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Group Additivity Analysis of the Heat Capacity Changes Associated with the Dissolution into Water of Different Organic Compounds

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Abstract: A group additivity approach is applied to the large positive heat capacity changes associated with the dissolution process into water of different classes of organic molecules. The results show that the contribution of nonpolar CH groups is approximately constant for all the organic molecules studied, regardless of their chemical nature and originating phase. Further analysis leads to the conclusion that the unique properties of water are the main physical cause of these results.

Introduction

Hydrophobic hydration and hydrophobic interactions are still very controversial subjects.[1−3] Their complete understanding and explanation in molecular terms are important for research due to their fundamental role in the stabilization of micelles, biomembranes, and native globular protein structures, and because they are generally involved in any molecular recognition process, e.g., the specific binding of substrates in the active site of enzymes, quaternary protein structure formation, protein−DNA interactions, and host−guest binding. These subjects, however, are problematic even on a semantic level.[4,5] Some authors[6−12] have pointed out the inconsistency of the largely accepted view that water structure enhancement around a nonpolar solute causes the hydrophobicity, e.g., the "icebergs" model,[13] or the "flickering clusters" model.[14] This water reorganization would be the cause of the strong entropy decrease and exothermic heat effect associated with the process of transferring a nonpolar molecule from pure gas phase into water at room temperature. But, the iceberg or cluster formation, by augmenting the order of water molecules and strengthening the hydrogen bond pattern, would give rise to an enthalpy−entropy compensation little affecting the Gibbs energy change.[3,7,10−12] Furthermore, due to the well-known strong temperature dependence of the associated enthalpy and entropy changes, the transfer process would be entropy driven in one temperature range and enthalpy driven in another temperature range. Actually, temperature has a remarkably small influence on the positive Gibbs energy of transfer. Clearly these thermodynamic results contrast with the traditional idea that the structural changes in the water cosphere cause the low solubility of nonpolar compounds. Among the new approaches to the hydrophobicity puzzle, Lee's[12] treatment stressed that the negative enthalpy change can be accounted for just by the direct nonpolar solute−water interactions, and that the negative entropy change is caused by an excluded-volume effect which is related to cavity formation and enlarged by the very small size of water molecules.

Some authors, such as Baldwin,[15] Murphy et al.,[16] and Dill,[17] however, have suggested that the large positive heat capacity change associated with the transfer process of nonpolar molecules from pure phase into water must be regarded as the specific and fundamental feature of hydrophobic hydration. Arnett and co-workers[18] have also experimentally demonstrated that this "excess" heat capacity for the transfer of nonpolar molecules is the property which clearly distinguishes water from all other solvents. In addition, problems related to the choice of standard state do exist for the entropy and Gibbs energy changes; they are, however, less important for the enthalpy and heat capacity changes.[19−22]

Adopting these interpretations, we studied the heat capacity changes associated with the transfer process of small organic molecules from different phases (solid, liquid, and gaseous) into water in order to reach results of general validity. We analyzed a large amount of literature data from various authors according to a simple group additivity scheme in order to separate the contribution of nonpolar groups. The analysis gives the value of $\Delta_{tr}C_p{}^\circ{}_{CH}$, i.e., the heat capacity associated with the interaction of water molecules with a single CH group, and leads to the conclusion that this value is approximately constant for all the different chemical series *regardless of the starting phase*. The

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agreement between the obtained value and that calculated using the independent two-state model proposed by Gill and colleagues is important and should be noted.[23] These findings demonstrate that only the water molecules in the first hydration shell are responsible for the heat capacity change which is found to be proportional to the nonpolar accessible surface area of the solute.[24,25]

