | -32.5 | -31.0 | -32.8 | -47.7 | -127.2 |
| | 25 | -30.3 | -27.0 | -26.2 | -35.7 | -102.5 |
| | 50 | -28.5 | -24.1 | -21.7 | -27.7 | -85.9 |
| | 75 | -27.1 | -22.0 | -18.6 | -22.6 | -75.3 |
| | 100 | -25.9 | -20.5 | -16.8 | -19.8 | -69.6 |
| | 125 | -25.0 | -19.6 | -15.9 | -18.9 | -67.7 |
| | 150 | -24.2 | -19.2 | -15.9 | -19.5 | -69.1 |

*[a]* All the numbers are in units of kilojoules per mole. See text for further details.
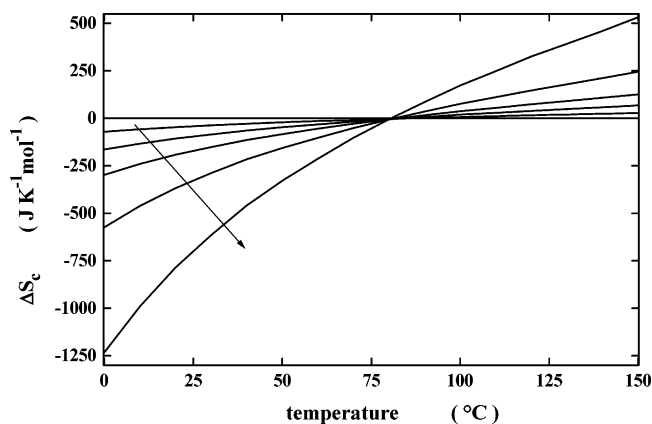


**Figure 2.** Plot of $\Delta S^\bullet = \Delta S_c$ versus temperature in water for different cavity diameters. The arrow indicates entropy curves for cavities with a diameter of 3, 5, 7, 10, and 15 Å, respectively. The convergence temperature is close to 81 °C.

different solute diameters, $\sigma_2 = 3, 5, 7, 10$, and 15 Å, over the temperature range 0–150 °C, using eqs 9, 11, and 12. Some representative numbers are listed in Table 2. The $\Delta G_c$ values, even though large and positive at any temperature, show a nonmonotonic trend, with a flat maximum at about 85 °C (see part A of Table 2). This trend is due to the temperature dependence of both the density of water and the effective size of water molecules.[9] The $\Delta G_a(\text{vdW})$ values are negative at any temperature and decrease in magnitude with increasing temperature (see part B of Table 2). The $\Delta G^\bullet$ values are large and negative over the whole temperature range 0–150 °C and for the larger solutes present a flat maximum at about 125 °C.

By performing a numerical differentiation with respect to temperature of the $\Delta G_c$ functions, $\Delta S_c$ estimates have been calculated over the 0–150 °C temperature range (see Figure 2). They are large and negative at low temperature but increase markedly with temperature, becoming positive above 90 °C. More importantly, these $\Delta S_c$ functions show convergence at about 80 °C, where $\Delta S_c \approx -5$ J K$^{-1}$ mol$^{-1}$ regardless of cavity diameter. This result is not new, since it was already shown
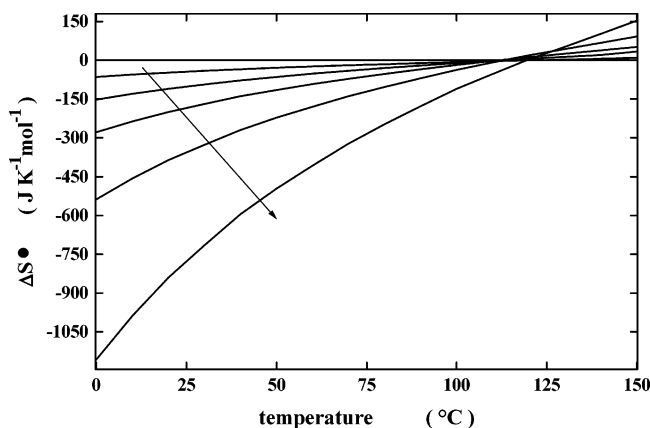
**Figure 3.** Plot of $\Delta S^\bullet = \Delta S_c + \Delta S_a(\text{vdW})$ versus temperature in water for different solute diameters. The arrow indicates entropy curves for solutes with a diameter of 3, 5, 7, 10, and 15 Å, respectively. The convergence temperature is close to 110 °C.
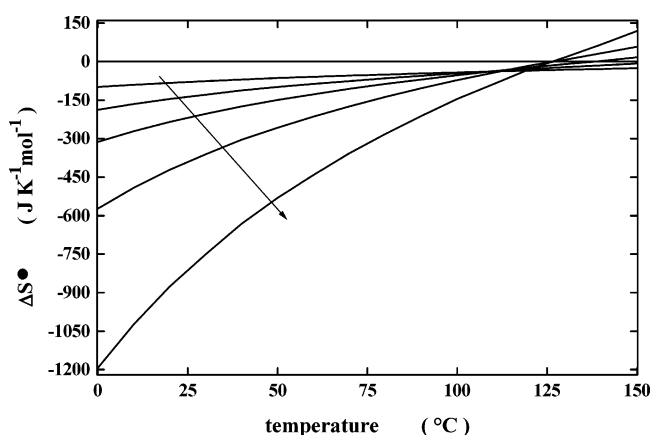