Analysis of the Heat Capacity Data

We have considered the heat capacity changes associated with the dissolution process from pure solid, liquid, or gaseous phases into water of several organic compounds. Although it has been firmly established from detailed experimental measurements[26−32] that these heat capacity changes are temperature dependent, their values still remain large and positive at temperatures above 370 K. For this reason and due to the lack of experimental data over a sufficiently wide temperature range, we analyzed the values of $\Delta_{tr}C_p°$ at only one temperature, namely 298.15 K (except in two cases), without a loss of physical meaning. The adopted group additivity scheme makes use of the nonpolar hydrogen atoms CH (i.e. hydrogen atoms bonded to a carbon atom, regardless of whether it is aliphatic or aromatic, and assuming, for instance, that a CH_3 group corresponds to three nonpolar hydrogens) to measure the nonpolar part of each compound.[33,34] The validity of this choice is grounded on the demonstration that the number of nonpolar hydrogen atoms is directly proportional to the nonpolar accessible surface area of the molecule, ASA_{np}.[35]

For each homologous series (i.e., liquid hydrocarbons, liquid alcohols, etc.), the heat capacity change is given by the sum of a constant contribution, due to the functional group common to all compounds, and a variable contribution due to the number of nonpolar hydrogen atoms present in each molecule. Therefore, at a fixed temperature, the heat capacity change can be described by the following equation:

$$\Delta_{tr}C_p° = \text{constant} + N_{CH}\cdot\Delta_{tr}C_p°_{CH} \qquad (1)$$

where $\Delta_{tr}C_p°_{CH}$ is the heat capacity change due to a single nonpolar hydrogen atom. We have analyzed the following series: (a) gaseous hydrocarbons;[32,36] (b) gaseous alcohols;[37] (c) liquid alcohols;[37,38] (d) liquid ethers;[39] (e) liquid carboxylic acids;[40] (f) liquid amines;[40] (g) liquid amides;[40,41] (h) solid α-amino acids;[42,43] (i) solid linear dipeptides;[44] (j) sodium carboxylates;[45] (k) tetralkylammonium bromides;[46] and (l) sodium alkylsulfates.[47] Tables 1−12 of the Appendix (see supporting information) report the various compounds with their corresponding values of N_{CH}, $\Delta_{tr}H°$(298.15K) in kJ·mol^{-1} units, based on the mole fraction standard state, and $\Delta_{tr}C_p°$(298.15K) in J·K^{-1}·mol^{-1} units. For the liquid hydrocarbons, we used the least-squares analysis reported by Gill and Wadso;[33] and for the solid cyclic dipeptides (diketopiperazines, DKP) we used the least-squares analysis of Murphy and Gill.[35]

Table 1. Number of Compounds in Each Class, Values of Linear Regression Coefficient, Values of Plot Intercept, and Values of the Heat Capacity Change due to a CH Group, at 298.15 K, Calculated from Least-Squares Regressions with Respect to Equation 1

compounds	N	r	intercept	$\Delta_{tr}C_p°_{CH}$ (J·K^{-1}·mol^{-1})
gaseous hydrocarbons[a,b]	13	0.976	103.7 ± 15.5	30.6 ± 2.1
liquid hydrocarbons[c]	15	0.998	7 ± 11	33.4 ± 0.9
gaseous alcohols[d]	7	0.996	51.6 ± 9.3	30.0 ± 1.2
liquid alcohols[d]	10	0.985	20.6 ± 15.0	29.1 ± 1.8
liquid alcohols[e]	8	0.998	5.7 ± 7.4	28.2 ± 0.7
liquid ethers[f]	10	0.996	−88.7 ± 11.4	28.4 ± 1.0
liquid carboxylic acids[g]	5	0.998	−35.5 ± 4.4	27.8 ± 0.9
liquid amines[g]	6	0.996	−40.2 ± 12.6	30.2 ± 1.3
liquid amides[g,h]	11	0.998	−65.5 ± 5.1	29.0 ± 0.6
solid α-amino acids[i,j]	5	0.998	−111.5 ± 7.2	31.7 ± 1.1
solid cyclic dipeptides[k]	5	0.997	−120 ± 12	28.1 ± 1.1
solid linear dipeptides[l]	4	0.998	−153.7 ± 13.1	33.0 ± 1.5[p]
sodium carboxylates[m]	10	0.985	−119.8 ± 15.7	28.8 ± 1.8[p]
TAA bromides[n]	5	0.995	−453.4 ± 56.7	31.7 ± 1.9
sodium alkylsulfates[o]	6	0.998	−158.6 ± 7.7	29.4 ± 0.9
unweighted mean value $\Delta_{tr}C_p°_{CH}$ = 30.0 ± 2.0 J·K^{-1}·mol^{-1} [q]				

[a] Reference 32. [b] Reference 36. [c] Reference 33. [d] Reference 37. [e] Reference 38. [f] Reference 39. [g] Reference 40. [h] Reference 41. [i] Reference 42. [j] Reference 43. [k] Reference 35. [l] Reference 44. [m] Reference 45. [n] Reference 46. [o] Reference 47. [p] These values refer to 303.15 K. [q] The reported error corresponds to the standard deviation of the normal distribution of the single values, assumed as independent estimates.

The results of the unweighted least-squares regressions are summarized in Table 1 of the text, where the number of compounds in each series, the values of the linear correlation coefficient, the values of $\Delta_{tr}C_p°_{CH}$, and the values of the plot intercept are reported. The polar groups (i.e. COOH, CONH, and NH_2) make negative contributions to the heat capacity changes, as has been firmly established.[48,49] However, the hydroxyl group makes a positive contribution from both the liquid and gaseous phases. This last finding agrees with a recent group additivity analysis of the hydration of gaseous alcohols by Murphy.[50] In contrast, the work of Franks et al.[51] suggests that the $\Delta_{tr}C_p°$ value greatly decreases as the number of hydroxyl groups on a solute increases. These researchers found that the

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changes in heat capacity for the dissolution into water at 25 °C of liquid propane, propan-1-ol, propan-2-ol, propane-1,2-diol, propane-1,3-diol, and glycerol were 293.0, 202.1, 209.2, 97.5, 85.4, and 4.2 $J\cdot K^{-1}\cdot mol^{-1}$, respectively.

It is noteworthy that the plot intercept corresponding to the gaseous hydrocarbons (i.e., 103.7 ± 15.4 $J\cdot K^{-1}\cdot mol^{-1}$) is large and positive, whereas it is practically zero for liquid hydrocarbons. This difference can only be in part ascribed to the heat capacity change associated with the gas-to-liquid phase transition of pure solute, which amounts to an average of 40–60 $J\cdot K^{-1}\cdot mol^{-1}$ at room temperature.[52] This discrepancy may be attributed to the fact that, with regard to any property which changes regularly as a function of an increasing molecular parameter (in this case, the number of nonpolar hydrogens), the "heads of the compound series" can introduce a large error in the plot intercept value. For instance, C_2H_2, CH_4, and C_2H_4 are not well represented by two and four nonpolar hydrogens, respectively.

Since the value of the linear correlation coefficient is always greater than 0.97, the validity of group additivity is confirmed, at least for these limiting properties.[53] More importantly, the value of $\Delta_{tr}C_p°_{CH}$ is practically constant for all the considered series (the mean value of $\Delta_{tr}C_p°_{CH} = 30.0 \pm 2.0$ $J\cdot K^{-1}\cdot mol^{-1}$), *regardless of the starting phase* (i.e., solid, liquid, or gaseous). Thus, it may be concluded that the nature of the hydrophylic group, ionic or non-ionic, attached to the nonpolar moiety, and the nature of the originating phase, condensed or gaseous, do not significantly influence the contribution of a CH group to the transfer heat capacity change. It seems that the value of $\Delta_{tr}C_p°_{CH}$ is entirely determined by the unique physicochemical properties of water. This result is not completely new,[54–59] but we have here verified its validity for a large number of organic compounds, using the available experimental data obtained by different laboratories and researchers over the last 25 years. The finding that the heat capacity increment of nonpolar groups is independent of the starting phase would seem to contrast with Sturtevant's position[60] that changes in the frequency of "soft" vibrational modes can contribute significantly to the heat capacity change on protein unfolding and/or ligand binding. Probably this contribution is very small for low molecular weight compounds, such as those considered in this work.