**Figure 4.** Plot of $\Delta S^\bullet = \Delta S_c + \Delta S_a(\text{vdW}) + \Delta S_a(\text{H-bond})$ versus temperature in water for different solute diameters. The arrow indicates entropy curves for solutes with a diameter of 3, 5, 7, 10, and 15 Å, respectively. The convergence temperature is close to 110 °C.

that entropies of cavity creation show convergence.[9,17–19] However, in the case of *n*-alcohols, one cannot consider that all the hydration entropy change is due to the cavity creation step, neglecting the contribution associated with turning on solute–water attractions.

A numerical differentiation with respect to temperature of $\Delta G_c + \Delta G_a(\text{vdW})$ provided estimates of $\Delta S_c + \Delta S_a(\text{vdW})$ over the 0–150 °C temperature range (see Figure 3). These entropy functions show convergence but at higher temperature with respect to $\Delta S_c$ alone, $T_S^* \cong 110$ °C versus 80 °C, even though the entropy at $T_S^*$ amounts to about $-3$ J K$^{-1}$ mol$^{-1}$. It is also evident that the entropy functions of the two larger solutes, $\sigma_2$ = 10 and 15 Å, do not converge at 110 °C (see Figure 3). This defocusing is an expected result because it was pointed out that sharp entropy convergence should occur only for a limited size range of the solutes.[9,44] In this respect, one has to consider that the effective hard sphere diameters of the eight *n*-alcohols considered range from 3.83 Å of methanol up to 6.69 Å of *n*-octanol.[45]

In addition, even though at $T_S^* \cong 110$ °C the values of $\Delta S_c$ + $\Delta S_a(\text{vdW})$ are negative, in agreement with experimental data, their magnitude is significantly smaller. Such a discrepancy should be attributed to the neglect of the entropy contribution associated with turning on the H-bonding potential between solute and water molecules, that is expected to be a negative quantity. By considering the temperature derivative of $\Delta G^\bullet = \Delta G_c + \Delta G_a(\text{vdW}) + \Delta G_a(\text{H-bond})$, the functions $\Delta S^\bullet = \Delta S_c$

+ $\Delta S_a(\text{vdW}) + \Delta S_a(\text{H-bond})$ increase markedly with temperature, passing from large and negative values at low temperature to large and positive values at high temperature. They converge at $T_S^* \cong 110$ °C, where the entropy is large and negative, about $-40$ J K$^{-1}$ mol$^{-1}$, in agreement with experimental data for the hydration of *n*-alcohols. Therefore, it is possible to reproduce in a more-than-qualitative manner the entropy convergence characterizing the hydration thermodynamics of *n*-alcohols by considering the entropy contributions associated with the three subprocesses in which their hydration can be divided: cavity creation, turning on solute–water van der Waals attractions, and turning on the solute–water H-bonding potential.

## Discussion

Entropy convergence occurs in the transfer thermodynamics of several compounds in water, and it should be a reflection of some of the special properties of water, as pointed out in detailed theoretical analyses of entropy convergence for nonpolar solutes.[9,17–19] Its importance may be appreciated by considering that, recently, the existence of entropy convergence has been used by (a) Muñoz and colleagues[46] in the development of a statistical mechanical model accounting for specific features of the folding/unfolding thermodynamics of globular proteins in aqueous solutions and (b) Chandler and co-workers[47] in the development of a theoretical approach of the formation and stability of micelles in water.

In this study, I have shown the existence of entropy convergence in the hydration thermodynamics of *n*-alcohols and devised a somewhat heuristic approach to reproduce and explain this finding. The experimentally observed nonconvergence of methanol parallels that of helium and neon in the hydration thermodynamics of noble gases.[9] It appears that for very small solutes in water the conditions for entropy convergence are not fulfilled. As indicated by the figures, the nonconvergence of very small solutes is not reproduced by the present heuristic approach. Unfortunately, I am not able to provide a robust explanation of this deficiency.