The above proposed additivity scheme can be used to further prove the validity of the present results. If the values $\Delta_{tr}C_p°_{CH} = 30$ $J\cdot K^{-1}\cdot mol^{-1}$ and $\Delta_{tr}C_p°_{CONH} = -60$ $J\cdot K^{-1}\cdot mol^{-1}$ (a figure obtained from solid DKP[35]) are used, the heat capacity change for the dissolution into water of the two isomeric, solid amides, tBuNHCOMe and MeNHCOtBu, is calculated to be 300 $J\cdot K^{-1}\cdot mol^{-1}$. This value agrees with the experimentally determined ones, 308 ± 4 and 293 ± 6 $J\cdot K^{-1}\cdot mol^{-1}$, respectively.[40] Finally, the value obtained for $\Delta_{tr}C_p°_{CH}$, allows an accurate estimate of the nonpolar contribution to the net heat capacity change associated with the thermal denaturation process of globular proteins, as demonstrated by various authors.[35,49,57,58,61] Indeed, the unfolding of the tertiary structure of globular proteins can be mimicked by the transfer process of amino acid residues from the protein interior to water. Therefore the value of $\Delta_{tr}C_p°_{CH} = 30.0$ $J\cdot K^{-1}\cdot mol^{-1}$ seems to be a generally constant quantity for processes in which water molecules are the main actors.

Discussion

X-ray studies on clathrate hydrate crystals of many nonpolar substances have well established that water molecules reorganize themselves around a nonpolar solute by forming a wide set of host–guest inclusion cages to maximize and strengthen the hydrogen bonds.[62] In aqueous solutions, direct measurements of water reorganization are very difficult and the interpretation of experiments may be misleading. Nevertheless, computer simulation studies[63–66] have confirmed that the waters in the first hydration shell reorient themselves near the solute boundary surface by pointing, on the average, the hydrogen atoms tangentially on the solute to avoid the waste of hydrogen bonds. But there is no convincing evidence that the number and/or strength of hydrogen bonds increases,[1] as recently confirmed by Finney and Soper[67] from neutron scattering studies on aqueous solutions of tetramethylammonium ion and alcohols. Even though the water reorganization is a compensating process[3,7,10–12] that little affects the transfer Gibbs energy, it is believed to be the cause of the large positive heat capacity changes. The geometrical reorganization can be described by a very simple model in which each water molecule has two accessible states separated by a small amount of energy. The enthalpy fluctuations associated with the Boltzmann distribution of waters over the two states give rise to the excess heat capacity. Dill[17] has written the following: "At room temperature, the water molecules surrounding the nonpolar solute principally populate a low-energy, low-entropy state: the waters are ordered so as to form good water–water hydrogen bonds. With increasing temperatures, the waters surrounding the nonpolar solute principally populate a higher energy, higher entropy state: they are less ordered and have weakened attractions. The reason this results in a large heat capacity is that the two different energetic states of water provide an energy storage mechanism. The reason this heat capacity is so large per solute molecule is because each solute molecule is surrounded by a large number (more than 10) of first-shell water molecules, each of which can partipicate in this energy storage mechanism." Even Lumry and colleagues[7,68,69] ascribed the large positive heat capacity of hydrophobic hydration to a two-state "geometrical relaxation" of pentameric water clusters, which fluctuate, more or less independently of each other, between one state with short and strong hydrogen bonds and another state with long and weak hydrogen bonds.

Moreover, Lee[12] suggested on the basis of scaled particle theory (even though this theory underestimates the heat capacity

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in aqueous solutions, because it does not consider the directional hydrogen-bonding properties of water) that the unusually large enthalpy fluctuations associated with the reorganization process of water molecules in the presence of a nonpolar solute can be well estimated from a two-state model along the lines developed by Gill and colleagues.[23] Based on the above considerations, we calculated the value of $\Delta_{tr}C_p{}^\circ{}_{CH}$ assuming that the heat capacity change is entirely determined by the excess heat capacity of water molecules that directly interact with the nonpolar solute molecule. Each water molecule is assumed to behave independently of its neighbors, and cooperative effects are neglected. The validity of this model to predict the temperature dependence of heat capacity changes has been verified for a certain number of nonpolar molecules.[23,54] The formula proposed by Gill and colleagues is given by:

$$\Delta_{tr}C_p{}^\circ{}_{CH} = N_{H_2O}(\Delta H^2/RT^2)\exp[-(\Delta H/R)(1/T - 1/T_m)]/\{1 + \exp[-(\Delta H/R)(1/T - 1/T_m)]\}^2 \quad (2)$$

where ΔH is the enthalpy difference per molecule of water between the upper enthalpy state and the lower enthalpy state of each water molecule in the presence of the solute; T_m is the temperature at which the two states are equally populated by water molecules and, according to Shinoda,[70] $T_m = 370$ K; $T = 298.15$ K; and N_{H_2O} is the number of water molecules in the first hydration shell around a CH group, calculated from the ratio of the accessible surface area of a CH group ($ASA_{CH} = 15.1$ Å^2, ref 56) to the accessible surface area of a water molecule ($ASA_{H_2O} = 9.0$ Å^2, ref 24). Therefore, one gets:

$$N_{H_2O} = ASA_{CH}/ASA_{H_2O} = 15.1\ \text{Å}^2/9.0\ \text{Å}^2 = 1.68 \text{ water molecules per CH group}$$

This figure is in good agreement with the results obtained by Jorgensen and co-workers,[71] who utilizing very large sample Monte Carlo calculations determined the number of water molecules around a CH group to be 1.61. Thus we used the value $N_{H_2O} = 1.68$ water molecules per CH, obtained from the ratio of cavity surface areas. By inserting the values $\Delta H = 7.4$, 7.7, and 8.0 kJ·(mol of water)$^{-1}$ into eq 2, we obtained $\Delta_{tr}C_p{}^\circ{}_{CH} = 28.6$, 30.8, and 33.0 J·K^{-1}·mol^{-1}, respectively. Clearly these results agree with those calculated from least-squares regressions, and this agreement confirms the direct proportionality between heat capacity change and the nonpolar accessible surface area of solutes. The ΔH value of approximately 7.5 kJ·(mol of water)$^{-1}$ is less than the ΔH value which corresponds to the breakage of one water–water hydrogen bond in the liquid phase,[72] further, it may correspond to an average of values associated with the deformation and rupture of hydrogen bonds and other interactions. The values of ΔH, however, reasonably agree with the breaking energy of a hydrogen bond used by Nemethy and Scheraga[73–75] in their statistical mechanical model of water.

The model of Gill and colleagues[23] reproduces well the experimental results, but it does not give a physical explanation of the fact that the starting phase is not important in determining the value of $\Delta_{tr}C_p{}^\circ{}_{CH}$. However, the model's heuristic strength validates the group additivity approach because it assumes the independent behavior of each water molecule. This independent behavior is in contrast with the cooperative mechanism suggested for the icebergs and flickering clusters formation.[13,14] It is worth noting that also the Muller's "modified hydration-shell hydrogen-bond" model,[76] which well accounts for some features of hydrophobic hydration, is based on the independence of hydrogen bonds from each other.