A molecular level understanding of the occurrence of entropy convergence in the hydration thermodynamics of *n*-alcohols can be reached by analyzing the behavior of the entropy contributions that add up to produce the overall entropy change. The temperature dependence of $\Delta S_c$ can be rationalized by means of eq 7 that is of general validity. The values of $\Delta S_c$, $\Delta S_{c,\text{xv}} = -\Delta G_c/T$, and $\Delta S_{c,\text{sr}} = \Delta S_c - \Delta S_{c,\text{xv}}$ are reported in columns 4–6 of Table 3 for $\sigma_c = 5$ and 10 Å, respectively, over the range 0–150 °C. The $\Delta S_{c,\text{xv}}$ estimates are negative over the whole temperature range and prove to be dominant around room temperature; their magnitude diminishes with temperature because the void volume increases due to the decrease of both the water density and size of the water molecules (i.e., both $\xi$ and $\sigma_1$ become smaller with temperature; see Table 1). The $\Delta S_{c,\text{sr}}$ estimates are negative at 0 °C, increase markedly with temperature, being positive above the temperature of maximum density of water, and are dominating above 90 °C. This behavior can be rationalized by remembering that (a) $\Delta S_{c,\text{xv}} = -\Delta G_c/T$ depends on the water density and so its temperature dependence is slight because the density of water decreases by less than 10% over the 0–150 °C temperature range;[34] (b) $\Delta S_{c,\text{sr}} = \Delta H_c/T$ is proportional to the thermal expansion coefficient of the solvent,[30] $\alpha$; and (c) the temperature dependence of $\alpha$ in the case of water is strong,[34] as can be appreciated by the experimental values listed in the fourth column of Table 1. The fact that the reorganization of H-bonds is proportional to $\alpha$ is not surprising because, according to statistical mechanics,[48] $\alpha$

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**TABLE 3: Estimates of the Total Entropy Change, $\Delta S^\bullet$, the Entropy Change Associated with Cavity Creation, $\Delta S_c = -(\partial \Delta G_c / \partial T)_P$, the Cavity Excluded Volume Entropy Contribution, $\Delta S_{c,xv} = -\Delta G_c/T$, the Cavity Structural Reorganization Entropy Contribution $\Delta S_{c,sr} = \Delta S_c - \Delta S_{c,xv}$, and the Entropy Contribution due to the Structural Reorganization upon Turning on Solute−Water van der Waals Attractions, $\Delta S_a(\text{vdW})$, as a Function of Temperature for $\sigma_2 = 5$ and 10 Å, Respectively[a]**

| $\sigma_2$, Å | $T$, °C | $\Delta S^\bullet$ | $\Delta S_c$ | $\Delta S_{c,xv}$ | $\Delta S_{c,sr}$ | $\Delta S_a(\text{vdW})$ |
|---|---|---|---|---|---|---|
| 5 | 0 | −187.3 | −164.7 | −108.7 | −56.0 | 12.4 |
| | 25 | −136.8 | −95.7 | −110.3 | 14.6 | −6.1 |
| | 50 | −99.0 | −47.3 | −107.1 | 59.8 | −16.7 |
| | 75 | −70.1 | −11.4 | −101.4 | 90.0 | −23.7 |
| | 100 | −45.9 | 18.6 | −94.6 | 113.2 | −29.5 |
| | 125 | −25.5 | 44.2 | −86.1 | 130.8 | −34.7 |
| | 150 | −7.2 | 68.0 | −78.2 | 146.2 | −40.2 |
| 10 | 0 | −573.0 | −574.3 | −375.6 | −198.7 | 36.3 |
| | 25 | −391.6 | −328.3 | −381.0 | 52.7 | −28.3 |
| | 50 | −256.9 | −156.1 | −369.8 | 213.7 | −65.8 |
| | 75 | −155.5 | −28.9 | −349.8 | 320.9 | −91.6 |
| | 100 | −71.9 | 76.0 | −324.8 | 400.8 | −112.9 |
| | 125 | −3.0 | 164.3 | −296.9 | 461.2 | −132.3 |
| | 150 | 57.7 | 245.0 | −267.3 | 512.3 | −152.3 |

[a] All the entropy numbers are in units of joules per kelvin-mole.

represents the ensemble correlation between volume fluctuations and enthalpy fluctuations, and the latter in water are usually attributed to the transient H-bond reorganization.[49] It is worth noting that the relationship between entropy convergence and the thermal expansion coefficient of water has already been provided by Debenedetti and colleagues.[19]

Therefore, above the temperature of maximum density of water, the structural reorganization of water molecules upon cavity creation causes an increase of entropy that becomes larger with temperature, as more H-bonds are broken due to the increasing random thermal energy. Entropy convergence occurs because, even though the magnitude of $\Delta S_{c,xv}$ depends on the cavity size, also the rate of increase with temperature of $\Delta S_{c,sr}$ is proportional to the cavity size. Therefore, there should be a temperature at which $\Delta S_c = \Delta S_{c,xv} + \Delta S_{c,sr}$ has the same value regardless of the cavity diameter.

The entropy contribution upon turning on solute−water van der Waals attractions, $\Delta S_a(\text{vdW})$, is expected to be a negative quantity. By looking at the values listed in the last column of Table 3, one finds that this expectation is verified above the temperature of maximum density of water. This is simply because eq 11, describing the solute−water van der Waals attractions, depends on the water density. The magnitude of $\Delta S_a$(vdW) increases with temperature and shifts the entropy convergence at a higher temperature: $T_S^*$ passes from 80 to 110 °C. Obviously, one has to think that part of the entropy gain due to the structural reorganization of water molecules upon cavity creation is compensated for by the entropy loss upon turning on van der Waals attractions (see the last two columns of Table 3). The treatment of solute−water van der Waals attractions is approximate, but equations similar to Pierotti's equation are used by other scientists[50] and usually provide reliable results.

By adding to $\Delta S_c$ and $\Delta S_a$(vdW) a negative and constant entropy contribution for the formation of alcohol−water H-bonds, the entropy convergence temperature does not change, but the magnitude of $\Delta S^\bullet(T_S^*)$ passes from about −3 to about −40 J K$^{-1}$ mol$^{-1}$. Clearly, this result is entirely dependent on the reliability of eq 12 that does not really possess a theoretical foundation. In this respect, it is worth noting that both thermodynamic analyses[23,24] and computer simulations[39,42] have

found that the alcohol−water H-bonds provide a large and negative contribution to the $\Delta G^\bullet$ values for the hydration of *n*-alcohols, whose magnitude is constant regardless of the alkyl chain length at a fixed temperature. Thus, it should be a reliable first approximation to assume that also the entropy contribution $\Delta S_a$(H-bond) is a constant negative quantity for all the considered *n*-alcohols.

In conclusion, even though the devised heuristic approach cannot be considered entirely satisfactory, it emphasizes that the density of liquid water, the size of water molecules, and their respective temperature dependence, together with the fact that the alcohol hydroxyl group forms the same number of H-bonds with water molecules regardless of the length of the alkyl chain, are the properties determining the occurrence of entropy convergence in the hydration thermodynamics of *n*-alcohols. Finally, I would like to point out that the present work tries to follow Occam's razor: the fewest possible assumptions should be made in explaining a thing, or the simplest explanation of a phenomenon is usually the correct one.

**Appendix. Entropy Change Associated with the Creation of a Point Cavity**

The reversible work associated with the creation of a point cavity (i.e., a cavity of diameter $\sigma_c = 0$) is given by an exact relationship grounded in the geometric statistical mechanics:[11,29]

$$\Delta G_c(\sigma_c = 0) = -RT \ln(1 - \xi) \qquad (A1)$$

where $\xi$ is the volume packing density of the liquid. Clearly, $\Delta G_c(\sigma_c = 0)$ is a positive quantity, because there is an excluded volume effect also for the creation of a point cavity. Indeed, the spherical shell between the point cavity and its solvent accessible surface proves to be inaccessible to the center of all solvent molecules because the cavity region has to be void. The corresponding entropy and enthalpy changes are obtained by direct application of equilibrium thermodynamics:

$$\Delta S_c(\sigma_c = 0) = -[\partial \Delta G_c(\sigma_c = 0)/\partial T]_P = R \ln(1 - \xi) - [RT/(1 - \xi)](\partial \xi/\partial T) \quad (A2)$$

$$\Delta H_c(\sigma_c = 0) = -T^2\{\partial[\Delta G_c(\sigma_c = 0)/T]/\partial T\}_P = -[RT^2/(1 - \xi)](\partial \xi/\partial T) \quad (A3)$$

It is clear that the entropy change, also for the creation of a point cavity, is made up of two contributions. The first term on the right-hand side of eq A2 is the excluded volume contribution, $\Delta S_{c,xv} = -\Delta G_c/T$, and is a negative quantity; the second term represents the solvent structural reorganization contribution, that is proportional to the thermal expansion coefficient of the liquid, and is perfectly compensated for by the enthalpy change for cavity creation, $\Delta S_{c,sr} = \Delta H_c/T$. The aim of this analysis is to underscore that (a) the excluded volume entropy contribution is directly related to the work of cavity creation and (b) it does not correspond to $\Delta S_c$ because the latter contains also a contribution due to the structural reorganization of solvent molecules.

**Supporting Information Available:** Table showing thermodynamic data for the hydration process of *n*-alcohols, referred

to the Ben-Naim standard conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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