Moreover, Costas et al.[77] have recently presented a new approach to explain the origin of hydrophobicity, but they used a two-state model of water reorganization very similar to that of Gill and colleagues[23] to calculate the heat capacity changes. Costas et al. determined different values for the thermodynamic parameters of the model, $\Delta H = 5.32$ kJ·(mol of water)$^{-1}$ and $T_m = 220$ K. Using these values the contribution of a CH group is underestimated, i.e., $\Delta_{tr}C_p{}^\circ{}_{CH}(298.15\text{K}) = 16.6$ J·K^{-1}·mol^{-1}. This discrepancy is probably due to the fact that these authors included only liquid alkylbenzenes in their fitting procedure. Indeed, Makhatadze and Privalov[78] estimated that the heat capacity increment due to aromatic groups is only 60% of the effect of aliphatic groups with the same number of carbons, because aromatic carbon atoms are more polar than aliphatic ones.[79]

The fact that the starting phase does not influence the value of $\Delta_{tr}C_p{}^\circ{}_{CH}$ requires a physical explanation. We believe that the insensitivity of the $\Delta_{tr}C_p{}^\circ{}_{CH}$ value to the choice of nonaqueous phase demonstrates that the cause of this insensitivity does not reside in the interaction between the nonpolar solute and water molecules, but resides in the water reorganization process itself. It appears that the large temperature coefficient of the reorganization process of the water molecules overwhelms all other contributions. Probably the cause must be ascribed to the unique hydrogen-bonding properties of water.

A reasonable physical interpretation of this "insensitivity" can be based on Lee's scaled particle theory approach to hydrophobicity.[8] Lee showed that the thermodynamics of solvent reorganization is correlated to the thermal expansion coefficient, α, of pure solvent. Thus, the excess heat capacity due to the solvent reorganization is proportional to the temperature derivative of α. The strong and anomalous temperature dependence of the thermal expansion coefficient of water with respect to all other solvents is well documented: α is negative below 4 °C, zero at 4 °C, positive above 4 °C, and increases with rising temperature. This accounts for the large heat capacity associated with hydrophobic hydration. Furthermore, the temperature derivative of α is proportional to the "ensemble correlation between volume fluctuations and the fluctuation in the breath of enthalpy fluctuations". Hence, it appears that the anomalous temperature dependence of the thermal expansion coefficient of water reflects the unique fluctuational behavior of water's tetrahedral hydrogen-bonding network.

The dissolution into water of a number of ω-amino acids[43] (i.e. β-alanine, γ-aminobutyric acid, δ-norvaline, ϵ-norleucine, 7-aminoheptanoic acid, and 8-aminocaprylic acid) produced a noteworthy exception to the practically constant value of $\Delta_{tr}C_p{}^\circ{}_{CH}$. The experimental thermodynamic values are shown in Table 13 of the Appendix. With the inclusion of glycine, the value of $\Delta_{tr}C_p{}^\circ{}_{CH}$ at 30 °C is found to be 25.5 ± 2.1

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$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$. This discrepancy may be due to the fact that the water molecules in the two separate solvation shells of the fixed charges are oriented oppositely. This opposing orientation surely perturbs the reorganization of the solvent around the interposed CH groups. Another possible explanation is that the ω-amino acids undergo conformational changes in water in order to bring the two oppositely charged groups closer together. In general, the additivity principle for the analysis of different physicochemical properties suffers for the presence in the molecules of several polar groups, because the latter cause conformational effects and inductive electron correlations, more or less strong, depending on their relative distance. For instance, in the case of the excess thermodynamic properties, the popular Savage and Wood approach,[34] SWAG, has been criticized for the lack of general validity.[80,81] This approach may be used to focus attention on the exceptions. In fact, the SWAG procedure represents a basis to understand how very weak specific interactions rise up from a purely additive background.[82,83] On the other hand, α-amino acids have $\Delta_{tr}C_p{^\circ}_{CH} = 31.7 \pm 1.1$ $\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$; this agrees with the constant value of 30.0 $\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$ discussed above and may be due to the unique perturbing effect on water reorganization produced by the closeness of the two opposite charges.

Finally, the direct proportionality between $\Delta_{tr}C_p^\circ$ and the nonpolar accessible surface area, $\mathrm{ASA_{np}}$, of the solute should be emphasized. Indeed, by assuming, as above, that $\mathrm{ASA_{CH}} = 15.1$ Å^2, the contribution to $\Delta_{tr}C_p^\circ$ per square angstrom of $\mathrm{ASA_{np}}$ is calculated to be $(30.0 \pm 2.0)/15.1 = 1.99 \pm 0.13$ $\mathrm{J \cdot K^{-1} \cdot mol^{-1} \cdot Å^{-2}}$ of $\mathrm{ASA_{np}}$. To confirm the validity of the above conclusion, i.e., that the value of $\Delta_{tr}C_p{^\circ}_{CH}$ is approximately constant, we analyzed the heat capacity changes associated with the dissolution into water of noble gases, calculated on the basis of detailed solubility measurements in two different laboratories.[84,85] Table 2 of the text shows the values of ASA and the solution enthalpy and heat capacity changes at 298.15 K for each gas. From the least-squares regression of $\Delta_{tr}C_p^\circ$ vs ASA, a good linear correlation is obtained in both cases ($r = 0.981$ and 0.999, respectively), with a slope of 1.93 ± 0.22 $\mathrm{J \cdot K^{-1} \cdot mol^{-1} \cdot Å^{-2}}$ for the data of Wilhelm, Battino, and Wilcok[84] and 2.00 ± 0.06 $\mathrm{J \cdot K^{-1} \cdot mol^{-1} \cdot Å^{-2}}$ for the data of Krause and Benson.[85] Therefore, for noble gases the contribution to $\Delta_{tr}C_p^\circ$ amounts to an average of 2.00 $\mathrm{J \cdot K^{-1} \cdot mol^{-1} \cdot Å^{-2}}$ of ASA; this agrees well with the value obtained from the ratio $\Delta_{tr}C_p{^\circ}_{CH}/\mathrm{ASA_{CH}}$.

Table 2. Accessible Surface Area Values and Enthalpy and Heat Capacity Changes Associated with the Transfer Process of Noble Gases into Water at 298.15 K

	ASA (Å^2)	$\Delta_{tr}H^\circ$ ($\mathrm{kJ \cdot mol^{-1}}$)	$\Delta_{tr}C_p^\circ$ ($\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$)
He	105	−0.67[a]	117.0[a]
		−0.54[b]	121.8[b]
Ne	116	−3.76[a]	149.0[a]
		−3.64[b]	143.0[b]
Ar	143	−12.27[a]	178.0[a]
		−11.92[b]	194.5[b]
Kr	155	−15.51[a]	210.0[a]
		−15.34[b]	217.5[b]
Xe	168	−19.18[a]	250.0[a]
		−19.06[b]	250.4[b]

[a] $r = 0.981$; $\Delta_{tr}C_p^\circ = (-83.8 \pm 30.6) + (1.93 \pm 0.22)\cdot\mathrm{ASA}$, in $\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$ (from ref 84). [b] $r = 0.999$; $\Delta_{tr}C_p^\circ = (-89.5 \pm 8.4) + (2.00 \pm 0.06)\cdot\mathrm{ASA}$, in $\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$ (from ref 85).

Concluding Remarks

The above analysis demonstrates that the contribution of nonpolar groups to the heat capacity change associated with the transfer process of several small organic substances to water is approximately constant, *regardless of the molecular species and originating phase*. The unique properties of water are the main cause of these results. Furthermore, the independent two-state model of Gill, Dec, Olofsson, and Wadso[22] correctly predicts the value of this constant quantity. However, the large positive heat capacity change affects both enthalpy and entropy changes, and its influence on the Gibbs energy change should be rather small. Thus, we agree with Lee's view[2,11] regarding, first, the compensating behavior of the temperature dependence of thermodynamic functions and, secondly, that the cause of hydrophobicity (i.e., the poor solubility of nonpolar molecules in water) must be ascribed to the very small size of water molecules which renders the Gibbs energy of cavitation very large with respect to all other solvents.

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Supporting Information Available: Tables of enthalpy and heat capacity changes (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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